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APPLICATION NUMBER: *13/592,202*
FILING DATE: *August 22, 2012*
PATENT NUMBER: *8731963*
ISSUE DATE: *May 20, 2014*

Certified by

David J. Kappos

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Dayton T. Reardan Ph.D et al.
Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
Attorney Docket No.: 101.031US9
Customer No.: 21186

PATENT APPLICATION TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We are transmitting herewith the following attached items and information (as indicated with an "X"):

X **CONTINUATION under 37 CFR 1.53(b) of prior Patent Application No. 13/013,680 comprising:**
- X Specification (22 pgs, including claims numbered 1 through 26 and 1 page Abstract).
- X Formal Drawing(s) (16 sheets).
- X Copy of signed Combined Declaration and Power of Attorney (4 pgs) from prior application.
- X From prior application: Copy of Signed Power of Attorney and Statement Under 3.73(b) (1 pg);
- X Authorization to charge Deposit Account 19-0743 in the amount of $710.00 to pay the filing fee.
- X Incorporation by Reference herein in its entirety: *The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied herewith, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein in its entirety.*

X Prior application is assigned of record to Orphan Medical, Inc.
X Nonpublication Request Under 35 U.S.C. 122(b)(2)(B)(i) (1 pg).
X Application Data Sheet (3 pgs.).
X Certification and Request for Prioritized Examination (Track I) (1 pg), including authorization to charge the Deposit Account No. 19-0743 in the amount of $4800.00 for the Prioritized Examination (Track I) filing fee as set forth in 37 CFR 1.17(c); Authorization to charge the Deposit Account for the Publication Fee as set forth in 37 CFR 1.18(d) in the amount of $300.00; and Authorization to charge the Deposit Account for the Processing Fee (Track I) set forth in 37 CFR 1.17(i) in the amount of $130.00.

The filing fee has been calculated below as follows:

	No. Filed	No. Extra	Rate	Fee
TOTAL CLAIMS	26- 20	6	x $60.00 =	**$360.00**
INDEPENDENT CLAIMS	3 - 3	0	x $250.00 =	**$0.00**
[]MULTIPLE DEPENDENT CLAIMS PRESENTED				**$0.00**
BASIC FEE				**$190.00**
SEARCH FEE				**$620.00**
EXAMINATION FEE				**$250.00**
PRIORITIZED EXAMINATION (TRACK 1) FEES				**$5230.00**
TOTAL				**$6650.00**

Please charge any additional required fees or credit overpayment to Deposit Account No. 19-0743.

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
Customer Number: 21186

By: / /
David D'Zurilla
Reg. No. 36,776

Date of Deposit: August 22, 2012
This paper or fee is being filed on the date indicated above using the USPTO's electronic filing system EFS-Web, and is addressed to The Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

APPLICATION DATA SHEET

Application Information

Application Type::	Regular
Subject Matter::	Utility
CD-ROM or CD-R?::	None
Title::	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
Attorney Docket Number::	101.031US9
Request for Early Publication?::	No
Request for Non-Publication?::	Yes
Authorization to Permit Access to Application (PTO/SB/39) ::	No
Total Drawing Sheets::	16
Small Entity::	No
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

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Correspondence Information

Correspondence Customer Number:: 21186

Representative Information

Representative Customer Number:: 21186

Domestic Benefit/National Stage Information:

Application No.:	Continuity Type:	Parent Application:	Parent Filing Date: (YYYY-MMM-DD)
This Application	Continuation	13/013,680	2011-JAN-25
13/013,680	Continuation	12/704,097	2010-FEB-11
12/704,097	Continuation	10/322,348	2002-DEC-17

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Respectfully submitted,

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Date August 22, 2012

By / /
David D'Zurilla
Reg. No. 36,776

Date of Deposit: August 22, 2012
This paper or fee is being filed on the date indicated above using the USPTO's electronic filing system EFS-Web, and is addressed to The Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

PTO/SB/35 (12-08)
Approved for use through 01/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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NONPUBLICATION REQUEST UNDER 35 U.S.C. § 122(b)(2)(B)(i)	First Named Inventor	Dayton T. Reardan Ph.D et al.
	Title	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
	Atty Docket Number	101.031US9

I hereby certify that the invention disclosed in the attached application **has not and will not be** the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

I hereby request that the attached application not be published under 35 U.S.C. § 122(b).

/ / August 22, 2012

Signature Date

David D'Zurilla, Reg No. 36,776 (612) 371-2140

Typed or printed name Telephone Number

This request must be signed in compliance with 37 C.F.R. § 1.33(b) and submitted with the application **upon filing.**

Applicant may rescind this nonpublication request at any time. If applicant rescinds a request that an application not be published under 35 U.S.C. § 122(b), the application will be scheduled for publication at eighteen months from the earliest claimed filing date for which a benefit is claimed.

If applicant subsequently files an application directed to the invention disclosed in the attached application in another country, or under a multilateral international agreement, that requires publication of applications eighteen months after filing, the applicant **must** notify the United States Patent and Trademark Office of such filing within forty-five (45) days after the date of the filing of such foreign or international application. **Failure to do so will result in abandonment of this application (35 U.S.C. § 122(b)(2)(B)(iii)).**

Date of Deposit: August 22, 2012

This paper or fee is being filed on the date indicated above using the USPTO's electronic filing system EFS-Web, and is addressed to The Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Dayton T. Reardan et al.	Examiner: Lena Najarian
Serial No.:	12/704,097	Group Art Unit: 3686
Filed:	February 11, 2010	Docket: 101.031US5
Customer No.	21186	
Title:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD	

POWER OF ATTORNEY
CERTIFICATE UNDER 37 CFR § 3.73(b)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In accordance with 37 C.F.R. § 1.36, M.P.E.P. §§ 402.05 and 402.07, please appoint the following attorneys and/or patent agents to prosecute this application and to transact all business in the Patent and Trademark Office in connection therewith:

Customer Number: 21186

CERTIFICATE UNDER 37 CFR § 3.73(b)

Jazz Pharmaceuticals, Inc. hereby certifies that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of an assignment from the inventor(s) recorded November 17, 2010 on Reel025304, Frames 0081-0084in the instant Application. To the best of my knowledge and belief, title is in Jazz Pharmaceuticals, Inc., the assignee.

Pursuant to 37 C.F.R. § 3.73(b) I hereby declare that I am empowered to sign this certificate on behalf of Jazz Pharmaceuticals, Inc., the assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true.

Please direct all correspondence in this case to:

Schwegman, Lundberg & Woessner, P.A.
Customer No. 21186

Date 11/04/2011

By _____
Name: Carol Gamble
Title: Sr. Vice President and General Counsel

Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
First Named Inventor/Applicant Name:	Dayton T. Reardan
Filer:	Katherine D. Lee/antonette brinsfield
Attorney Docket Number:	101.031US9
Filed as Large Entity	

Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	380	380
Utility Search Fee	1111	1	620	620
Utility Examination Fee	1311	1	250	250
Request for Prioritized Examination	1817	1	4800	4800
Pages:				
Claims:				
Claims in excess of 20	1202	6	60	360
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- early, voluntary, or normal	1504	1	300	300
Processing Fee, except for Provis. apps	1808	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**6840**

Electronic Acknowledgement Receipt	
EFS ID:	13565960
Application Number:	13592202
International Application Number:	
Confirmation Number:	5805
Title of Invention:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
First Named Inventor/Applicant Name:	Dayton T. Reardan
Customer Number:	21186
Filer:	Katherine D. Lee/antonette brinsfield
Filer Authorized By:	Katherine D. Lee
Attorney Docket Number:	101.031US9
Receipt Date:	22-AUG-2012
Filing Date:	
Time Stamp:	19:26:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$6840
RAM confirmation Number	7829
Deposit Account	190743
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		101_031US9_CONsigned.pdf	9001045 314b9b7a7d6d9bd82023e2e72f1eebdc2164b48d	yes	49

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal of New Application	1	1
Application Data Sheet	2	4
Nonpublication request from applicant.	5	5
TrackOne Request	6	6
Specification	7	19
Claims	20	27
Abstract	28	28
Drawings-only black and white line drawings	29	44
Oath or Declaration filed	45	48
Power of Attorney	49	49

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	41995 3d59ade7519b2fb2a44fe2ee2ccfbb9495b592dc	no	2

Warnings:

Information:

Total Files Size (in bytes):	9043040

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/SB/424 (09-11)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION (TRACK I) (Page 1 of 1)

First Named Inventor:	Dayton T. Reardan Ph.D	Nonprovisional Application Number (if known):	Unknown
Title of Invention:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION (TRACK I) FOR THE ABOVE-IDENTIFIED APPLICATION.

1. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

   OR

   (b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper. (Note: Plant applications cannot be filed via EFS-Web.)

   Note: The following are excluded from the Track I program: design applications, provisional applications, national stage applications, PCT international applications, reissue applications, and reexamination proceedings.

2. The following fees (in amounts consistent with the current fee schedule available at http://www.uspto.gov/about/offices/cfo/finance/fees.jsp) are filed with the application: (1) basic filing fee; (2) search fee; (3) examination fee; (4) any required excess claims fees; (5) any required application size fee; (6) publication fee; (7) processing fee (Track I) set forth in 37 CFR 1.17(i); and (8) prioritized examination fee (Track I) set forth in 37 CFR 1.17(c).

3. An executed oath or declaration under 37 CFR 1.63 is filed with the application.

4. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

Signature /David D'Zurilla/	Date August 22, 2012
Name (Print/Typed) David D'Zurilla	Practitioner Registration Number 36,776

Note *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below*.*

*Total of 1 forms are submitted.

Sensitive Drug Distribution System and Method

Related Application

This application a Continuation of U.S. Application Serial No. 13/013,680, filed on January 25, 2011, which is a Continuation of U.S. Application Serial No. 12/704,097, filed on February 11, 2010 and issued on February 22, 2011 as U.S. Patent No. 7,895,059, which is a Continuation of U.S. Application Serial No. 10/322,348, filed on December 17, 2002 and issued on February 23, 2010 as U.S. Patent No. 7,668,730, which applications are incorporated by reference herein in their entirety.

Field of the Invention

The present invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs.

Background of the Invention

Sensitive drugs are controlled to minimize risk and ensure that they are not abused, or cause adverse reactions. Such sensitive drugs are approved for specific uses by the Food and Drug Administration, and must be prescribed by a licensed physician in order to be purchased by consumers. Some drugs, such as cocaine and other common street drugs are the object of abuse and illegal schemes to distribute for profit. Some schemes include Dr. shopping, diversion, and pharmacy thefts. A locked cabinet or safe is a requirement for distribution of some drugs.

Certain agents, such as gamma hydroxy buterate (GHB) are also abused, yet also are effective for therapeutic purposes such as treatment of daytime cataplexy in patients with narcolepsy. Some patients however, will obtain prescriptions from multiple doctors, and have them filled at different pharmacies. Still further, an unscrupulous physician may actually write multiple prescriptions for a patient, or multiple patients, who use cash to pay for the drugs. These patients will then sell the drug to dealers or others for profit.

There is a need for a distribution system and method that directly addresses these abuses. There is a further need for such a system and method that provides education and limits the potential for such abuse.

Summary of the Invention

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in a central database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database for a valid DEA license, and optionally state medical boards to determine whether any corrective or approved disciplinary actions relating to controlled substances have been brought against the physician. Multiple controls beyond those for traditional drugs are imposed on the distribution depending on the sensitivity of the drug.

Education is provided to both physician and patient. Prior to shipping the drug for the first time, the patient is contacted to ensure that product and abuse related educational materials have been received and/or read. The patient may provide the name of a designee to the central pharmacy who is authorized to accept shipment of the drug. Receipt of the initial drug shipment is confirmed by contacting the patient. Either a phone call or other communication to the patient within a set time after delivery may be made to ensure receipt. Further, a courier service's tracking system is used to confirm delivery in further embodiments. If a shipment is lost, an investigation is launched to find it.

In one embodiment, the drug may be shipped by the central pharmacy to another pharmacy for patient pick-up. The second pharmacy's ability to protect against diversion before shipping the drug must be confirmed. This ability may be checked through NTIS and State Boards of Pharmacy.

Prescription refills are permitted in the number specified in the original prescription. In addition, if a prescription refill is requested by the patient prior to

the anticipated due date, such refills will be questioned. A lost, stolen, destroyed or spilled prescription/supply is documented and replaced to the extent necessary to honor the prescription, and will also cause a review or full investigation.

The exclusive central database contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information. Several queries and reports are run against the database to provide information which might reveal potential abuse of the sensitive drug, such as early refills.

Brief Description of the Drawings

FIG. 1 is a block diagram of a computer system for use in implementing the system and method of the present invention.

FIGS. 2A, 2B and 2C are a flowchart describing a method for sensitive drug distribution at least partially utilizing a computer system such as that shown in FIG. 1.

FIG. 3 is a flowchart of a physician success program at least partially implemented on a computer system such as that shown in FIG. 1.

FIGS. 4A and 4B are a flowchart describing a method for handling refill requests at least partially utilizing a computer system such as that shown in FIG. 1.

FIG. 5 is a flowchart of a process for requesting special reimbursement when a patient is uninsured or underinsured at least partially utilizing a computer system as that shown in FIG. 1.

FIG. 6 is a flowchart of a process for inventory control at least partially utilizing a computer system such as that shown in FIG. 1.

FIG. 7 is a block diagram of database fields.

FIG. 8 is a block diagram showing a list of queries against the database fields.

FIG. 9 is a copy of one example prescription and enrollment form.

FIG. 10 is a copy of one example of a NORD application request form for patient financial assistance.

FIG. 11 is a copy of one example voucher request for medication for use with the NORD application request form of FIG. 10.

FIG. 12 is a copy of certificate of medical need.

FIGS. 13A, 13B and 13C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. 7.

Detailed Description of the Invention

In the following description, reference is made to the accompanying drawings that form a part hereof, and in which is shown by way of illustration specific embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that other embodiments may be utilized and that structural, logical and electrical changes may be made without departing from the scope of the present invention. The following description is, therefore, not to be taken in a limited sense, and the scope of the present invention is defined by the appended claims.

The functions or algorithms described herein are implemented in software or a combination of software and human implemented procedures in one embodiment. The software comprises computer executable instructions stored on computer readable media such as memory or other type of storage devices. The term "computer readable media" is also used to represent carrier waves on which the software is transmitted. Further, such functions correspond to modules, which are software, hardware, firmware of any combination thereof. Multiple functions are performed in one or more modules as desired, and the embodiments described are merely examples. The software is executed on a digital signal processor, ASIC, microprocessor, or other type of processor operating on a computer system, such as a personal computer, server or other computer system.

A sensitive drug is one which can be abused, or has addiction properties or other properties that render the drug sensitive. One example of such a drug is

sodium oxybate, also known as gamma hydroxy butyrate (GHB $C_4H_7NaO_3$) which is useful for treatment of cataplexy in patients with narcolepsy. GHB is marketed under the trademark of Xyrem® (sodium oxybate oral solution), which trademark can be used interchangeably with GHB herein. Sensitive drugs also include narcotics or other drugs which require controls on their distribution and use to monitor behaviors to prevent abuse and adverse side effects.

In one embodiment, Xyrem® is subject to a restricted distribution program. One aspect of the program is to educate physicians and patients about the risks and benefits of Xyrem, including support via ongoing contact with patients and a toll free helpline. Initial prescriptions are filled only after a prescriber and patient have received and read the educational materials. Further, patient and prescribing physician registries are maintained and monitored to ensure proper distribution.

In a further embodiment, bulk sodium oxybate is manufactured at a single site, as is the finished drug product. Following manufacture of the drug product, it is stored at a facility compliant with FDA Schedule III regulations, where a consignment inventory is maintained. The inventory is owned by a company, and is managed by a central pharmacy, which maintains the consignment inventory. Xyrem® is distributed and dispensed through a primary and exclusive central pharmacy, and is not stocked in retail pharmacy outlets. It is distributed by overnight carriers, or by US mail in one embodiment to potentially invoke mail fraud laws if attempts of abuse occur.

FIG. 1 is a simplified block diagram of a computer system 100, such as a personal computer for implementing at least a portion of the methods described herein. A central processing unit (CPU) 110 executes computer programs stored on a memory 120. Memory 120 in one embodiment comprises one or more levels of cache as desired to speed execution of the program and access to data on which the programs operate. The CPU is directly coupled to memory 120 in one embodiment. Both CPU 110 and memory 120 are coupled to a bus 130. A storage 140, I/O 150 and communications 160 are also coupled to the bus 130. Storage 140 is usually a long term storage device, such as a disk drive, tape drive, DVD, CD or other type of storage device. In one embodiment, storage 140 is used to house a database for use

with the present invention. I/O 150 comprises keyboards, sound devices, displays and other mechanisms by which a user interacts with the computer system 100. Communications 160 comprises a network, phone connection, local area network, wide area network or other mechanism for communicating with external devices. Such external devices comprise servers, other peer computers and other devices. In one embodiment, such external device comprises a database server that is used in place of the database on storage 140. Other computer system architectures capable of executing software and interacting with a database and users may also be used. Appropriate security measures such as encryption are used to ensure confidentiality. Further, data integrity and backup measures are also used to prevent data loss.

FIGS. 2A, 2B and 2C represent an initial prescription order entry process for a sensitive drug, such as Xyrem. At 202, a medical doctor (MD) sends a Rx/enrollment form via mail, fax, email or other means to an intake/reimbursement specialist at 204, who makes a copy of the RX/enrollment form that is stamped "copy". The original fax is forwarded to a pharmacy team. The enrollment form contains prescriber information, prescription information, checkboxes for the prescriber indicating they have read materials, educated the patient, understand the use in treatment, and understand certain safety information, and also contains patient information.

The prescriber information contains standard contact information as well as license number, DEA number and physician specialty. Patient and prescription information includes name, social security number, date of birth, gender, contact information, drug identification, patient's appropriate dosage, and number of refills allowed, along with a line for the prescriber's signature. Patient insurance information is also provided.

There are two workflows involved at the pharmacy team, intake reimbursement 206 and pharmacy workflow 208, which may proceed in parallel or serially. The intake work flow 206 starts with an intake reimbursement specialist entering the patient and physician information into an application/database referred to as CHIPS, which is used to maintain a record of a client home infusion program (CHIP) for Xyrem®. A check is made to ensure the information is complete at 212.

If not, at 214, an intake representative attempts to reach the MD or prescriber to obtain the missing information. If the missing information has not been obtained within a predetermined period of time, such as 24 hours at 216, the Rx/Enrollment form is sent back to the MD with a rejection explanation. A note is entered in CHIPS that the application was rejected.

If the information is complete at 212, the MD is contacted at 220 to verify receipt and accuracy of the patient's Rx. This contact is recorded in CHIPS. The intake and reimbursement specialist then sends a consent form and a cover letter to the patient at 224. The insurance provider is contacted at 226 to verify coverage and benefits. At 228, a determination is made regarding coverage for the drug. If it is not available, it is determined at 230 whether the patient is willing and able to pay. If not, a process is performed for handling patients who are uninsured or underinsured. In one embodiment, the process is referred to as a NORD process.

If the patient is willing and able to pay at 230, the patient is informed of the cost of the product and is given payment options at 234. At 236, once payment is received, the intake reimbursement specialist submits a coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. If coverage is approved at 228, the intake reimbursement specialist also submits the coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. Processing of the prescription is described below.

Upon receipt and initial processing of the prescription enrollment form and sending an original to the pharmacy work flow block 208, the patient is shipped a Xyrem® success packet via mail. In one embodiment, the Xyrem® success packet contains educational material for a patient that advises of the proper use, care and handling of the drug and consequences of diversion at 268. The medical doctor's credentials are checked to determine if the physician has a current DEA license to prescribe controlled substances and if he or she has had any actions related to misuse/misprescribing of controlled drugs against him or her, within a predetermined time, such as three months at 270. If they have, a pharmacist holds

the prescription until receiving a coverage approval form from the intake reimbursement specialist at 272.

If the credentials have not been recently checked, the pharmacist verifies the credentials and enters all findings in the database at 274. If the credentials are approved at 276, the physician is indicated as approved in a physician screen populated by information from the database at 280. The prescription is then held pending coverage approval at 282.

If any disciplinary actions are identified, as referenced at block 278, management of the pharmacy is notified and either approves processing of the prescription with continued monitoring of the physician, or processing of the prescription is not performed, and the physician is noted in the database as unapproved at 284. The enrollment form is then mailed back to the physician with a cover letter reiterating that the prescription cannot be processed at 288. The patient is also sent a letter at 290 indicating that the prescription cannot be processed and the patient is instructed to contact their physician.

Actual filling of the approved prescription begins with receipt of the coverage approval form as indicated at 240. The patient is contacted by the pharmacy, such as by a technician to complete a technician section of a patient counseling checklist. If a pharmacist verifies that the program materials were not read at 242, the receipt of the material is confirmed at 244 and another call is scheduled to counsel the patient before the drug is shipped.

If the program materials, were read at 242, the checklist is completed at 246 and the technician transfers the patient to the pharmacist who reviews the entire checklist and completes remaining pharmacist specified sections. At 248, the pharmacists indicates in the database that the patient counseling and checklist was successfully completed, indicating the date completed.

At 250, the pharmacist schedules the patient's shipment for the next business day or the next business day that the patient or designee is able to sign for the package. Further, as indicated at 252, the shipment must be sent to the patient's home address unless the patient is traveling or has moved. In that event, the pharmacist may determine that an exception may be made. The patient or the

patient's designee who is at least 18 years old, must sign for the package upon delivery.

At 254, the pharmacist enters the prescription order in the database, creating an order number. The pharmacist then verifies at 256 the prescription and attaches a verification label to the hard copy prescription. At 258, a pick ticket is generated for the order and the order is forwarded to the pharmacy for fulfillment. The shipment is confirmed in the database at 260, and the order is shipped by USPS Express Mail. Use of the US mail invokes certain criminal penalties for unauthorized diversion. Optionally, other mail services may be used. Potential changes in the law may also bring criminal penalties into play. Following shipment, the patient is called by the central pharmacy to confirm that the prescription was received.

As noted at 266, for the sensitive drug, Xyrem, all inventory is cycle counted and reconciled with the database system quantities before shipments for the day are sent. This provides a very precise control of the inventory.

A physician success program materials request process begins at 310 in FIG. 3. At 320, the MD calls to the central pharmacy to request program materials. A special phone number is provided. MD demographics, DEA number, and data or request are entered into the database at 330. At 340, a request is made to ship the materials to the MD via a fulfillment website, or other mechanism. The request process ends at 350.

A refill request process begins at 302 in FIGS. 4A and 4B. There are two different paths for refills. A first path beginning at 404 involves generating a report from the central database of patients with a predetermined number of days or product remaining. A second path beginning at 406 is followed when a patient calls to request an early refill.

In the first path, a copy of the report is provided to an intake reimbursement specialist at 408. No sooner than 8 days before the medication depletion, a pharmacy technician contacts the patient at 410 to complete the pre-delivery checklist. At 412, if the patient is not reached, a message is left mentioning the

depletion, and a return number at 414. A note is also entered into the database indicating the date the message was left at 416.

If the patient is reached at 412, the next shipment is scheduled at 418, the prescription is entered into the database creating an order at 420, the pharmacist verifies the prescription and attaches a verification label at 422 and the shipment is confirmed in the database at 424. Note at 426 that the inventory is cycle counted and reconciled with the database quantities before the shipments for a day or other time period are sent. A pick ticket is generated for the order and the order is forwarded for fulfillment at 428, with the first path ending at 430.

The second path, beginning at 406 results in a note code being entered into the database on a patient screen indicating an early refill request at 432. The pharmacist evaluates the patient's compliance with therapy or possible product diversion, misuse or over-use at 436. In one embodiment, cash payers are also identified. The pharmacist then contacts the prescribing physician to alert them of the situation and confirm if the physician approves of the early refill at 438. If the physician does not approve as indicated at 440, the patient must wait until the next scheduled refill date to receive additional product as indicated at 442, and the process ends at 444.

If the physician approves at 440, the pharmacist enters a note in the database on a patient screen that the physician approves the request at 446. The pharmacist notifies an intake reimbursement specialist to contact the patient's insurance provider to verify coverage for the early refill at 448. If the insurance provider will pay as determined at 450, the specialist submits the coverage approval form as notification that the refill may be processed at 452. At 454, the pharmacy technician contacts the patient to schedule shipment of the product for the next business day, and the process of filling the order is continued at 456 by following the process beginning at 240.

If the insurance provider will not pay at 450, it is determined whether the patient is willing and/or able to pay at 458. If not, the patient must wait until the next scheduled refill date to receive additional product at 460. If it was determined at 458 that the patient was willing and able to pay, the patient is informed of the cost

of the product and is given payment options at 462. Once payment is received as indicated at 464, the specialist submits a coverage approval form to the pharmacy team as notification that the refill request can be processed at 466. At 468, the pharmacy technician contacts the patient to schedule shipment. The process of filling the order is continued at 470 by following the process beginning at 240.

A process, referred to as a NORD process in one embodiment is used to determine whether donated, third party funds are available for paying for prescriptions where neither insurance will, nor the patient can pay. The process begins at 510 upon determining that a patient is uninsured or underinsured. A reimbursement specialist explains the NORD program to the patient and faxes an application request form to NORD for the patient. At 515, the intake reimbursement specialist documents in the database that an application has been received through NORD. At 520, NORD mails an application to the patient within one business day.

A determination is made at 525 by NORD whether the patient is approved. If not, at 530, NORD sends a denial letter to the patient, and it is documented in the database at 540 that the patient was denied by NORD. If the patient is approved, NORD sends an acceptance letter to the patient and faxes a voucher to the central pharmacy (SDS in one embodiment) to indicate the approval at 545. At 550, an intake reimbursement specialist submits a coverage approval form to the pharmacy team as notification that the patient has been approved for coverage. The process of filling the order is continued at 555 by following the process beginning at 240.

An inventory control process is illustrated in FIG. 6 beginning at 610. Each week, a responsible person at the central pharmacy, such as the director of the pharmacy transfers inventory for the week's shipments to a segregated warehouse location for production inventory. At 620, a purchase order is generated for the inventory transferred to the production location and is sent, such as by fax, to a controller, such as the controller of the company that obtained approval for distribution and use of the sensitive drug. At 630, the controller invoices the central pharmacy for the product moved to production. The process ends at 640.

The central database described above is a relational database running on the system of FIG. 1, or a server based system having a similar architecture coupled to workstations via a network, as represented by communications 160. The database is likely stored in storage 140, and contains multiple fields of information as indicated at 700 in FIG. 7. The organization and groupings of the fields are shown in one format for convenience. It is recognized that many different organizations or schemas may be utilized. In one embodiment, the groups of fields comprise prescriber fields 710, patient fields 720, prescription fields 730 and insurance fields 740. For purposes of illustration, all the entries described with respect to the above processes are included in the fields. In further embodiments, no such groupings are made, and the data is organized in a different manner.

Several queries are illustrated at 800 in FIG. 8. There may be many other queries as required by individual state reporting requirements. A first query at 810 is used to identify prescriptions written by physician. The queries may be written in structured query language, natural query languages or in any other manner compatible with the database. A second query 820 is used to pull information from the database related to prescriptions by patient name. A third query 830 is used to determine prescriptions by frequency, and a n^{th} query finds prescriptions by dose at 840. Using query languages combined with the depth of data in the central database allows many other methods of investigating for potential abuse of the drugs. The central database ensures that all prescriptions, prescribers and patients are tracked and subject to such investigations. In further embodiments, the central database may be distributed among multiple computers provided a query operates over all data relating to such prescriptions, prescribers and patients for the drug.

An example of one prescription and enrollment form is shown at 900 in FIG. 9. As previously indicated, several fields are included for prescriber information, prescription information and patient information.

FIG. 10 is a copy of one example NORD application request form 1000 used to request that an application be sent to a patient for financial assistance.

FIG. 11 is a copy of one example application 1100 for financial assistance as requested by form 1000. The form requires both patient and physician information.

Social security number information is also requested. The form provides information for approving the financial assistance and for tracking assistance provided.

FIG. 12 is a copy of one example voucher request for medication for use with the NORD application request form of FIG. 10. In addition to patient and physician information, prescription information and diagnosis information is also provided.

FIGS. 13A, 13B and 13C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. 7. The activities grouped by sales, regulatory, quality assurance, call center, pharmacy, inventory, reimbursement, patient care and drug information. Each report has an associated frequency or frequencies. The reports are obtained by running queries against the database, with the queries written in one of many query languages.

While the invention has been described with respect to a Schedule III drug, it is useful for other sensitive drugs that are DEA or Federally scheduled drugs in Schedule II-V, as well as still other sensitive drugs where multiple controls are desired for distribution and use.

SCHWEGMAN ■ LUNDBERG ■ WOESSNER ■ KLUTH

United States Patent Application

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**.

The specification of which was filed on December 17, 2002 as application serial no. 10/322,348.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 C.F.R. § 1.56 (attached hereto). I also acknowledge my duty to disclose all information known to be material to patentability which became available between a filing date of a prior application and the national or PCT international filing date in the event this is a Continuation-In-Part application in accordance with 37 C.F.R. § 1.63(e).

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on the basis of which priority is claimed:

No such claim for priority is being made at this time.

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

No such claim for priority is being made at this time.

I hereby claim the benefit under 35 U.S.C. § 120 or 365(c) of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. § 1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

No such claim for priority is being made at this time.

I hereby appoint the following attorney(s) and/or patent agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith:

Anglin, J. M	Reg. No. 24,916	Harris, Robert J	Reg. No. 37,346	Nielsen, Walter W	Reg. No. 25,539
Arora, Suneel	Reg. No. 42,267	Jackson Huebsch, Katharine A	Reg. No. 47,670	Padys, Danny J	Reg. No. 35,635
Beekman, Marvin L	Reg. No. 38,377	Jurkovich, Patti J	Reg. No. 44,813	Parker, J. K	Reg. No. 33,024
Bianchi, Timothy E	Reg. No. 39,610	Kalis, Janal M	Reg. No. 37,650	Peacock, Gregg A	Reg. No. 45,001
Billion, Richard E	Reg. No. 32,836	Klima-Silberg, Catherine I	Reg. No. 40,052	Perdok, Monique M	Reg. No. 42,989
Black, David W	Reg. No. 42,331	Kluth, Daniel J	Reg. No. 32,146	Peret, Andrew R	Reg. No. 41,246
Brennan, Thomas F	Reg. No. 35,075	Lacy, Rodney L	Reg. No. 41,136	Peterson, David C	Reg. No. 47,857
Chadwick, Robin A	Reg. No. 36,477	Lemaire, Charles A	Reg. No. 36,198	Prout, William F	Reg. No. 33,995
Clark, Barbara J	Reg. No. 38,107	Lundberg, Steven W	Reg. No. 30,568	Puckett, Ph. D., Craig L	Reg. No. 43,023
Clise, Timothy B	Reg. No. 40,957	Maki, Peter C	Reg. No. 42,832	Schumm, Sherry W	Reg. No. 39,422
Cochran, David R	Reg. No. 46,632	Malen, Peter L	Reg. No. 44,894	Schwegman, Micheal L	Reg. No. 25,816
Dahl, John M	Reg. No. 44,639	Mates, Robert E	Reg. No. 35,271	Speier, Gary J	Reg. No. 45,458
Drake, Eduardo E	Reg. No. 40,594	McCrackin, Ann M	Reg. No. 42,858	Steffey, Charles E	Reg. No. 25,179
Embretson, Janet E	Reg. No. 39,665	McGough, Kevin J	Reg. No. 31,279	Stordal, Leif T	Reg. No. 46,251
Forrest, Bradley A	Reg. No. 30,837	McTavish, Hugh E	Reg. No. 48,341	Terry, Kathleen R	Reg. No. 31,884
Gorrie, Gregory J	Reg. No. 36,530	Mehrle, Joseph P	Reg. No. 45,535	Tong, Viet V	Reg. No. 45,416
Gortych, Joseph E	Reg. No. 41,791	Muller, Mark V	Reg. No. 37,509	Viksnins, Ann S	Reg. No. 37,748
Greaves, John N	Reg. No. 40,362	Nama, Prakash	Reg. No. 44,255	Woessner, Warren D	Reg. No. 30,440
Haack, John L	Reg. No. 36,154	Nelson, A. J	Reg. No. 28,650		

I hereby authorize them to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/organization/who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct Schwegman, Lundberg, Woessner & Kluth, P.A. to the contrary.

Please direct all correspondence in this case to **Schwegman, Lundberg, Woessner & Kluth, P.A.** at the address indicated below:

P.O. Box 2938, Minneapolis, MN 55402
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of joint inventor number 1 : **Dayton T. Reardan Ph.D.**
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Dayton T. Reardan Ph.D.

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Post Office Address: 852 Basswood Lane
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Signature: Patti A. Engel Date: May 13, 2003
Patti ~~Engle~~
PATTI A. ENGEL

X Additional inventors are being named on separately numbered sheets, attached hereto.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of joint inventor number 3 : **Bob Gagne**
Citizenship: **United States of America** Residence: **St. Paul, MN**
Post Office Address: 202 So. Wheeler Street
St. Paul, MN 55015

Signature: Bob Gagne Date: 1 May 2003
Bob Gagne

§ 1.56 Duty to disclose information material to patentability.

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and

(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

(c) Individuals associated with the filing or prosecution of a patent application within the meaning of this section are:

(1) Each inventor named in the application:

(2) Each attorney or agent who prepares or prosecutes the application; and

(3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

(d) Individuals other than the attorney, agent or inventor may comply with this section by disclosing information to the attorney, agent, or inventor.

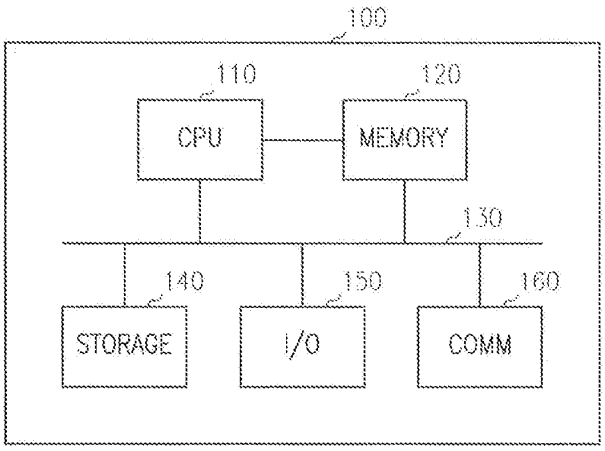

FIG. 1

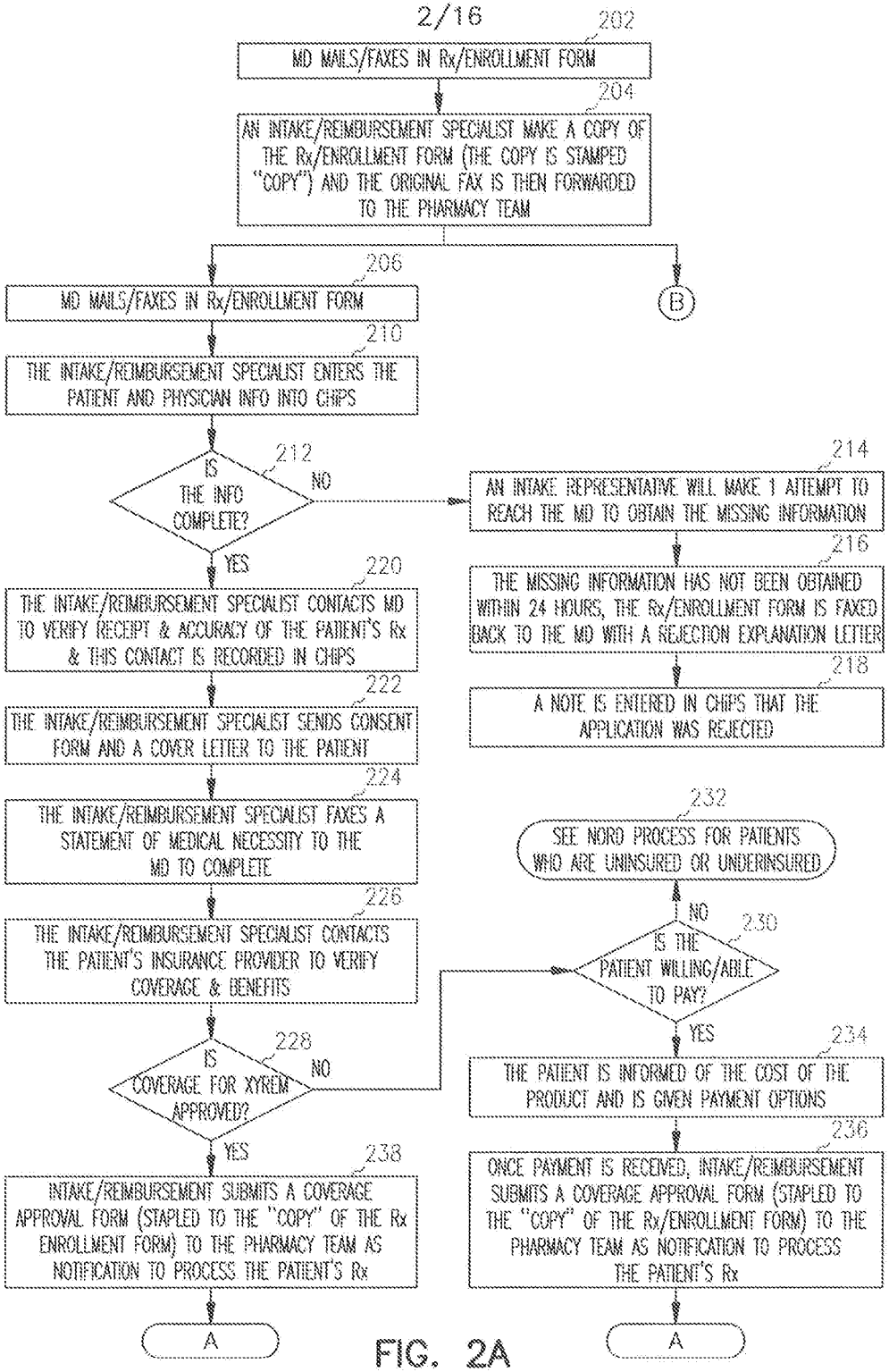
202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHIPS
212
IS THE INFO COMPLETE?
NO
214
AN INTAKE REPRESENTATIVE WILL MAKE 1 ATTEMPT TO REACH THE MD TO OBTAIN THE MISSING INFORMATION
YES
220
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS MD TO VERIFY RECEIPT & ACCURACY OF THE PATIENT'S Rx & THIS CONTACT IS RECORDED IN CHIPS
216
THE MISSING INFORMATION HAS NOT BEEN OBTAINED WITHIN 24 HOURS, THE Rx/ENROLLMENT FORM IS FAXED BACK TO THE MD WITH A REJECTION EXPLANATION LETTER
218
A NOTE IS ENTERED IN CHIPS THAT THE APPLICATION WAS REJECTED
222
THE INTAKE/REIMBURSEMENT SPECIALIST SENDS CONSENT FORM AND A COVER LETTER TO THE PATIENT
224
THE INTAKE/REIMBURSEMENT SPECIALIST FAXES A STATEMENT OF MEDICAL NECESSITY TO THE MD TO COMPLETE
232
SEE NORD PROCESS FOR PATIENTS WHO ARE UNINSURED OR UNDERINSURED
226
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE & BENEFITS
NO
230
IS THE PATIENT WILLING/ABLE TO PAY?
228
IS COVERAGE FOR XYREM APPROVED?
NO
YES
234
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
YES
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
236
ONCE PAYMENT IS RECEIVED, INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx/ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
A

FIG. 2A

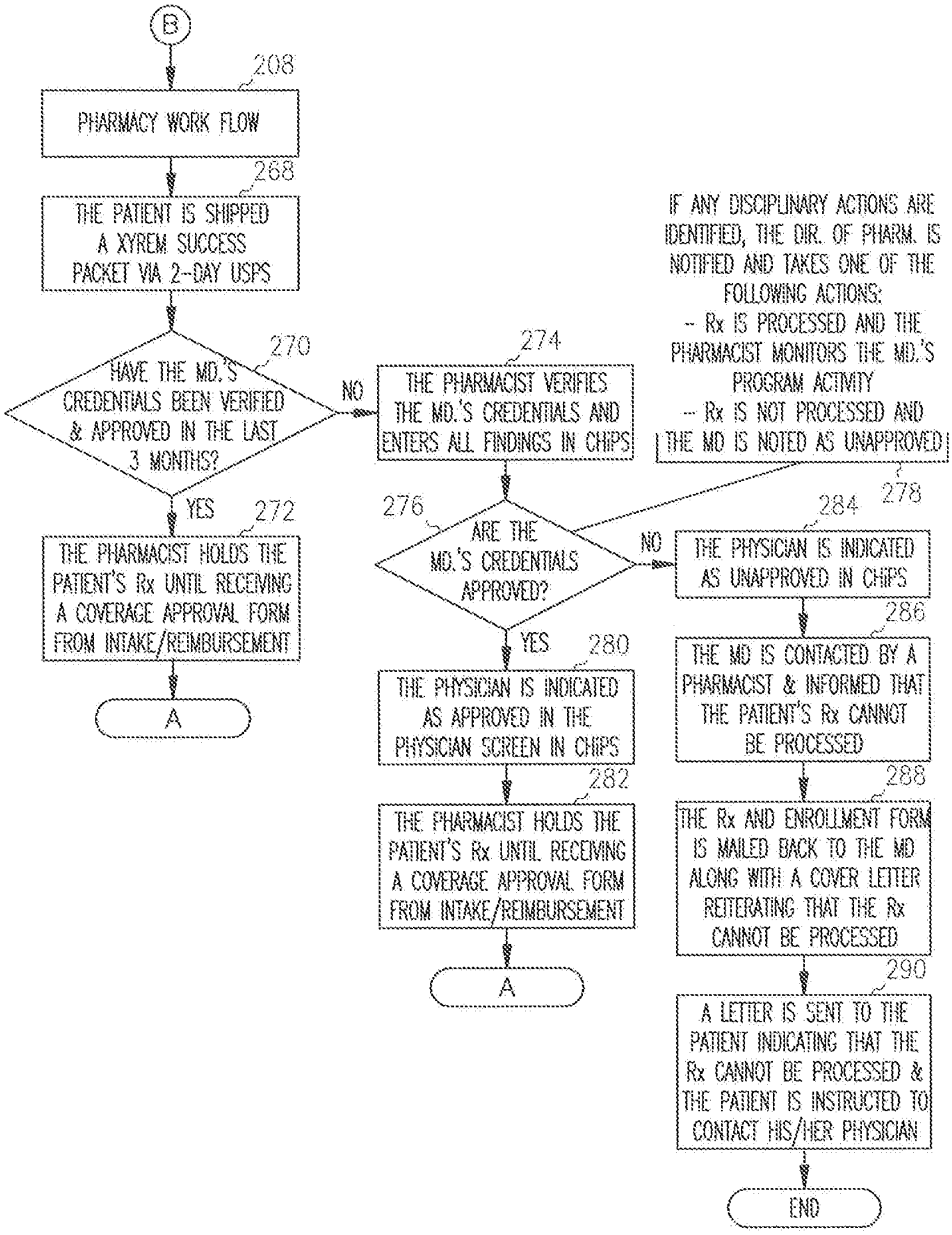
B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHIPS
276
ARE THE MD.'S CREDENTIALS APPROVED?
NO
YES
280
THE PHYSICIAN IS INDICATED AS APPROVED IN THE PHYSICIAN SCREEN IN CHIPS
282
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
IF ANY DISCIPLINARY ACTIONS ARE IDENTIFIED, THE DIR. OF PHARM. IS NOTIFIED AND TAKES ONE OF THE FOLLOWING ACTIONS:
– Rx IS PROCESSED AND THE PHARMACIST MONITORS THE MD.'S PROGRAM ACTIVITY
– Rx IS NOT PROCESSED AND THE MD IS NOTED AS UNAPPROVED
278
284
THE PHYSICIAN IS INDICATED AS UNAPPROVED IN CHIPS
286
THE MD IS CONTACTED BY A PHARMACIST & INFORMED THAT THE PATIENT'S Rx CANNOT BE PROCESSED
288
THE Rx AND ENROLLMENT FORM IS MAILED BACK TO THE MD ALONG WITH A COVER LETTER REITERATING THAT THE Rx CANNOT BE PROCESSED
290
A LETTER IS SENT TO THE PATIENT INDICATING THAT THE Rx CANNOT BE PROCESSED & THE PATIENT IS INSTRUCTED TO CONTACT HIS/HER PHYSICIAN
END

FIG. 2B

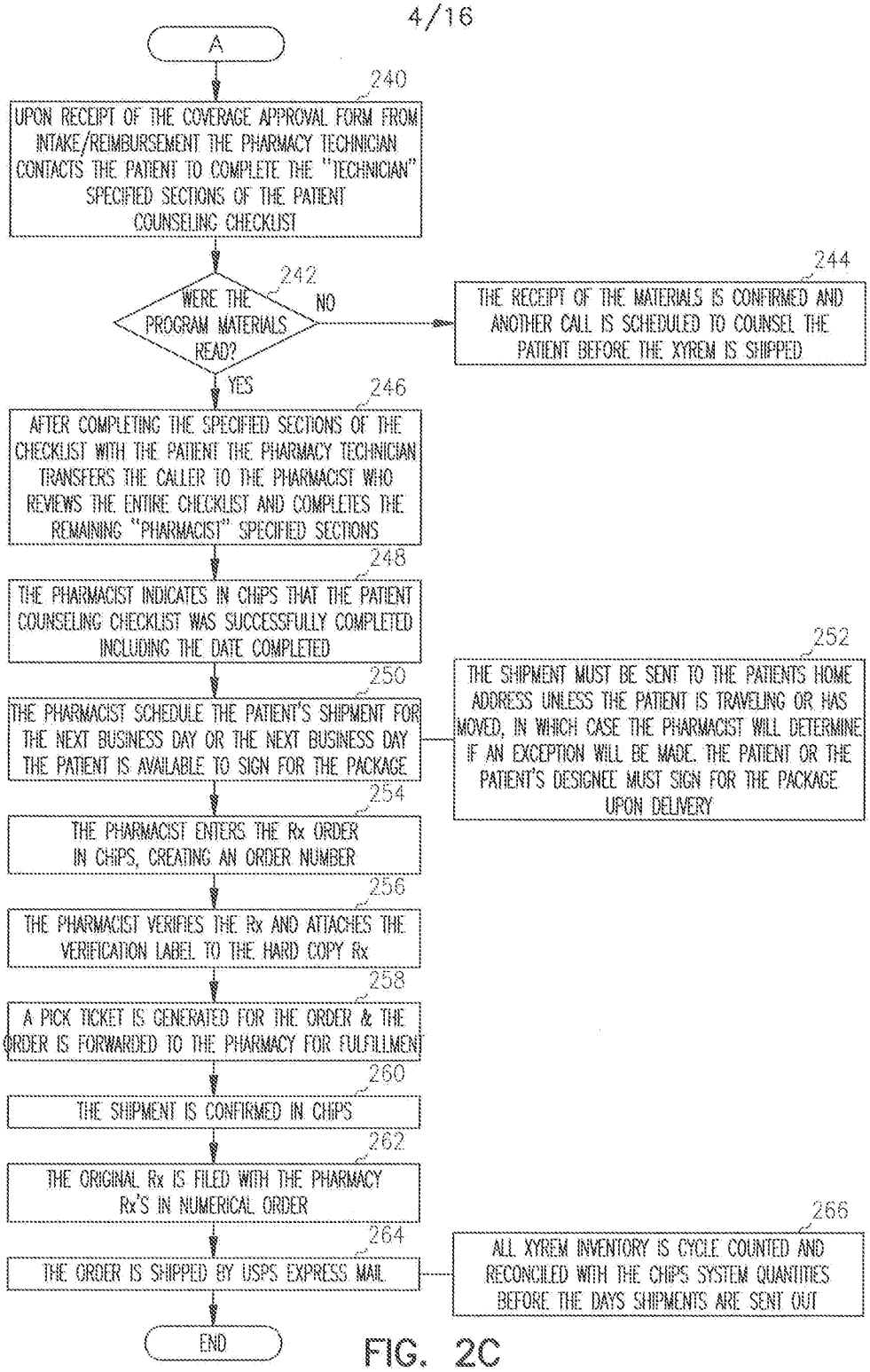
A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER CALL IS SCHEDULED TO COUNSEL THE PATIENT BEFORE THE XYREM IS SHIPPED
YES
246
AFTER COMPLETING THE SPECIFIED SECTIONS OF THE CHECKLIST WITH THE PATIENT THE PHARMACY TECHNICIAN TRANSFERS THE CALLER TO THE PHARMACIST WHO REVIEWS THE ENTIRE CHECKLIST AND COMPLETES THE REMAINING "PHARMACIST" SPECIFIED SECTIONS
248
THE PHARMACIST INDICATES IN CHIPS THAT THE PATIENT COUNSELING CHECKLIST WAS SUCCESSFULLY COMPLETED INCLUDING THE DATE COMPLETED
252
THE SHIPMENT MUST BE SENT TO THE PATIENTS HOME ADDRESS UNLESS THE PATIENT IS TRAVELING OR HAS MOVED, IN WHICH CASE THE PHARMACIST WILL DETERMINE IF AN EXCEPTION WILL BE MADE. THE PATIENT OR THE PATIENT'S DESIGNEE MUST SIGN FOR THE PACKAGE UPON DELIVERY
250
THE PHARMACIST SCHEDULE THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
254
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
256
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
258
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
260
THE SHIPMENT IS CONFIRMED IN CHIPS
262
THE ORIGINAL Rx IS FILED WITH THE PHARMACY Rx'S IN NUMERICAL ORDER
266
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
264
THE ORDER IS SHIPPED BY USPS EXPRESS MAIL
END

FIG. 2C

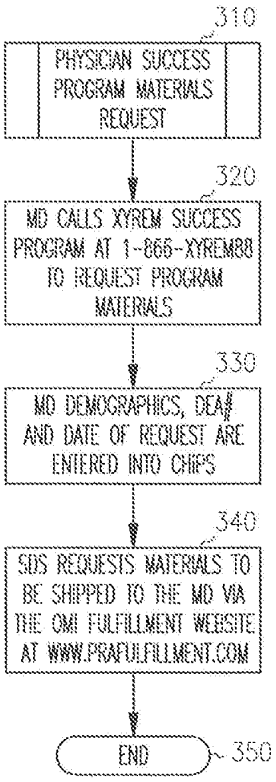
310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHIPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM
END
350

FIG. 3

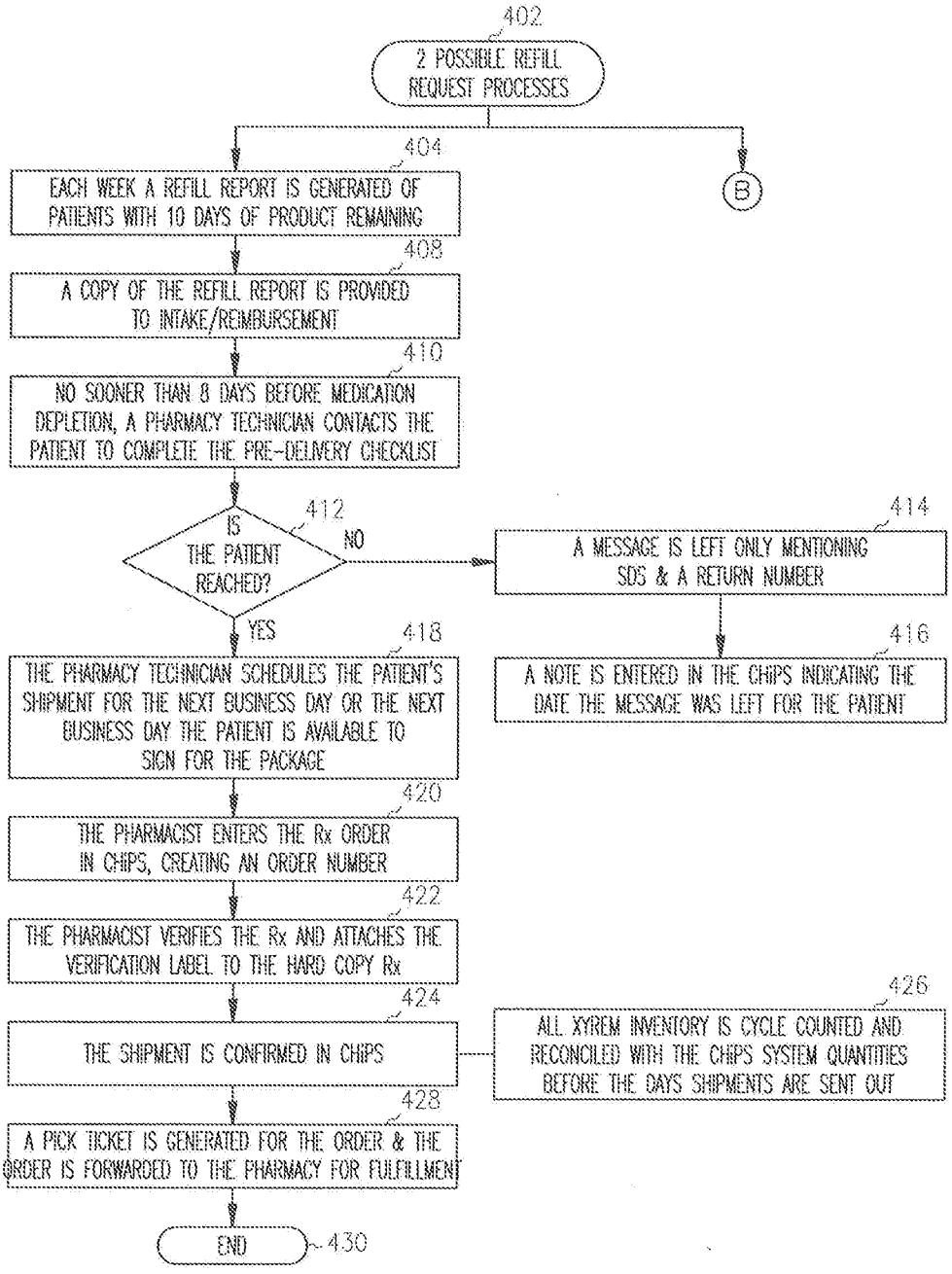
402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE PRE-DELIVERY CHECKLIST
412
IS THE PATIENT REACHED?
NO
414
A MESSAGE IS LEFT ONLY MENTIONING SDS & A RETURN NUMBER
YES
418
THE PHARMACY TECHNICIAN SCHEDULES THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
416
A NOTE IS ENTERED IN THE CHIPS INDICATING THE DATE THE MESSAGE WAS LEFT FOR THE PATIENT
420
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
422
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
424
THE SHIPMENT IS CONFIRMED IN CHIPS
426
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
428
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
END
430

FIG. 4A

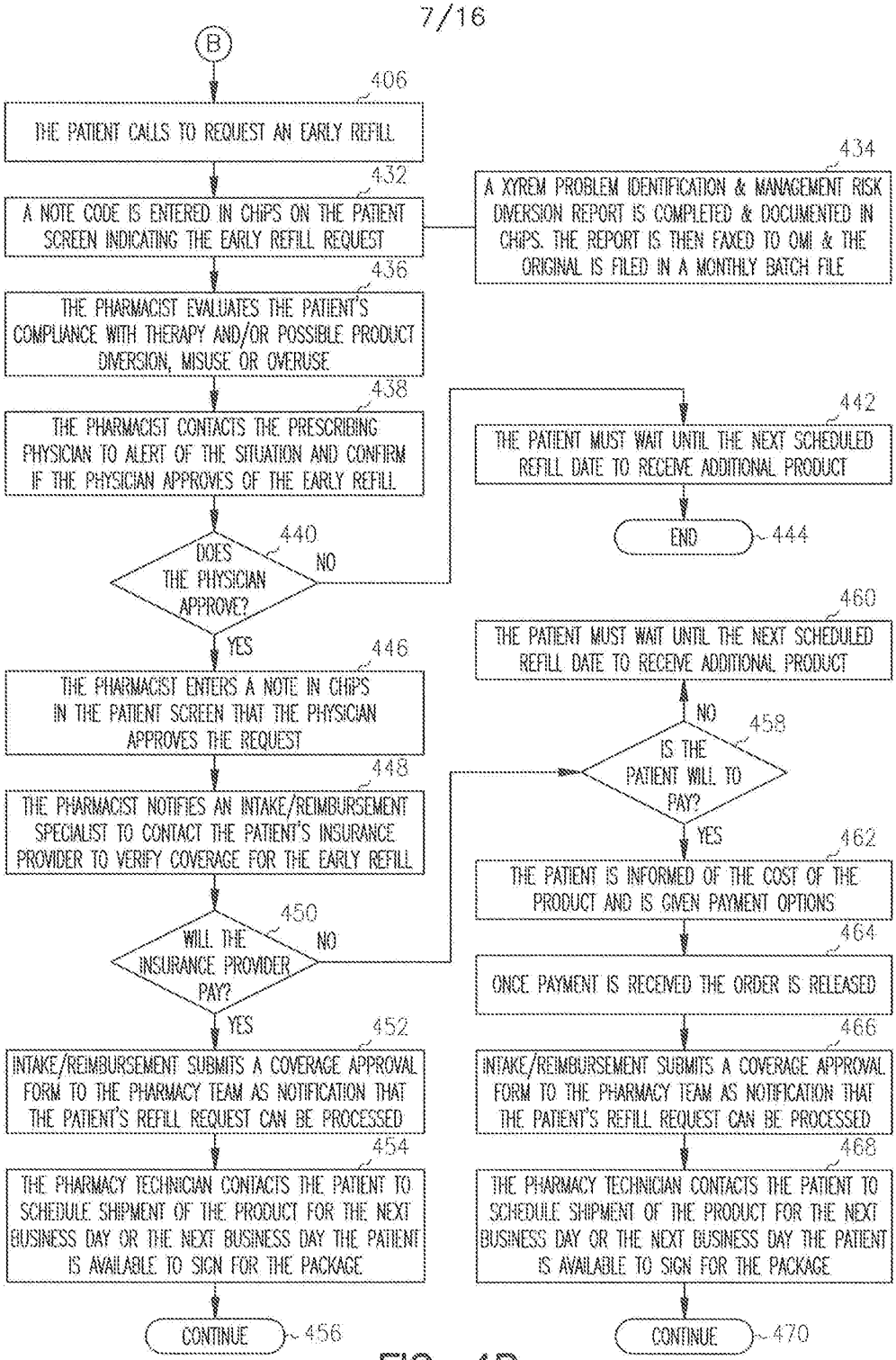
B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYREM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS FILED IN A MONTHLY BATCH FILE
436
THE PHARMACIST EVALUATES THE PATIENT'S COMPLIANCE WITH THERAPY AND/OR POSSIBLE PRODUCT DIVERSION, MISUSE OR OVERUSE
438
THE PHARMACIST CONTACTS THE PRESCRIBING PHYSICIAN TO ALERT OF THE SITUATION AND CONFIRM IF THE PHYSICIAN APPROVES OF THE EARLY REFILL
440
DOES THE PHYSICIAN APPROVE?
NO
442
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
END
444
YES
446
THE PHARMACIST ENTERS A NOTE IN CHIPS IN THE PATIENT SCREEN THAT THE PHYSICIAN APPROVES THE REQUEST
448
THE PHARMACIST NOTIFIES AN INTAKE/REIMBURSEMENT SPECIALIST TO CONTACT THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE FOR THE EARLY REFILL
450
WILL THE INSURANCE PROVIDER PAY?
NO
YES
452
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
454
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
456
460
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
NO
458
IS THE PATIENT WILL TO PAY?
YES
462
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
464
ONCE PAYMENT IS RECEIVED THE ORDER IS RELEASED
466
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
468
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
470

FIG. 4B

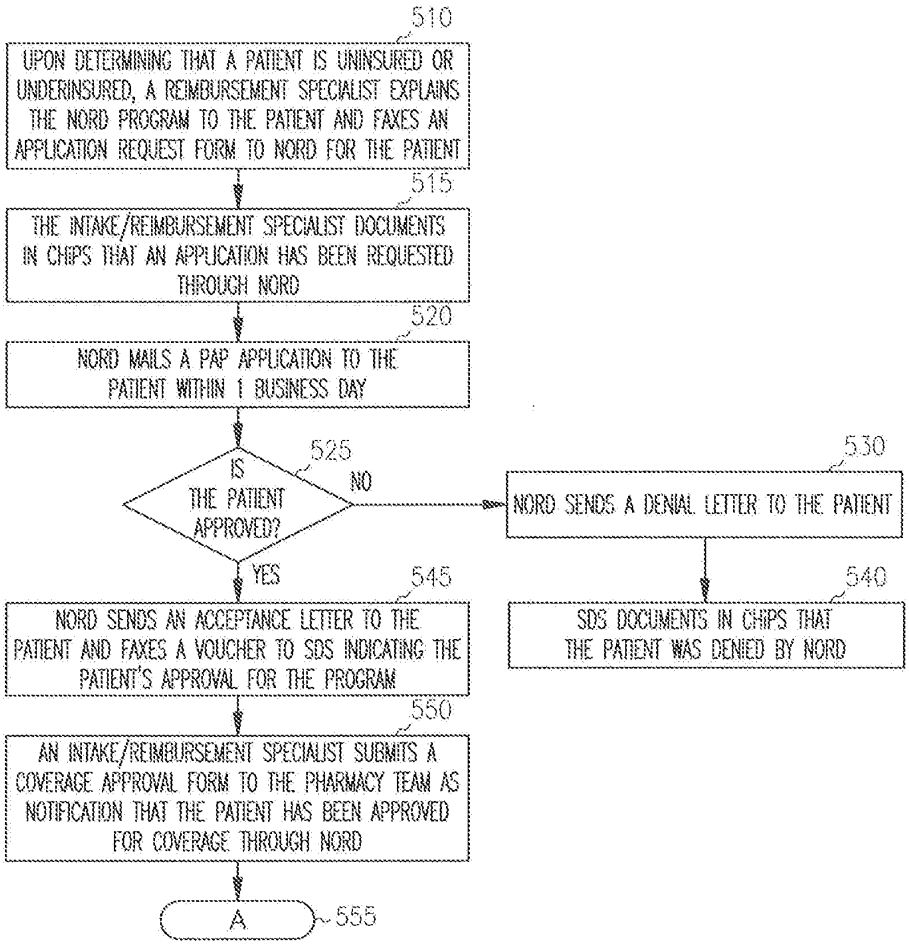
510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHIPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH NORD
520
NORD MAILS A PAP APPLICATION TO THE PATIENT WITHIN 1 BUSINESS DAY
525
IS THE PATIENT APPROVED?
NO
530
NORD SENDS A DENIAL LETTER TO THE PATIENT
YES
545
NORD SENDS AN ACCEPTANCE LETTER TO THE PATIENT AND FAXES A VOUCHER TO SDS INDICATING THE PATIENT'S APPROVAL FOR THE PROGRAM
540
SDS DOCUMENTS IN CHIPS THAT THE PATIENT WAS DENIED BY NORD
550
AN INTAKE/REIMBURSEMENT SPECIALIST SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT HAS BEEN APPROVED FOR COVERAGE THROUGH NORD
A
555

FIG. 5

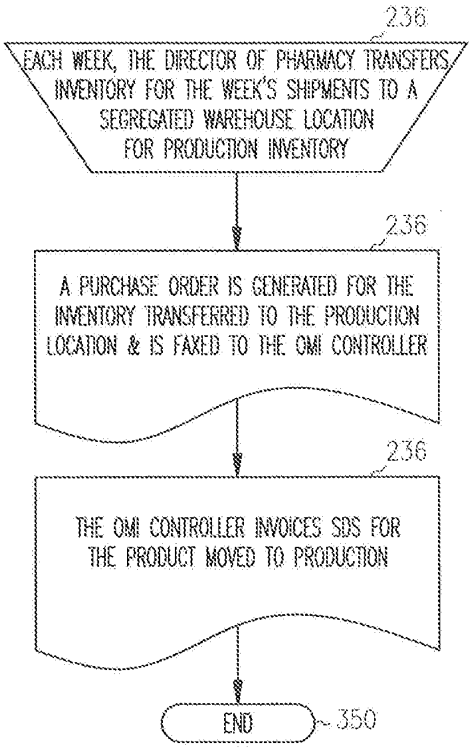

FIG. 6

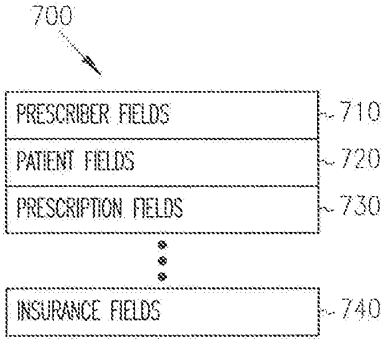

FIG. 7

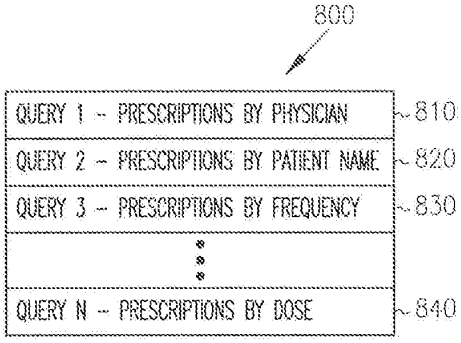

FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

PRESCRIBER'S NAME: ..... OFFICE CONTACT: .....
STREET ADDRESS: .....
CITY: ..... STATE: ..... ZIP: .....
PHONE: ..... FAX: .....
LICENSE NUMBER: ..... DEA NUMBER: .....
MD SPECIALTY: .....

PRESCRIPTION FORM

PATIENT NAME: ..... SS#: ..... DOB: ..... SEX M / F
ADDRESS: .....
CITY: ..... STATE: ..... ZIP: .....
Rx: XYREM ORAL SOLUTION (500 mg/mL) 180 ML BOTTLE QUANTITY: ..... MONTHS SUPPLY
SIG: TAKE ..... GMS P.O. DILUTED IN 60 mL WATER AT H.S. AND THEN AGAIN 2 1/2 TO 4 HOURS LATER
REFILLS (CIRCLE ONE): 0 1 2 (MAXIMUM OF 3 MONTH SUPPLY)
..... DATE: ...../...../.....
PRESCRIBER'S SIGNATURE

PHYSICIAN DECLARATION–PLEASE CHECK EACH BOX | TO BE COMPLETED AT INITIAL PRESCRIPTION ONLY

☐ I HAVE READ THE MATERIALS IN THE XYREM PHYSICIAN SUCCESS PROGRAM
☐ I VERIFY THAT THE PATIENT HAS BEEN EDUCATED WITH RESPECT TO XYREM PREPARATION, DOSING AND SCHEDULING.
☐ I UNDERSTAND THAT XYREM IS APPROVED FOR THE TREATMENT OF CATAPLEXY IN PATIENTS WITH NARCOLEPSY, AND THAT SAFETY OR EFFICACY HAS NOT BEEN ESTABLISHED FOR ANY OTHER INDICATION.
☐ I UNDERSTAND THAT THE SAFETY OF DOSES GREATER THAN 9gm/DAY HAS NOT BEEN ESTABLISHED

PATIENT INFORMATION

BEST TIME TO CONTACT PATIENT: ☐ DAY ☐ NIGHT
DAY #: ..... EVENING #: .....
INSURANCE COMPANY NAME: ..... PHONE #: .....
INSURED'S NAME: ..... RELATIONSHIP TO PATIENT: .....
IDENTIFICATION NUMBER: ..... POLICY/GROUP NUMBER: .....
PRESCRIPTION CARD: ☐ NO ☐ YES IF YES, CARRIER: ..... POLICY #: ..... GROUP: .....

PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

FAX COMPLETED FORM TO XYREM SUCCESS PROGRAM (TOLL-FREE) 1-866-470-1744
FOR INFORMATION, CALL THE XYREM TEAM (TOLL FREE) AT 1-866-XYREM88 (1-866-997-3688)

FIG. 9

1000

PATIENT ASSISTANCE APPLICATION REQUEST FORM

DATE:

TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS

FAX #: 203-798-2291

PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:

PATIENT NAME _____

ADDRESS _____

_____

_____

TELEPHONE: ( ) _____

PATIENT DOSAGE: _____ (GRAMS) TWICE NIGHTLY FOR A TOTAL DOSAGE OF _____ (GRAMS)

_____ BOTTLES (THREE MONTHS SUPPLY)

BACKGROUND INFORMATION:

_____

_____

_____

_____

_____

_____

FIG. 10

1100

SENSITIVE DRUG PATIENT ASSISTANCE PROGRAM

VOUCHER REQUEST FOR MEDICATION

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

CASE CODE: ********

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml btl	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

CASE CODE: ********

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREM 180ml btl	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

FIG. 11

1200

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE
OF MEDICAL NEED

PATIENT INFORMATION

DATE: .....

NAME: .....
LAST FIRST M

DATE OF BIRTH: .....

DRUG BEING PRESCRIBED: XYREM

DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: .....

ICD-9: .....

PHYSICIAN INFORMATION

PHYSICIAN'S NAME (PLEASE PRINT): .....

PHYSICIAN'S SIGNATURE: ..... DATE: .....

PLEASE FAX BACK TO SENSITIVE DRUG SUCCESS PROGRAM: (1-800-TOLL FREE NUMBER)

FIG. 12

ACTIVITY REPORTS

	REPORT FREQUENCY		
	WEEKLY	MONTHLY	QUARTERLY
SALES			
Rx BY ZIP (NEW AND TOTAL)	X	X	X
Rx BY PHYSICIAN BY ZIP	X	X	
$ BY ZIP	X	X	X
REGULATORY			
# OF PHYSICIAN REGISTRIES		X	
# OF DENIED PHYSICIAN REGISTRIES AND REASON		X	
# OF COMPLETED PATIENT REGISTRIES		X	
# OF PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORTS COMPLETED	X		
# OF CYCLE COUNTS PERFORMED & ACCURACY OF EACH		X	
QUALITY ASSURANCE			
# OF PRODUCT DEFECTS/COMPLAINTS REPORTED, TYPE AND LOT #		X	
CALL CENTER			
# OF CALLS RECEIVED		X	
# OF CALLS INITIATED		X	
# OF CALLS ANSWERED IN 30 SECONDS, ETC.		X	
PERCENTAGE OF CALLS ANSWERED IN 30 SECONDS		X	
# OF ABANDONED CALLS		X	
% OF ABANDONED CALLS		X	
AVERAGE CALL LENGTH		X	
PHARMACY			
# OF FAXED Rx/ENROLLMENT FORMS		X	
# OF MAILED Rx/ENROLLEMENT FORMS		X	
# OF Rx'S SHIPPED WITH 1, 2, 3, 4 ETC. DAYS (FROM THE TIME INITIAL RECEIPT TO SHIPMENT OF Rx)		X	
# OF PATIENT SUCCESS PACKETS SHIPPED		X	

FIG. 13A

ACTIVITY REPORTS

PHARMACY			X	
# OF PHYSICIAN SUCCESS PACKETS SHIPPED			X	
# OF COMPLETED SHIPMENTS			X	
# OF INCOMPLETE SHIPMENTS AND REASON			X	
# OF SHIPPING ERRORS			X	
# OF PAP SHIPMENTS			X	
# OF PAP APPLICATIONS			X	
# OF PAP APPROVALS			X	
# OF CANCELED ORDERS			X	
# OF USPS ERRORS			X	
INVENTORY			X	
# OF RETURNED PRODUCTS AND REASON			X	
# OF OUTDATED BOTTLES OF PRODUCT			X	
INVENTORY COUNTS OF CONSIGNMENT & PRODUCTION INVENTORY			X	
# OF UNITS RECEIVED			X	
LOTS RECEIVED			X	
REIMBURSEMENT			X	
# OF PENDED AND WHY			X	
# OF APPROVALS			X	
# OF DENIALS			X	
# OF REJECTIONS			X	
PAYOR TYPES			X	

FIG. 13B

ACTIVITY REPORTS

PATIENT CARE			X	
# OF ADVERSE EVENTS REPORTED AND TYPE			X	
# OF ADVERSE EVENTS SENT TO OMI			X	
# OF DOSING PROBLEMS AND TYPE			X	
# OF NONCOMPLIANCE EPISODES AND REASON			X	
# OF PATIENT COUNSELED AND REASON			X	
# OF PATIENTS DISCONTINUED AND REASON			X	
PATIENT CARE			X	
# OF PATIENTS REFERRED TO PHYSICIAN AND REASON			X	
# OF ACTIVE PATIENTS			X	
# OF NEW PATIENTS			X	
# OF RESTART PATIENTS			X	
# OF DISCONTINUED PATIENTS AND REASON			X	
DRUG INFORMATION			X	
# OF DRUG INFORMATION REQUESTS AND TYPE			X	
# OF CALLS TRIAGED TO OMI			X	

FIG. 13C

Abstract

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in the database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database, and optionally whether any actions are taken against the physician. Multiple controls beyond those for normal drugs are imposed on the distribution depending on the sensitivity of the drug.

Claims

1. A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising:

one or more computer memories for storing a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug;

said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

said prescriber fields, contained within the database schema, storing information sufficient to identify a physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug;

a data processor for processing a database query that operates over all data related to the prescription fields, prescriber fields, and patient fields for the prescription drug;

said database query identifying information in the prescription fields and patient fields for reconciling inventory of the prescription drug before the shipments for a day or other time period are sent.

2. The system of claim 1, wherein the data processor is configured to process a second database query that identifies: whether the narcoleptic patient is a cash payer and a physician that is interrelated with the narcoleptic patient through the schema of the single computer database;

said identifying by said second database query being an indicator of a potential misuse, abuse or diversion by the narcoleptic patient and being used to notify the physician that is interrelated with the narcoleptic patient through the schema of the single computer database.

3. The system of claim 1, wherein the data processor is configured to process a second database query that identifies a potential misuse, abuse or diversion by the narcoleptic patient.

4. The system of claim 3, wherein the data processor selectively blocks shipment of the prescription drug to the patient based upon said identifying by the database query.

5. The system of claim 3, wherein the prescription drug is shipped to the narcoleptic patient if no potential misuse, abuse or diversion is found for the narcoleptic patient.

6. The system of claim 1, wherein the single computer database is an exclusive database that receives data associated with all patients being prescribed the prescription drug that are associated with the company.

7. The system of claim 1, wherein an exclusive central pharmacy controls the single computer database.

8. The system of claim 1 wherein the prescription drug comprises gamma hydroxyl butyrate (GHB).

9. The system of claim 1, wherein the single computer database comprises a relational database.

10. The system of claim 1, where the single computer database is distributed among multiple computers provided the database query that operates over all data relating to said prescription fields, prescriber fields, and patient fields for the prescription drug.

11. The system of claim 1, wherein the data processor is configured to initiate an inquiry to a prescriber when one or more prescription fields, patient fields, or prescriber fields are incomplete in the computer database.

12. The system of claim 1, wherein the data processor is configured to process a second database query that identifies an expected date for a refill of the prescription drug.

13. The system of claim 12, wherein the expected date is based on a prescription for the prescription drug and a date of a previous filling of the prescription.

14. The system of claim 13, wherein the prescription identifies an amount of the prescription drug to be provided and a schedule for consumption of the prescription drug.

15. The system of claim 1, wherein the database schema further contains and interrelates insurance fields, wherein the insurance fields, contained within the database schema, store information sufficient to identify an insurer to be contacted for payment for prescription drugs of an associated patient.

16. The system of claim 1, wherein the single computer database is used to identify a current pattern or an anticipated pattern of abuse of the prescription drug; wherein the current pattern or the anticipated pattern are identified using periodic reports generated from the single computer database.

17. The system of claim 16, wherein one or more controls for distribution of the prescription drug are selected based on the identified pattern.

18. The system of claim 17, wherein the one or more controls are submitted to an approval body for approval of distribution of the prescription drug.

19. The system of claim 1, wherein additional controls for distribution are selected in a negotiation with an approval body to garner the approval of distribution.

20. The system of claim 19, wherein the data processor is used to add further controls until approval is obtained.

21. The system of claim 20, wherein the approval body is the Food and Drug Administration (FDA) or the Drug Enforcement Agency (DEA).

22. The system of claim 1, wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent.

23. A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising:

one or more computer memories for storing an exclusive computer database of a company that obtained approval to distribute the prescription drug that has a potential for misuse, abuse or diversion, the exclusive computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields relating to the company's prescription drug;

said prescription fields, contained within the database schema, storing prescriptions for the company's prescription drug that has a potential for abuse, misuse or diversion, wherein all prescriptions for the company's prescription drug are stored only in the exclusive computer database of the company that obtained approval to distribute the prescription drug, and wherein the company's prescription drug is sold or distributed by the company using only the exclusive computer database;

said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug that has a potential for misuse, abuse or diversion is prescribed, wherein the patient fields comprise all patients being prescribed the company's prescription drug;

said prescriber fields, contained within the database schema, storing information sufficient to identify a physician or other prescriber of the company's prescription drug that has a potential for misuse, abuse or diversion, and said prescriber fields storing information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug, wherein the prescriber fields include all physicians or other prescribers allowed to prescribe the company's prescription drug; and

a data processor for processing a database query to identify information in said prescription fields, said patient fields, and said prescriber fields for reconciling inventory of the prescription drug that has a potential for misuse, abuse or diversion before shipments of the prescription drug for a day or other time period are sent.

24. The computer-implemented system of claim 23, wherein the database query operates over all the data related to said prescription fields, said prescriber fields, and said patient fields for the prescription drug that has a potential for misuse, abuse or diversion.

25. A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising:

one or more computer memories for storing a single computer database of a company that obtained approval to distribute the prescription drug that has a potential for misuse, abuse or diversion, the single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said prescription fields, contained within the database schema, storing prescriptions for the company's prescription drug that has a potential for abuse, misuse or diversion, wherein the prescription drug is sold or distributed by the company that obtained approval for distribution of the prescription drug, wherein the prescription fields store all prescription requests, for all patients being prescribed the company's prescription drug, only in the single computer database of the company, from all physicians or other prescribers allowed to prescribe the company's prescription drug, such that all prescriptions for the company's prescription drug are processed using only the company's single computer database;

said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug that has a potential for abuse, misuse or diversion is prescribed;

said prescriber fields, contained within the database schema, storing information sufficient to identify a physician or other prescriber of the company's prescription drug that has a potential for abuse, misuse or diversion, and said prescriber fields storing information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug;

a data processor for processing a database query to identify information in said prescription fields, said patient fields, and said prescriber fields for reconciling inventory of the prescription drug that has a potential for abuse, misuse or diversion before shipments of the company's prescription drug for a day or other time period are sent.

26. The computer-implemented system of claim 25, wherein the database query operates over all data related to said prescription fields, said prescriber fields, and said patient fields for the prescription drug that has a potential for misuse, abuse or diversion.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/592,202	08/22/2012	3626	1910	101.031US9	26	3

CONFIRMATION NO. 5805

21186
SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

FILING RECEIPT

OC000000056310700

Date Mailed: 09/07/2012

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Dayton T. Reardan, Shorewood, MN;
Patti A. Engel, Eagan, MN;
Bob Gagne, St. Paul, MN;

Assignment For Published Patent Application

Orphan Medical, Inc., Palo Alto, CA

Power of Attorney: The patent practitioners associated with Customer Number 21186

Domestic Priority data as claimed by applicant

This application is a CON of 13/013,680 01/25/2011 ABN
which is a CON of 12/704,097 02/11/2010 PAT 7895059
which is a CON of 10/322,348 12/17/2002 PAT 7668730

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 08/31/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/592,202**

Projected Publication Date: Request for Non-Publication Acknowledged

Non-Publication Request: Yes

Early Publication Request: No

Title

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

Preliminary Class

705

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

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No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/592,202	08/22/2012	Dayton T. Reardan	101.031US9

CONFIRMATION NO. 5805

21186
SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

POA ACCEPTANCE LETTER

OC000000056310578

Date Mailed: 09/07/2012

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/22/2012.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/dnguyen/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/592,202

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	380
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	26 minus 20 =	* 6			OR	x 60 =	360
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 250 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1610

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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Substitute for form 1449A/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)	*Complete if Known*	
	Application Number	13/592,202
	Filing Date	August 22, 2012
	First Named Inventor	Dayton T. Reardan Ph.D
	Group Art Unit	3626
	Examiner Name	Unknown
Sheet 1 of 5	Attorney Docket No: 101.031US9	

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Examiner Initial *	USP Document Number	Publication Date	Name of Patentee or Applicant of cited Document
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EXAMINER **DATE CONSIDERED**

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	Group Art Unit	3626
	Examiner Name	Unknown
Sheet 2 of 5	Attorney Docket No: 101.031US9	

US PATENT DOCUMENTS

Examiner Initial *	USP Document Number	Publication Date	Name of Patentee or Applicant of cited Document
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	Group Art Unit	3626
	Examiner Name	Unknown
Sheet 3 of 5	Attorney Docket No: 101.031US9	

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Sheet 4 of 5	Attorney Docket No: 101.031US9	

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	"Letter from Theodora McCormick to Magistrate Judge Cathy L. Waldor", (w/ Exhibits), (02/27/12), 60 pgs	
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	"Reply To Counterclaims", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 11-660 (SDW) (MCA) Lead Action CV-10-6108), (04/18/11), 6 pgs	
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims To Plaintiff's Complaint", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 10-6108 (ES) (CLW), (12/29/10), 21 pgs	
	"Roxane Laboratories, Inc.'s Initial Invalidity And Noninfringement Contentions Pursuant To Local Patent Rule 3.6", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 2:10-cv-06108 (SDW) (MCA)), (04/14/11), 317 pgs	
	"Roxane Laboratories, Inc.'s Opening Markman Brief In Support Of Its Claim Constructions", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 2.10-cv-06108 (ES) (CLW)), (12/05/11), 37 pgs	
	"Roxane Laboratories, Inc.'s Responsive Markman Brief In Support Of Its Claim Constructions", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 2:10-cv-06108 (ES) (CLW)), (02/21/12), 27 pgs	
	"System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) Starter Kit", Celgene Corporation, (2001), 103 pgs.	
	UKENS, C., "Specialty Pharmacy", Drug Topics, 144, (June 5, 2000), 40-47	

EXAMINER **DATE CONSIDERED**

* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant is to place a check mark here if English language Translation is attached

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Dayton T. Reardan Ph.D et al.	Examiner:	Unknown
Serial No.:	13/592,202	Group Art Unit:	3626
Filed:	August 22, 2012	Docket:	101.031US9
Customer No.:	21186	Confirmation No.:	5805
Title:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD		

INFORMATION DISCLOSURE STATEMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In compliance with the duty imposed by 37 C.F.R. § 1.56, and in accordance with 37 C.F.R. §§ 1.97 *et. seq*., the enclosed materials are brought to the attention of the Examiner for consideration in connection with the above-identified patent application. Applicants respectfully request that this Information Disclosure Statement be entered and the documents listed on the attached PTO 1449 Form be considered by the Examiner and made of record. Pursuant to the provisions of MPEP 609, Applicant requests that a copy of the PTO 1449 Form, initialed as being considered by the Examiner, be returned to the Applicant with the next official communication.

Pursuant to 37 C.F.R. § 1.97(b), it is believed that no fee or statement is required with the Information Disclosure Statement. However, if an Office Action on the merits has been mailed, the Commissioner is hereby authorized to charge the required fees to Deposit Account No. 19-0743 in order to have this Information Disclosure Statement considered.

Pursuant to 37 C.F.R. § 1.98(d), copies of the listed documents are not provided as these references were previously cited by or submitted to the U.S. Patent Office in connection with Applicants' prior U.S. application, Serial No. 13/013,680, filed on January 25, 2011, which is relied upon for an earlier filing date under 35 U.S.C. § 120.

Copies of sixteen (16) documents, not previously cited in connection with the Applicants' prior U.S. Application, Serial No. 13/013,680, are attached. These documents are highlighted in boldface on the attached Form 1449's (on pages 3-5).

Pursuant to 37 C.F.R. § 1.98(a)(2), copies of cited U.S. Patents and Published Applications, and Non-Published Applications identifiable by USPTO Serial Number, are no longer required to be provided to the Office. Applicants acknowledge the requirement to submit copies of foreign patent documents and non-patent literature in accordance with 37 C.F.R § 1.98(a)(2).

The Examiner is invited to contact the undersigned at the telephone number indicated if there are any questions regarding this communication.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 371-2140

Date October 4, 2012 By /David D'Zurilla/

David D'Zurilla
Reg. No. 36,776

DDZ:vam

ANDA,LEAD,RULE16,SCHEDO

U.S. District Court
District of New Jersey [LIVE] (Newark)
CIVIL DOCKET FOR CASE #: 2:10-cv-06108-ES-CLW

JAZZ PHARMACEUTICALS, INC. v. ROXANE LABORATORIES, INC.
Assigned to: Judge Esther Salas
Referred to: Magistrate Judge Cathy L. Waldor
Cause: 35:183 Patent Infringement

Date Filed: 11/22/2010
Jury Demand: None
Nature of Suit: 830 Patent
Jurisdiction: Federal Question

Plaintiff

JAZZ PHARMACEUTICALS, INC. represented by **CHARLES MICHAEL LIZZA**
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V.

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Counter Claimant

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V.

Counter Defendant

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(See above for address)
ATTORNEY TO BE NOTICED

WILLIAM C. BATON
(See above for address)
ATTORNEY TO BE NOTICED

Date Filed	#	Docket Text
11/22/2010	1	COMPLAINT against ROXANE LABORATORIES, INC. (Filing fee $ 350 receipt number 3434643.) NO JURY DEMANDED., filed by JAZZ

		PHARMACEUTICALS, INC.. (Attachments: # 1 Civil Cover Sheet, # 2 Exhibit A, # 3 Exhibit B, # 4 Exhibit C, # 5 Summons)(rac,) (Entered: 11/29/2010)
11/22/2010	2	Corporate Disclosure Statement by JAZZ PHARMACEUTICALS, INC. identifying NONE as Corporate Parent. KOHLBERG KRAVIS ROBERTS & CO manage an investment fund that holds over 10% of JAZZ PHARMACEUTICALS, INC. stock. (rac,) (Entered: 11/29/2010)
11/22/2010	3	AO120 Patent/Trademark Form filed. (rac,) (Entered: 11/29/2010)
11/29/2010	4	SUMMONS ISSUED as to ROXANE LABORATORIES, INC. Attached is the official court Summons, please fill out Defendant and Plaintiffs attorney information and serve. Issued By *Robert A. Cirello* (rac,) (Entered: 11/29/2010)
11/29/2010	5	NOTICE of Appearance by WILLIAM C. BATON on behalf of JAZZ PHARMACEUTICALS, INC. (BATON, WILLIAM) (Entered: 11/29/2010)
12/03/2010	6	AFFIDAVIT of Service for Summons and Complaint served on M. Habans on 11/29/10, filed by JAZZ PHARMACEUTICALS, INC.. (LIZZA, CHARLES) (Entered: 12/03/2010)
12/13/2010	7	Application and Proposed Order for Clerk's Order to extend time to answer Attorney JOSEPH NICHOLAS FROEHLICH for ROXANE LABORATORIES, INC. added. (Attachments: # 1 Text of Proposed Order) (FROEHLICH, JOSEPH) (Entered: 12/13/2010)
12/14/2010		CLERKS TEXT ORDER - The Application for a Clerks Order Extending Time to Answer - Document #7 submitted by J. FROEHLICH on 12/13/2010 has been GRANTED. The answer due date has been set for 1/3/2011 (nr,) (Entered: 12/14/2010)
12/29/2010	8	NOTICE of Appearance by MARK S. OLINSKY on behalf of ROXANE LABORATORIES, INC. (OLINSKY, MARK) (Entered: 12/29/2010)
12/29/2010	9	NOTICE of Appearance by THEODORA T. MCCORMICK on behalf of ROXANE LABORATORIES, INC. (MCCORMICK, THEODORA) (Entered: 12/29/2010)
12/29/2010	10	ANSWER to Complaint, COUNTERCLAIM against JAZZ PHARMACEUTICALS, INC. by ROXANE LABORATORIES, INC.. (OLINSKY, MARK) (Entered: 12/29/2010)
12/29/2010	11	Corporate Disclosure Statement by ROXANE LABORATORIES, INC. identifying Boehringer Ingelheim Corporation as Corporate Parent.. (OLINSKY, MARK) (Entered: 12/29/2010)
01/04/2011	12	LETTER ORDER - A Scheduling Conference is set for 2/7/2011 at 12:00 PM in Newark - Courtroom 2A before Magistrate Judge Madeline C. Arleo. JOINT DISCOVERY PLAN MUST BE SUBMITTED PRIOR TO THE CONFERENCE. CM/ECF IS MANDATORY FOR ALL FILINGS.Signed by Magistrate Judge Madeline C. Arleo on 1/4/2011. (kd) (Entered: 01/04/2011)

01/14/2011	13	MOTION for Leave to Appear Pro Hac Vice by ROXANE LABORATORIES, INC.. (Attachments: # 1 Declaration of Theodora McCormick, # 2 Declaration of Alan B. Clement, # 3 Declaration of Andrea L. Wayda, # 4 Declaration of Myoka Goodin, # 5 Declaration of Scott B. Feder, # 6 Text of Proposed Order)(MCCORMICK, THEODORA) (Entered: 01/14/2011)
01/18/2011	14	Application and Proposed Order for Clerk's Order to extend time to answer as to Defendants Answer, Affirmative Defenses, and Counterclaims.. (LIZZA, CHARLES) (Entered: 01/18/2011)
01/18/2011	15	NOTICE of Appearance by PETER HWICHAN NOH on behalf of ROXANE LABORATORIES, INC. (NOH, PETER) (Entered: 01/18/2011)
01/19/2011		CLERKS TEXT ORDER - The Application for a Clerks Order Extending Time to Answer - Document #14 submitted by L. CHARLES on (1/14/2011 has been GRANTED. The answer due date has been set for 2/7/2011 (nr,) Modified on 1/20/2011 (nr). Modified on 2/3/2011 (nr). (Entered: 01/19/2011)
01/19/2011	16	ORDER granting 13 Motion for Alan B. Clement, Dr. Andrea L. Wayda, Scott B. Feder to Appear Pro Hac Vice. Signed by Magistrate Judge Madeline C. Arleo on 01/18/2011. (nr,) (Entered: 01/20/2011)
01/26/2011		Pro Hac Vice fee: $ 600.00, receipt number NEW005455 Re Alan B. Clement, Andrea l. Wayda, Scott B. Feder and Myoka Kim Goodin (nr,) (Entered: 01/31/2011)
01/31/2011	17	Notice of Request by Pro Hac Vice Alan B. Clement to receive Notices of Electronic Filings. (MCCORMICK, THEODORA) (Entered: 01/31/2011)
01/31/2011	18	Notice of Request by Pro Hac Vice Andrea L. Wayda to receive Notices of Electronic Filings. (MCCORMICK, THEODORA) (Entered: 01/31/2011)
01/31/2011	19	Notice of Request by Pro Hac Vice Myoka Kim Goodin to receive Notices of Electronic Filings. (MCCORMICK, THEODORA) (Entered: 01/31/2011)
01/31/2011	20	Notice of Request by Pro Hac Vice Scott B. Feder to receive Notices of Electronic Filings. (MCCORMICK, THEODORA) (Entered: 01/31/2011)
02/04/2011	21	Letter from Plaintiff to the Hon. Madeline C. Arleo, U.S.M.J. re: Joint Discovery Plan. (LIZZA, CHARLES) (Entered: 02/04/2011)
02/07/2011		Minute Entry for proceedings held before Magistrate Judge Madeline C. Arleo: Scheduling Conference held on 2/7/2011, (In-Person Conference set for 3/22/2011 at 12:30 PM in Newark - Courtroom 2A before Magistrate Judge Madeline C. Arleo.). (kd) (Entered: 02/07/2011)
02/07/2011	22	ANSWER to Counterclaim by JAZZ PHARMACEUTICALS, INC.. (Attachments: # 1 Certificate of Service)(LIZZA, CHARLES) (Entered: 02/07/2011)
02/10/2011	23	ORDER scheduling an in person conference for 3/22/2011 at 12:30p.m.. Signed by Magistrate Judge Madeline C. Arleo on 02/10/2011. (nr,)

		(Entered: 02/14/2011)
03/18/2011	24	Letter from the Parties to Hon. Madeline C. Arleo, U.S.M.J.. (LIZZA, CHARLES) (Entered: 03/18/2011)
03/22/2011		Minute Entry for proceedings held before Magistrate Judge Madeline C. Arleo: Status Conference Call held on 3/22/2011, on the record (In-Person Status Conference set for 6/6/2011 at 12:00 PM in Newark - Courtroom 2A before Magistrate Judge Madeline C. Arleo.). (11-03K,12:44)(kd) (Entered: 03/23/2011)
03/23/2011	25	Transcript of Proceedings held on 3/22/11, before Judge Arleo. Court Reporter/Transcriber Sara L. Kern/King Transcription Service, Telephone number 973 237 6080. Tape Number: Teleconference. **NOTICE REGARDING REDACTION OF TRANSCRIPTS:** The parties have seven (7) calendar days to file with the Court a Notice of Intent to Request Redaction of this Transcript. Redaction Request due 4/13/2011. Redacted Transcript Deadline set for 4/25/2011. Release of Transcript Restriction set for 6/21/2011. (tjg,) (Entered: 03/23/2011)
03/29/2011	26	Letter from the Parties to the Hon. Madeline C. Arleo, U.S.M.J.. (LIZZA, CHARLES) (Entered: 03/29/2011)
04/06/2011	27	ORDER consolidating this matter with Civil No. 11-660 for all purposes. Signed by Magistrate Judge Madeline C. Arleo on 04/06/2011. (nr,) (Entered: 04/07/2011)
04/18/2011	46	REPLY TO COUNTERCLAIMS of deft Roxane Laboratories, Inc. by pltf Jazz Pharmaceuticals, Inc. (inadvertently filed in cv-11-660 consolidated action)(sr,) (Entered: 06/30/2011)
05/05/2011	28	TEXT ORDER - Oral Argument via Telephone on the scope of the confidentiality order is scheduled for 5/20/2011 at 02:00 PM before Magistrate Judge Madeline C. Arleo. Plaintiff's Counsel shall initiate.Ordered by Magistrate Judge Madeline C. Arleo on 5/5/2011. (kd) (Entered: 05/05/2011)
05/16/2011	29	Letter from Plaintiff to the Hon. Madeline C. Arleo, U.S.M.J. re: Proposed Pretrial Scheduling Order. (LIZZA, CHARLES) (Entered: 05/16/2011)
05/17/2011	30	TEXT ORDER - Rescheduling an In Person Oral Argument from May 20, 2011 to JUNE 6, 2011 at 12:00 pm in Newark - Courtroom 2A before Magistrate Judge Madeline Cox Arleo.Ordered by Magistrate Judge Madeline C. Arleo on 5/17/2011. (kd) (Entered: 05/17/2011)
05/23/2011	31	Letter from Plaintiff to the Hon. Madeline C. Arleo, U.S.M.J.. (LIZZA, CHARLES) (Entered: 05/23/2011)
05/31/2011	32	Letter from Theodora McCormick to the Honorable Madeline Cox Arleo (with Exhibits A-E) re 29 Letter. (MCCORMICK, THEODORA) (Entered: 05/31/2011)
06/02/2011	33	Letter from Theodora McCormick to Judge Arleo (with Exhibits A through C). (MCCORMICK, THEODORA) (Entered: 06/02/2011)

06/02/2011	34	TEXT ORDER - Rescheduling Oral Argument from June 6, 2011 at 12:00 pm to JUNE 6, 2011 at 1:00 pm in Newark - Courtroom 2A before Magistrate Judge Madeline Cox Arleo.Ordered by Magistrate Judge Madeline C. Arleo on 6/2/2011. (kd) (Entered: 06/02/2011)
06/02/2011	35	Letter from the Parties to the Hon. Madeline C. Arleo, U.S.M.J.. (LIZZA, CHARLES) (Entered: 06/02/2011)
06/02/2011	36	APPLICATION/PETITION for the Admission Pro Hac Vice of F. Dominic Cerrito, Daniel L. Malone, Eric Stops, Evangeline Shih, Gabriel P. Brier, and Andrew S. Chalson for by JAZZ PHARMACEUTICALS, INC.. (Attachments: # 1 Certification of C. Lizza, # 2 Certification of F.D. Cerrito, # 3 Certification of D. Malone, # 4 Certification of E. Stops, # 5 Certification of E. Shih, # 6 Certification of G. Brier, # 7 Certification of A. Chalson, # 8 Text of Proposed Order)(LIZZA, CHARLES) (Entered: 06/02/2011)
06/06/2011		Minute Entry for proceedings held before Magistrate Judge Madeline C. Arleo: Oral Argument held on 6/6/2011. (CD #11-06K, 1:22.) (kd) (Entered: 06/13/2011)
06/08/2011	37	LETTER ORDER: In person hrg. set for 7/19/2011 11:00 AM before Magistrate Judge Madeline C. Arleo.. Signed by Magistrate Judge Madeline C. Arleo on 06/07/2011. (nr,) (Entered: 06/08/2011)
06/08/2011	38	Transcript of Proceedings held on 6/6/11, before Judge Arleo. Court Reporter/Transcriber Sara L. Kern/King Transcription Service, Telephone number 973 237 6080. Tape Number: Hearing. **NOTICE REGARDING REDACTION OF TRANSCRIPTS:** The parties have seven (7) calendar days to file with the Court a Notice of Intent to Request Redaction of this Transcript. Redaction Request due 6/29/2011. Redacted Transcript Deadline set for 7/11/2011. Release of Transcript Restriction set for 9/6/2011. (tjg,) (Entered: 06/09/2011)
06/08/2011	39	ORDER admitting F. Dominic Cerrito, Daniel L. Malone, Eric Stops, Evangeline Shih, Gabriel P. Brier, and Andrew S. Chalson pro hac vice. Signed by Magistrate Judge Madeline C. Arleo on 06/08/2011. (nr,) (Entered: 06/09/2011)
06/13/2011	40	Letter from Plaintiff to the Hon. Madeline C. Arleo, U.S.M.J. re: Discovery Confidentiality Order. (Attachments: # 1 [proposed] Discovery Confidentiality Order, # 2 Certification in Support of [proposed] Discovery Confidentiality Order)(LIZZA, CHARLES) (Entered: 06/13/2011)
06/13/2011	41	Letter from Plaintiff to the Hon. Madeline C. Arleo, U.S.M.J. re: Joint Request and Order for Consolidation. (LIZZA, CHARLES) (Entered: 06/13/2011)
06/22/2011	42	TEXT ORDER - I am in receipt of the parties' joint proposed Discovery Confidentiality Order, resolving the issue of the scope of the patent prosecution bar and patents involving sodium oxybate. The Discovery Hearing set for 7/19/2011 at 11:00 AM in Newark - Courtroom 2A before Magistrate Judge Madeline C. Arleo will address the status of defendant's ability to provide third party samples to plaintiff and the sufficiency of

		plaintiff's responses to document requests. Affirmative letters shall be filed by June 24 and responsive letters shall be filed by July 8, 2011. The papers shall be e-filed, courtesy copy to Chambers.Ordered by Magistrate Judge Madeline C. Arleo on 6/22/2011. (kd) (Entered: 06/22/2011)
06/24/2011	43	Letter from Plaintiff to the Hon. Madeline C. Arleo, U.S.M.J. re 33 Letter. (LIZZA, CHARLES) (Entered: 06/24/2011)
06/27/2011	44	ORDER REASSIGNING CASE. Case reassigned to Judge Esther Salas for all further proceedings. Susan D. Wigenton no longer assigned to case. Signed by Chief Judge Garrett E. Brown, Jr on 6/27/2011. (in-ps,) (Entered: 06/27/2011)
06/28/2011	45	LETTER ORDER advising the parties that the Court will hold oral argument on 8/17/2011 at 2:00p.m. to address the outstanding discovery dispute. Signed by Judge Esther Salas on 06/28/2011. (nr,) Modified on 6/29/2011 (ps). (Entered: 06/28/2011)
07/06/2011	47	TEXT ORDER - The Oral Argument Re: Discovery Disputes scheduled for July 19, 2011 at 11:00 am before Magistrate Judge Madeline Cox Arleo is Adjourned.Ordered by Magistrate Judge Madeline C. Arleo on 7/6/2011. (kd) (Entered: 07/06/2011)
07/08/2011	48	Letter from T. McCormick. (MCCORMICK, THEODORA) (Entered: 07/08/2011)
07/11/2011	49	JOINT REQUEST AND ORDER FOR CONSOLIDATION WITH CIVIL ACTION NO. 10-6108. Signed by Magistrate Judge Madeline C. Arleo on 8/11/11. (dc,) (Entered: 07/11/2011)
07/11/2011	50	STATEMENT *Jazz Pharmaceuticals' Reply to Roxane's Counterclaims (D.I. 5 under Consolidated Civil Action No. 11-2523)* by JAZZ PHARMACEUTICALS, INC.. (Attachments: # 1 Certificate of Service) (LIZZA, CHARLES) (Entered: 07/11/2011)
07/12/2011	51	Letter from T. McCormick. (MCCORMICK, THEODORA) (Entered: 07/12/2011)
07/14/2011		Pro Hac Vice fee as to Daniel L. Malone, Eric Stops, Evangeline Shih, Gabriel P. Brier, and Andrew S. Chalson: $ 750.00, receipt number NEW008240 (jd,) (Entered: 07/14/2011)
07/14/2011	52	Notice of Request by Pro Hac Vice F.D. Cerrito, E. Stops, E. Shih, G. Brier and A. Chalson to receive Notices of Electronic Filings. (LIZZA, CHARLES) (Entered: 07/14/2011)
07/27/2011	53	Letter from Jazz Pharmaceuticals to the Hon. Madeline C. Arleo, U.S.M.J. re 51 Letter. (LIZZA, CHARLES) (Entered: 07/27/2011)
07/28/2011		Case Reassigned to Magistrate Judge Cathy L. Waldor. Magistrate Judge Madeline C. Arleo no longer assigned to the case. (nic,) (Entered: 07/28/2011)
07/28/2011	54	DISCOVERY PROTECTIVE ORDER. Signed by Judge Esther Salas on

		07/28/2011. (nr,) (Entered: 07/28/2011)
07/29/2011	55	ORDER rescheduling an in person Conference for 8/8/2011 02:00 PM before Judge Esther Salas; directing the parties to submit to the Court a joint letter, not to exceed ten pages in length, outlining all outstanding discovey; Signed by Judge Esther Salas on 7/28/2011. (nr,) (Entered: 07/29/2011)
08/02/2011		Reset Hearings: Please be advised that the Oral Argument scheduled for 8/8/2011 has been ADJOURNED and RESCHEDULED to 8/17/2011 at 2:00 PM in Newark - Courtroom 2D before Judge Esther Salas. The joint letter shall be submitted by 8/12/2011. (ps,) (Entered: 08/02/2011)
08/05/2011	56	Letter from T. McCormick re D. Abramowitz re pro hac vice. (MCCORMICK, THEODORA) (Entered: 08/05/2011)
08/12/2011	57	Letter from the Parties to the Hon. Esther Salas, U.S.D.J. re: Proposed Scheduling Order. (LIZZA, CHARLES) (Entered: 08/12/2011)
08/12/2011	58	Letter from Theodora McCormick: joint letter regarding outstanding discovery disputes. (MCCORMICK, THEODORA) (Entered: 08/12/2011)
08/15/2011		CHAMBERS NOTE: Please be advised, the Oral Argument scheduled for 8/17/11 has been ADJOURNED and RESCHEDULED to 9/1/11 at 11:00am before Magistrate Judge Waldor in Courtroom 4C. (rac,) (Entered: 08/15/2011)
09/02/2011	59	ORDER admitting David B. Abramowitz pro hac vice. Signed by Magistrate Judge Cathy L. Waldor on 9/2/2011. (nr,) (Entered: 09/06/2011)
09/02/2011	60	PRETRIAL SCHEDULING ORDER: Discovery due by 3/16/2012.. Signed by Magistrate Judge Cathy L. Waldor on 09/01/2011. (nr,) (Entered: 09/06/2011)
09/07/2011	61	LETTER ORDER directing the parties to submit a joint letter to chambers addressing the resolutions of the pending discovery disputes by 9/16/2011. Signed by Magistrate Judge Cathy L. Waldor on 09/07/2011. (nr,) (Entered: 09/07/2011)
09/16/2011	62	Letter from T.McCormick. (MCCORMICK, THEODORA) (Entered: 09/16/2011)
10/11/2011	63	Letter from Theodora McCormick regarding the parties' Joint Claim Construction and Prehearing Statement and claim construction briefing. (MCCORMICK, THEODORA) (Entered: 10/11/2011)
10/11/2011		Pro Hac Vice fee: $ 150, receipt number NEW009466 Re David D. Abramowitz (nr,) (Entered: 10/20/2011)
10/13/2011	64	Letter from T. McCormick. (MCCORMICK, THEODORA) (Entered: 10/13/2011)
10/17/2011	65	Letter from Theodora McCormick/Joint Letter Regarding Outstanding Discovery Disputes. (MCCORMICK, THEODORA) (Entered: 10/17/2011)
10/18/2011	66	APPLICATION/PETITION for for the Admission Pro Hac Vice of Gasper J.

		LaRosa and Richard G. Greco for by JAZZ PHARMACEUTICALS, INC.. (Attachments: # 1 Certification of C. Lizza, # 2 Certification of G. LaRosa, # 3 Certification of R. Greco, # 4 Text of Proposed Order)(LIZZA, CHARLES) (Entered: 10/18/2011)
10/20/2011	67	Notice of Request by Pro Hac Vice David Abramowitz to receive Notices of Electronic Filings. (MCCORMICK, THEODORA) (Entered: 10/20/2011)
10/21/2011	68	STATEMENT *Joint Claim Construction and Prehearing Statement* by JAZZ PHARMACEUTICALS, INC.. (Attachments: # 1 Certificate of Service) (LIZZA, CHARLES) (Entered: 10/21/2011)
11/14/2011	69	Letter from Jazz Pharmaceuticals to the Hon. Cathy L. Waldor, U.S.M.J. re: discovery disputes. (LIZZA, CHARLES) (Entered: 11/14/2011)
11/22/2011	70	Letter from T. McCormick. (MCCORMICK, THEODORA) (Entered: 11/22/2011)
11/26/2011	71	TEXT ORDER: Please be advised, a conference will be held on 12/9/11 at 2:00 P.M. with Magistrate Judge Waldor, to address the concerns outlined in the joint letter ECF-Filed on 11/14/11. All parties are required to appear telephonically. Counsel for Plaintiff Jazz Pharmaceuticals, Inc. shall initiate the call to chambers (973-776-7862) at the appropriate time. Any questions or concerns may be directed to chambers via fax (973-776-7865). Signed by Magistrate Judge Cathy L. Waldor on 11/26/11. (rac,) (Entered: 11/26/2011)
11/28/2011	72	Letter from Jazz Pharmaceuticals, Inc. to the Hon. Esther Salas, U.S.D.J. re 70 Letter. (LIZZA, CHARLES) (Entered: 11/28/2011)
11/29/2011	73	Letter from T.McCormick. (MCCORMICK, THEODORA) (Entered: 11/29/2011)
11/30/2011	74	Letter from T. McCormick. (MCCORMICK, THEODORA) (Entered: 11/30/2011)
12/01/2011	75	LETTER ORDER denying the request from Roxane Laboratories, Inc. to enlarge the page limit for opening Markman brief. Signed by Judge Esther Salas on 12/01/2011. (nr,) (Entered: 12/01/2011)
12/02/2011	76	STATEMENT */Revised Joint Claim Construction and Prehearing Statement* by ROXANE LABORATORIES, INC.. (MCCORMICK, THEODORA) (Entered: 12/02/2011)
12/05/2011	77	MARKMAN OPENING BRIEF */Roxane Laboratories, Inc.'s Opening Markman Brief in Support of Its Claim Constructions* filed by ROXANE LABORATORIES, INC.. (MCCORMICK, THEODORA) (Entered: 12/05/2011)
12/05/2011	78	Certification of Theodora McCormick on behalf of ROXANE LABORATORIES, INC.. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F, # 7 Exhibit G, # 8 Exhibit H, # 9 Exhibit I, # 10 Exhibit J, # 11 Exhibit K, # 12 Exhibit L (part 1 of 4), # 13 Exhibit L (part 2 of 4), # 14 Exhibit L (part 3 of 4), # 15 Exhibit L (part 4 of 4), # 16 Exhibit M, # 17 Exhibit N, # 18 Exhibit O, # 19 Exhibit P,

		# 20 Exhibit Q, # 21 Exhibit R, # 22 Exhibit S, # 23 Exhibit T (part 1 of 2), # 24 Exhibit T (part 2 of 2), # 25 Exhibit U, # 26 Exhibit V, # 27 Exhibit W) (MCCORMICK, THEODORA) (Entered: 12/05/2011)
12/05/2011	79	MOTION to Seal *Certain Materials Pursuant to L. Civ. R. 5.3* by JAZZ PHARMACEUTICALS, INC.. (Attachments: # 1 Brief, # 2 Text of Proposed Order, # 3 Certificate of Service)(LIZZA, CHARLES) (Entered: 12/05/2011)
12/05/2011	80	MARKMAN OPENING BRIEF filed by JAZZ PHARMACEUTICALS, INC.. (Attachments: # 1 Declaration of G. Brier - Part 1, # 2 Declaration of G. Brier - Part 2, # 3 Declaration of G. Brier - Part 3, # 4 Declaration of G. Brier - Part 4, # 5 Declaration of G. Brier - Part 5, # 6 Declaration of G. Brier - Part 6, # 7 Certificate of Service)(LIZZA, CHARLES) (Entered: 12/05/2011)
12/09/2011		Minute Entry for proceedings held before Magistrate Judge Cathy L. Waldor: Telephone Conference held on 12/9/2011. (rac,) (Entered: 12/09/2011)
12/13/2011	81	LETTER ORDER Telephone Status Conference set for 12/21/2011 02:00 PM before Magistrate Judge Cathy L. Waldor.,. Signed by Magistrate Judge Cathy L. Waldor on 12/12/2011. (nr,) (Entered: 12/13/2011)
12/17/2011		CHAMBERS NOTE: Please be advised, the Telephone Conference set for 12/21/11 at 2:00 P.M. will now take place at 11:00 A.M. Please adjust your schedules accordingly.(rac,) (Entered: 12/17/2011)
12/20/2011	82	Letter from Jazz to the Hon. Cathy L. Waldor, U.S.M.J.. (LIZZA, CHARLES) (Entered: 12/20/2011)
12/21/2011		Minute Entry for proceedings held before Magistrate Judge Cathy L. Waldor: Telephone Conference held on 12/21/2011. (rac,) (Entered: 12/24/2011)
12/27/2011	83	ORDER admitting Gasper J. LaRosa and Richard G. Greco pro hac vice. Signed by Magistrate Judge Cathy L. Waldor on 12/26/2011. (nr,) (Entered: 12/27/2011)
01/04/2012	84	Letter from Jazz to the Hon. Cathy L. Waldor, U.S.M.J. re: Order Concerning Outstanding Discovery Disputes. (LIZZA, CHARLES) (Entered: 01/04/2012)
01/06/2012	85	MOTION to Seal by ROXANE LABORATORIES, INC.. (Attachments: # 1 Brief, # 2 Declaration of David B. Abramowitz in Support of Motion to Seal, # 3 Text of Proposed Order, # 4 Certificate of Service)(MCCORMICK, THEODORA) (Entered: 01/06/2012)
01/06/2012	86	RESPONSE re 82 Letter. (MCCORMICK, THEODORA) (Entered: 01/06/2012)
01/06/2012	87	DECLARATION of Gregory M. Hicks *(Sealed Version)* by ROXANE LABORATORIES, INC.. (Attachments: # 1 Exhibit A)(MCCORMICK, THEODORA) (Entered: 01/06/2012)
01/06/2012	88	DECLARATION of Gregory M. Hicks *(Redacted Version)* by ROXANE LABORATORIES, INC.. (Attachments: # 1 Exhibit A)(MCCORMICK, THEODORA) (Entered: 01/06/2012)

01/06/2012		Set Deadlines as to 85 MOTION to Seal. Motion set for 2/6/2012 10:00 AM before Judge Esther Salas. The motion will be decided on the papers. No appearances required unless notified by the court. (nr,) (Entered: 01/09/2012)
01/09/2012	89	ORDER regarding outstanding discovery disputes. Signed by Magistrate Judge Cathy L. Waldor on 1/9/2012. (nr,) (Entered: 01/09/2012)
01/19/2012	90	MOTION to Seal *Certain Materials Pursuant to L. Civ. R. 5.3* by JAZZ PHARMACEUTICALS, INC.. (Attachments: # 1 Brief, # 2 Text of Proposed Order, # 3 Certificate of Service)(LIZZA, CHARLES) (Entered: 01/19/2012)
01/19/2012	91	Letter from Jazz to the Hon. Cathy L. Waldor, U.S.M.J. re 86 Response (NOT Motion), 82 Letter. (LIZZA, CHARLES) (Entered: 01/19/2012)
01/19/2012		Set Deadlines as to 90 MOTION to Seal *Certain Materials Pursuant to L. Civ. R. 5.3*. Motion set for 2/21/2012 10:00 AM before Judge Esther Salas. The motion will be decided on the papers. No appearances required unless notified by the court. (nr,) (Entered: 01/20/2012)
01/20/2012	92	Letter from Theodora McCormick supplementing defendant Roxane Laboratories, Inc.'s Motion to Seal re 85 MOTION to Seal. (MCCORMICK, THEODORA) (Entered: 01/20/2012)
01/20/2012		Minute Entry for proceedings held before Magistrate Judge Cathy L. Waldor: Telephone Conference held on 1/20/2012. (rac,) (Entered: 01/21/2012)
01/23/2012	93	ORDER granting pltf's 90 Motion to Seal exhibits A,B, and C to the 1/19/2012 letter. Signed by Magistrate Judge Cathy L. Waldor on 1/23/2012. (nr,) (Entered: 01/23/2012)
01/23/2012	94	ORDER of findingss of fact and conclusions of law granting motion to seal; sealing exhibit A of the Declaration of Gregory M. Hicks. Signed by Magistrate Judge Cathy L. Waldor on 1/23/2012. (nr,) (Entered: 01/23/2012)
01/23/2012		Pro Hac Vice fee: $ 300.00, receipt number NEW011952 Re Gasper J. LaRosa & Richard G. Greco (nr,) (Entered: 01/24/2012)
01/24/2012	95	ORDER granting 79 Motion to Seal Exhibit 13 to the Declaration of Gabriel P. Brier. Signed by Magistrate Judge Cathy L. Waldor on 1/24/2012. (nr,) (Entered: 01/24/2012)
02/01/2012	96	Letter from Jazz to the Hon. Cathy L. Waldor, U.S.M.J. re: Amended Scheduling Order. (LIZZA, CHARLES) (Entered: 02/01/2012)
02/02/2012	97	AMENDED SCHEDULING ORDER: granting Jazz Pharmaceuticals Inc's request to amend its infringement contentions; Telephone Status Conference set for 3/30/2012 12:00 PM before Magistrate Judge Cathy L. Waldor. Fact Discovery due by 3/30/2012.. Signed by Magistrate Judge Cathy L. Waldor on 2/2/2012. (nr,) (Entered: 02/02/2012)
02/21/2012	98	Defendant's Response Brief by ROXANE LABORATORIES, INC.. (Attachments: # 1 Declaration)(MCCORMICK, THEODORA) (Entered: 02/21/2012)
02/21/2012	99	MOTION to Seal *Certain Materials Pursuant to L. Civ. R. 5.3* by JAZZ

		PHARMACEUTICALS, INC.. (Attachments: # 1 Brief, # 2 Text of Proposed Order, # 3 Certificate of Service)(LIZZA, CHARLES) (Entered: 02/21/2012)
02/21/2012	100	MARKMAN RESPONSE BRIEF re 80 Markman Opening Brief, 77 Markman Opening Brief (Attachments: # 1 Declaration of G. Brier, # 2 Certificate of Service)(LIZZA, CHARLES) (Entered: 02/21/2012)
02/21/2012		Set Deadlines as to 99 MOTION to Seal *Certain Materials Pursuant to L. Civ. R. 5.3*. Motion set for 3/19/2012 10:00 AM before Judge Esther Salas. The motion will be decided on the papers. No appearances required unless notified by the court. (nr,) (Entered: 02/23/2012)
02/27/2012	101	Letter from Roxane Laboratories, Inc. Seeking Leave to Supplement its Initial Invalidity and Noninfringement Contentions. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F, # 7 Exhibit G, # 8 Exhibit H, # 9 Exhibit I)(MCCORMICK, THEODORA) (Entered: 02/27/2012)
02/28/2012	102	Letter from the Parties to the Hon. Esther Salas, U.S.D.J. re: scheduling of a Claim Construction Hearing. (LIZZA, CHARLES) (Entered: 02/28/2012)
02/29/2012	103	MOTION to Seal Document by ROXANE LABORATORIES, INC.. (Attachments: # 1 Brief, # 2 Text of Proposed Order)(MCCORMICK, THEODORA) (Entered: 02/29/2012)
02/29/2012	104	Letter from Theodora McCormick regarding Jazz's document production pursuant to February 2, 2012 Amended Scheduling Order. (Attachments: # 1 Exhibit A)(MCCORMICK, THEODORA) (Entered: 02/29/2012)
02/29/2012		Set Deadlines as to 103 MOTION to Seal Document. Motion set for 4/2/2012 10:00 AM before Judge Esther Salas. The motion will be decided on the papers. No appearances required unless notified by the court. (nr,) (Entered: 03/01/2012)
03/02/2012	105	LETTER ORDER scheduling a Markman hrg. for 4/26/2012. Signed by Judge Esther Salas on 3/2/2012. (nr,) (Entered: 03/05/2012)
03/07/2012		CHAMBERS NOTE: Please be advised that the Markman Hearing will start at 10:00 AM on 4/26/2012 before Judge Esther Salas - Courtroom 5A on the 5th Floor. (ps,) (Entered: 03/07/2012)
03/14/2012	106	MOTION to Seal *Certain Materials Pursuant to L. Civ. R. 5.3* by JAZZ PHARMACEUTICALS, INC.. (Attachments: # 1 Brief, # 2 Text of Proposed Order, # 3 Certificate of Service)(LIZZA, CHARLES) (Entered: 03/14/2012)
03/14/2012	107	Letter from Jazz to the Hon. Cathy L. Waldor, U.S.M.J. (Sealed Version) re 101 Letter,. (Attachments: # 1 Exhibit A through C, # 2 Exhibit D through K) (LIZZA, CHARLES) (Entered: 03/14/2012)
03/14/2012	108	Letter from Jazz to the Hon. Cathy L. Waldor, U.S.M.J. (Public Version) re 101 Letter,. (Attachments: # 1 Exhibit A through C, # 2 Exhibit D through K) (LIZZA, CHARLES) (Entered: 03/14/2012)
03/14/2012		Set Deadlines as to 106 MOTION to Seal *Certain Materials Pursuant to L.*

		Civ. R. 5.3. Motion set for 4/16/2012 10:00 AM before Judge Esther Salas. The motion will be decided on the papers. No appearances required unless notified by the court. (nr,) (Entered: 03/15/2012)
03/15/2012	109	Letter from Jazz to the Hon. Cathy L. Waldor, U.S.M.J. re 108 Letter, 101 Letter,. (LIZZA, CHARLES) (Entered: 03/15/2012)
03/19/2012	110	Letter from Theodora McCormick regarding Roxane's Reply in Further Support of Its Request for Leave to Amend Its Initial Invalidity and Noninfringement Contentions Pursuant to Local Patent Rule 3.7 re 101 Letter,. (Attachments: # 1 Exhibit J, # 2 Exhibit K, # 3 Exhibit L, # 4 Exhibit M, # 5 Exhibit N, # 6 Exhibit O, # 7 Exhibit P, # 8 Exhibit Q, # 9 Exhibit R) (MCCORMICK, THEODORA) (Entered: 03/19/2012)
03/29/2012	111	Letter from T. McCormick. (MCCORMICK, THEODORA) (Entered: 03/29/2012)
03/29/2012	112	Letter from Theodora McCormick re 110 Letter,. (Attachments: # 1 Exhibit A-1 (Part 1 of 2), # 2 Exhibit A-1 (Part 2 of 2), # 3 Exhibit A-2, # 4 Exhibit A-3, # 5 Exhibit B-1, # 6 Exhibit B-2 (Part 1 of 3), # 7 Exhibit B-2 (Part 2 of 3), # 8 Exhibit B-2 (Part 3 of 3), # 9 Exhibit C-1, # 10 Exhibit C-2, # 11 Exhibit C-3)(MCCORMICK, THEODORA) (Entered: 03/29/2012)
04/03/2012	113	Letter from T. McCormick. (MCCORMICK, THEODORA) (Entered: 04/03/2012)
04/03/2012		Minute Entry for proceedings held before Magistrate Judge Cathy L. Waldor: Telephone Conference held on 4/3/2012. (rac,) (Entered: 04/08/2012)
04/04/2012	114	Proposed Pretrial Order *agreements reached* by ROXANE LABORATORIES, INC.. (MCCORMICK, THEODORA) (Entered: 04/04/2012)
04/04/2012	115	LETTER ORDER: Telephone Conference set for 4/5/2012 04:00 PM before Judge Esther Salas.. Signed by Judge Esther Salas on 4/4/2012. (nr,) (Entered: 04/04/2012)
04/05/2012		Reset Hearings: Please be advised that the Telephone Status Conference previously set for 4/5/2012 has been ADJOURNED and RESCHEDULED to 4/10/2012 at 2:00 PM before Judge Esther Salas. (ps,) (Entered: 04/05/2012)
04/09/2012	116	SCHEDULING ORDER regarding discovery; and scheduling a status conference for 4/30/2012. Signed by Magistrate Judge Cathy L. Waldor on 4/9/2012. (nr,) (Entered: 04/10/2012)
04/10/2012		Minute Entry for proceedings held before Judge Esther Salas: Telephone Conference held on 4/10/2012. (ps,) (Entered: 05/02/2012)
04/13/2012	117	Letter from Theodora McCormick re 112 Letter,. (MCCORMICK, THEODORA) (Entered: 04/13/2012)
04/16/2012	118	Letter from Jazz to the Hon. Cathy L. Waldor, U.S.M.J. re 110 Letter, 101 Letter,. (LIZZA, CHARLES) (Entered: 04/16/2012)
04/18/2012		Minute Entry for proceedings held before Magistrate Judge Cathy L. Waldor:

		Discovery Hearing held on 4/18/2012. (Court Recorder ECR.) (rac,) (Entered: 04/20/2012)
04/20/2012	119	Letter from T. McCormick. (MCCORMICK, THEODORA) (Entered: 04/20/2012)
04/20/2012		CHAMBERS NOTE: Please be advised, the Telephone Conference set for 4/30/12 before U.S.M.J. Cathy L. Waldor will begin at 10:30 A.M. Please adjust your schedules accordingly. (rac,) Modified on 4/23/2012 (rac,). (Entered: 04/22/2012)
04/23/2012	120	MOTION for Leave to Appear Pro Hac Vice *Peter N. Fill, Esq.* by ROXANE LABORATORIES, INC.. (MCCORMICK, THEODORA) (Entered: 04/23/2012)
04/24/2012	121	Transcript of Proceedings held on 4/18/12, before Judge Waldor. Court Reporter/Transcriber Sara L. Kern/King Transcripts (973 237 6080). Tape Number: Hearing. **NOTICE REGARDING REDACTION OF TRANSCRIPTS:** The parties have seven (7) calendar days to file with the Court a Notice of Intent to Request Redaction of this Transcript. Redaction Request due 5/15/2012. Redacted Transcript Deadline set for 5/25/2012. Release of Transcript Restriction set for 7/23/2012. (tjg,) (Entered: 04/24/2012)
04/26/2012	122	Minute Entry for proceedings held before Judge Esther Salas: Markman Hearing held on 4/26/2012. (Court Reporter Lynne Johnson.) (ps,) (Entered: 04/27/2012)
04/27/2012	123	Letter from Jazz to the Hon. Cathy L. Waldor, U.S.M.J. re: Location of Depositions. (LIZZA, CHARLES) (Entered: 04/27/2012)
04/30/2012		Minute Entry for proceedings held before Magistrate Judge Cathy L. Waldor: Telephone Conference held on 4/30/2012. (rac,) (Entered: 04/30/2012)
05/04/2012	124	Letter from Jazz to the Hon. Cathy L. Waldor, U.S.M.J. re: Location of Depositions re 123 Letter. (LIZZA, CHARLES) (Entered: 05/04/2012)
05/30/2012	125	ORDER granting application for Peter N. Fill to appear pro hac vice. Signed by Magistrate Judge Cathy L. Waldor on 5/30/2012. (nr,) (Entered: 05/31/2012)
06/04/2012	126	Letter from Charles M. Lizza re: Notices of Electronic Filing. (LIZZA, CHARLES) (Entered: 06/04/2012)
06/12/2012	127	LETTER ORDER granting 99 Motion to Seal certain portions of responsive Markman Brief and exhibits 18,19 &20 to the supplemental Declaration of Gabriel P. Brier. Signed by Magistrate Judge Cathy L. Waldor on 6/12/2012. (nr,) (Entered: 06/13/2012)
06/13/2012	128	Letter from Jazz to the Hon. Cathy L. Waldor, U.S.M.J.. (BATON, WILLIAM) (Entered: 06/13/2012)
06/14/2012	129	Letter from Charles M. Lizza re: Notices of Electronic Filing. (LIZZA, CHARLES) (Entered: 06/14/2012)

06/19/2012	130	Letter from Jazz to the Hon. Cathy L. Waldor, U.S.M.J. re 128 Letter. (BATON, WILLIAM) (Entered: 06/19/2012)
06/19/2012	131	Letter from Jazz to the Hon. Cathy L. Waldor, U.S.M.J. re 54 Protective Order. (BATON, WILLIAM) (Entered: 06/19/2012)
06/22/2012	132	MOTION to Seal by ROXANE LABORATORIES, INC.. (Attachments: # 1 Brief Memorandum in Support of Motion to Seal, # 2 Declaration Declaration of Myoka Kim Goodin in Support of Motion to Seal, # 3 Text of Proposed Order)(MCCORMICK, THEODORA) (Entered: 06/22/2012)
06/22/2012	133	Letter from Theodora McCormick regarding fact deposition discovery. (Attachments: # 1 Exhibit A)(MCCORMICK, THEODORA) (Entered: 06/22/2012)
06/22/2012	134	Letter from Theodora McCormick regarding fact deposition discovery (Public Version). (Attachments: # 1 Exhibit A)(MCCORMICK, THEODORA) (Entered: 06/22/2012)
06/22/2012		Set Deadlines as to 132 MOTION to Seal . Motion set for 7/16/2012 10:00 AM before Judge Esther Salas. The motion will be decided on the papers. No appearances required unless notified by the court. (nr,) (Entered: 06/25/2012)
06/25/2012	135	ORDER modifying paragraph 31 of the discovery confidentiality order. Signed by Magistrate Judge Cathy L. Waldor on 6/25/2012. (nr,) (Entered: 06/25/2012)

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **v.** **ROXANE LABORATORIES, INC.,** **Defendant.**	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiff Jazz Pharmaceuticals, Inc. ("Jazz Pharmaceuticals"), by its undersigned attorneys, for its Complaint against defendant Roxane Laboratories, Inc. ("Roxane"), alleges as follows:

Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. §100, *et seq.*, arising from Roxane's filing of an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market a generic version of Jazz Pharmaceuticals' XYREM® drug product prior to the expiration of United States Patent Nos. 6,780,889 (the "'889 patent"), 7,262,219 (the "'219 patent"), 7,668,730 (the "'730 patent"), 7,765,106 (the "'106 patent"),

and 7,765,107 (the "'107 patent") owned by Jazz Pharmaceuticals (collectively, "the patents-in-suit").

The Parties

2. Plaintiff Jazz Pharmaceuticals is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304.

3. On information and belief, defendant Roxane is a corporation organized under the laws of Nevada, having a principal place of business at 1809 Wilson Road, Columbus, Ohio 43228.

4. On information and belief, Roxane is registered to do business in the State of New Jersey, and maintains a registered agent for service of process in New Jersey. On information and belief, Roxane regularly transacts business within this judicial district. Further, on information and belief, Roxane develops numerous generic drugs for sale and use throughout the United States, including in this judicial district. On information and belief, Roxane has litigated patent cases in this district in the past without contesting personal jurisdiction, and, in at least some of those actions, Roxane has asserted counterclaims.

Jurisdiction and Venue

5. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

6. This Court has personal jurisdiction over Roxane by virtue of, *inter alia,* its systematic and continuous contacts with the State of New Jersey. On information and belief, Roxane has purposefully availed itself of this forum by, among other things, making, shipping, using, offering to sell or selling, or causing others to use, offer to sell, or sell, pharmaceutical

products in the State of New Jersey and deriving revenue from such activities. Further, on information and belief, Roxane has customers in the State of New Jersey.

7. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

The Patents in Suit

8. On August 24, 2004, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '889 patent, entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy" to inventors Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan. A copy of the '889 patent is attached hereto as Exhibit A.

9. On August 28, 2007, the USPTO duly and lawfully issued the '219 patent, entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy" to inventors Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan. A copy of the '219 patent is attached hereto as Exhibit B.

10. On February 23, 2010, the USPTO duly and lawfully issued the '730 patent, entitled "Sensitive Drug Distribution System and Method" to inventors Dayton Reardan, Patti Engle and Bob Gagne. A copy of the '730 patent is attached hereto as Exhibit C.

11. On July 27, 2010, the USPTO duly and lawfully issued the '106 patent, entitled "Sensitive Drug Distribution System and Method" to inventors Dayton Reardan, Patti Engle and Bob Gagne. A copy of the '106 patent is attached hereto as Exhibit D.

12. On July 27, 2010, the USPTO duly and lawfully issued the '107 patent, entitled "Sensitive Drug Distribution System and Method" to inventors Dayton Reardan, Patti Engle and Bob Gagne. A copy of the '107 patent is attached hereto as Exhibit E.

The XYREM® Drug Product

13. Jazz Pharmaceuticals holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for sodium oxybate oral solution (NDA No. 21-196), which it sells under the trade name XYREM®. The claims of the patents-in-suit cover, *inter alia*, pharmaceutical compositions containing sodium oxybate, and methods of use and administration of sodium oxybate or pharmaceutical compositions containing sodium oxybate. Jazz Pharmaceuticals owns the patents-in-suit.

14. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the '889, '219, '730, '106 and '107 patents are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to XYREM®.

Acts Giving Rise to this Suit

15. Pursuant to Section 505 of the FFDCA, Roxane filed ANDA No. 202-090 ("Roxane's ANDA") seeking approval to engage in the commercial use, manufacture, sale, offer for sale or importation of 500 mg/ml sodium oxybate oral solution ("Roxane's Proposed Product"), before the patents-in-suit expire.

16. In connection with the filing of its ANDA as described in the preceding paragraph, Roxane has provided a written certification to the FDA, as called for by Section 505 of the FFDCA, alleging that the claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Roxane's ANDA.

17. No earlier than October 14, 2010, Roxane sent written notice of its ANDA certification to Jazz Pharmaceuticals ("Roxane's Notice Letter"). Roxane's Notice Letter alleged that the claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Roxane's ANDA. Roxane's Notice Letter also

informed Jazz Pharmaceuticals that Roxane seeks approval to market Roxane's Proposed Product before the patents-in-suit expire.

18. In Roxane's Notice Letter, it offered to provide access to certain confidential information and materials within Roxane's ANDA that would allow Jazz Pharmaceuticals to confirm Roxane's infringement of the patents-in-suit. In response, Jazz Pharmaceuticals wrote to Roxane regarding the terms of this offer and requesting access. To date, Roxane has not responded to this inquiry or provided any portion of its ANDA to counsel for Jazz Pharmaceuticals.

Count I: Infringement of the '889 Patent

19. Plaintiff repeats and realleges the allegations of paragraphs 1-18 as though fully set forth herein.

20. Roxane's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '889 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

21. There is a justiciable controversy between the parties hereto as to the infringement of the '889 patent.

22. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will infringe the '889 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States.

23. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will induce infringement of the '889 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States. On information and belief, upon FDA approval of Roxane's ANDA, Roxane will intentionally

encourage acts of direct infringement with knowledge of the '889 patent and knowledge that its acts are encouraging infringement.

24. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will contributorily infringe the '889 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States. On information and belief, Roxane has had and continues to have knowledge that Roxane's Proposed Product is especially adapted for a use that infringes the '889 patent and that there is no substantial non-infringing use for Roxane's Proposed Product.

25. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Roxane's infringement of the '889 patent is not enjoined.

26. Jazz Pharmaceuticals does not have an adequate remedy at law.

27. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count II: Infringement of the '219 Patent

28. Plaintiff repeats and realleges the allegations of paragraphs 1-27 as though fully set forth herein.

29. Roxane's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '219 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

30. There is a justiciable controversy between the parties hereto as to the infringement of the '219 patent.

31. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will infringe the '219 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States.

32. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will induce infringement of the '219 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States. On information and belief, upon FDA approval of Roxane's ANDA, Roxane will intentionally encourage acts of direct infringement with knowledge of the '219 patent and knowledge that its acts are encouraging infringement.

33. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will contributorily infringe the '219 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States. On information and belief, Roxane has had and continues to have knowledge that Roxane's Proposed Product is especially adapted for a use that infringes the '219 patent and that there is no substantial non-infringing use for Roxane's Proposed Product.

34. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Roxane's infringement of the '219 patent is not enjoined.

35. Jazz Pharmaceuticals does not have an adequate remedy at law.

36. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count III: Infringement of the '730 Patent

37. Plaintiff repeats and realleges the allegations of paragraphs 1-36 as though fully set forth herein.

38. Roxane's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '730 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

39. There is a justiciable controversy between the parties hereto as to the infringement of the '730 patent.

40. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will infringe the '730 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States.

41. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will induce infringement of the '730 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States. On information and belief, upon FDA approval of Roxane's ANDA, Roxane will intentionally encourage acts of direct infringement with knowledge of the '730 patent and knowledge that its acts are encouraging infringement.

42. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will contributorily infringe the '730 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States. On information and belief, Roxane has had and continues to have knowledge that Roxane's Proposed Product is especially adapted for a use that infringes the '730 patent and that there is no substantial non-infringing use for Roxane's Proposed Product.

43. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Roxane's infringement of the '730 patent is not enjoined.

44. Jazz Pharmaceuticals does not have an adequate remedy at law.

45. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IV: Infringement of the '106 Patent

46. Plaintiff repeats and realleges the allegations of paragraphs 1-45 as though fully set forth herein.

47. Roxane's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '106 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

48. There is a justiciable controversy between the parties hereto as to the infringement of the '106 patent.

49. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will infringe the '106 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States.

50. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will induce infringement of the '106 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States. On information and belief, upon FDA approval of Roxane's ANDA, Roxane will intentionally encourage acts of direct infringement with knowledge of the '106 patent and knowledge that its acts are encouraging infringement.

51. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will contributorily infringe the '106 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States. On

information and belief, Roxane has had and continues to have knowledge that Roxane's Proposed Product is especially adapted for a use that infringes the '106 patent and that there is no substantial non-infringing use for Roxane's Proposed Product.

52. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Roxane's infringement of the '106 patent is not enjoined.

53. Jazz Pharmaceuticals does not have an adequate remedy at law.

54. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count V: Infringement of the '107 Patent

55. Plaintiff repeats and realleges the allegations of paragraphs 1-54 as though fully set forth herein.

56. Roxane's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '107 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

57. There is a justiciable controversy between the parties hereto as to the infringement of the '107 patent.

58. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will infringe the '107 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States.

59. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will induce infringement of the '107 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States. On information and belief, upon FDA approval of Roxane's ANDA, Roxane will intentionally

encourage acts of direct infringement with knowledge of the '107 patent and knowledge that its acts are encouraging infringement.

60. Unless enjoined by this Court, upon FDA approval of Roxane's ANDA, Roxane will contributorily infringe the '107 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Roxane's Proposed Product in the United States. On information and belief, Roxane has had and continues to have knowledge that Roxane's Proposed Product is especially adapted for a use that infringes the '107 patent and that there is no substantial non-infringing use for Roxane's Proposed Product.

61. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Roxane's infringement of the '107 patent is not enjoined.

62. Jazz Pharmaceuticals does not have an adequate remedy at law.

63. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff Jazz Pharmaceuticals respectfully requests the following relief:

(A) A Judgment be entered that Roxane has infringed the '889, '219, '730, '106 and '107 patents by submitting ANDA No. 202-090;

(B) A Judgment be entered that Roxane has infringed, and that Roxane's making, using, selling, offering to sell, or importing Roxane's Proposed Product will infringe one or more claims of the '889, '219, '730, '106 and '107 patents;

(C) An Order that the effective date of FDA approval of ANDA No. 202-090 be a date which is not earlier than the later of the expiration of the '889, '219, '730, '106 and '107 patents, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Roxane and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, selling, offering to sell, or importing Roxane's Proposed Product until after the expiration of the '889, '219, '730, '106 and '107 patents, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(E) A permanent injunction be issued, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Roxane, its officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any compounds, methods or compositions as claimed in the '889, '219, '730, '106 and '107 patents, or from actively inducing or contributing to the infringement of any claim of any of the patents-in-suit, until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(F) A Declaration that the commercial manufacture, use, importation into the United States, sale, or offer for sale of Roxane's Proposed Product will directly infringe, induce and/or contribute to infringement of the '889, '219, '730, '106 and '107 patents;

(G) To the extent that Roxane has committed any acts with respect to the compounds, methods or compositions claimed in the '889, '219, '730, '106 and '107 patents, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), that Plaintiff Jazz Pharmaceuticals be awarded damages for such acts;

(H) If Roxane engages in the commercial manufacture, use, importation into the United States, sale, or offer for sale of Roxane's Proposed Product prior to the expiration of the '889, '219, '730, '106 and '107 patents, a Judgment awarding damages to Plaintiff Jazz Pharmaceuticals resulting from such infringement, together with interest;

(I) Attorneys' fees in this action as an exceptional case pursuant to 35 U.S.C. § 285;

(J) Costs and expenses in this action; and

(K) Such further and other relief as this Court may deem just and proper.

Dated: November 22, 2010

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CERTIFICATION PURSUANT TO L. CIV. R. 11.2

I hereby certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: November 22, 2010

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **v.** **ROXANE LABORATORIES, INC.,** **Defendant.**	**Civil Action No. 10-6108 (ES)(CLW)** **(Filed Electronically)**

JAZZ PHARMACEUTICALS, INC.'S OPENING *MARKMAN* BRIEF

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Regulations

Plaintiff Jazz Pharmaceuticals, Inc. ("Jazz") submits this brief in support of its proposed constructions of the disputed terms of United States Patent Nos. 6,472,431 (the "'431 patent"), 6,780,889 (the "'889 patent"), 7,262,219 (the "'219 patent") and 7,851,506 (the "'506 patent") (collectively, the "'431 patent family"), and 7,668,730 (the "'730 patent"), 7,765,106 (the "'106 patent"), 7,765,107 (the "'107 patent") and 7,895,059 (the "'059 patent") (collectively, the "'730 patent family") owned by Jazz (collectively, "the patents-in-suit").[1]

I. INTRODUCTION

There are eight patents-in-suit that cover novel aspects of the drug sodium oxybate. The first family of patents covers pharmaceutical compositions of sodium oxybate. There are nine disputed terms concerning these composition patents. Jazz's constructions of these terms derive directly from the intrinsic evidence, or use the ordinary meaning of the disputed term where the specification does not provide an explicit definition. This common-sense approach to claim construction follows the Federal Circuit's controlling guidance in *Phillips* and its progeny. By contrast, Roxane's proposed constructions violate several bedrock principles of claim construction. For example, they (1) ignore explicit definitions set forth in the specification; (2) read limitations into the claims that have no basis in the intrinsic evidence; and (3) limit claims to examples or embodiments.

The second family of patents covers methods of safely distributing and treating patients with sodium oxybate. The claims of these patents use easily understandable, non-technical language whose meaning is readily apparent. Accordingly, Jazz submits that no construction is necessary for the majority of the terms of these patents. Roxane apparently disagrees and has

[1] Ex. 1 through Ex. 8, respectively. "Ex. __" herein refers to the exhibits to the Declaration of Gabriel P. Brier in support of Jazz Pharmaceuticals, Inc.'s Opening *Markman* Brief.

proposed construing twenty-five terms from these patents. Roxane's proposed constructions are unnecessary and complicate the claims.

For at least these reasons, and those discussed below, this Court should adopt Jazz's proposed constructions.

II. BACKGROUND

A. XYREM®

Jazz is a specialty pharmaceutical company. It markets the drug product XYREM® to treat patients with two of the most prevalent symptoms of narcolepsy – excessive daytime sleepiness and cataplexy. Narcolepsy is a sleep disorder that affects about 150,000 to 200,000 patients in the United States. All patients with narcolepsy suffer from excessive daytime sleepiness, which is so overpowering that it results in involuntary sleep attacks while the patient is engaged in everyday activities such as talking, walking, eating, standing, and driving. Narcolepsy patients also commonly suffer from cataplexy, a condition manifested by episodes of loss of muscle control leading to the patient collapsing. Cataplexy can be triggered by emotional responses such as laughter, anger, embarrassment, or surprise. Most people with narcolepsy also suffer from irregular sleep patterns that cause some of narcolepsy's symptoms.

B. The '431 Patent Family

XYREM® is sold as a concentrated oral solution that is diluted by the patient with water prior to its use at bedtime. Under certain conditions, the active ingredient in XYREM®, sodium oxybate (a/k/a gamma-hydroxybutyrate or "GHB"), may become chemically unstable and break down. GHB solutions may also become prone to microbial contamination. The inventors of the '431 patent family discovered that GHB solutions could be rendered self-stabilizing and resistant to microbial growth without the use of preservatives. Jazz's claims in the '431 patent family cover novel pharmaceutical compositions containing sodium oxybate that are self-stabilizing and

resistant to microbial growth without the use of a preservative. Other claims in the '431 patent family cover methods of making and using these novel pharmaceutical compositions.

C. The '730 Patent Family

While XYREM® is a life-changing drug for many people, its benefits do not come without potential risks. In the 1990s, GHB became notorious for its use and abuse as a recreational drug in clubs and by bodybuilders. Abuse of GHB led to hospitalizations resulting from GHB overdoses, especially when combined with alcohol. GHB was also implicated in a number of drug-facilitated sexual assaults. This led to GHB being labeled as a "date-rape" drug, and its listing as a Schedule I controlled substance by the U.S. Drug Enforcement Administration.

To prevent abuse, misuse, and diversion of XYREM®, Orphan Medical, Inc.[2] and Jazz developed a restricted distribution program that is designed to ensure the safe and proper treatment of patients using XYREM®. Certain of Jazz's claims in the '730 patent family cover these methods of safely treating patients with GHB. The restrictions on XYREM®'s distribution include a single, centralized pharmacy housed in a secure facility, physician and patient registries, XYREM Success Program® educational materials for physicians and patients, and post-marketing surveillance for abuse, misuse, and diversion associated with XYREM®. The controlled distribution program ensures responsible distribution of XYREM® to patients with narcolepsy and educates patients and physicians about safety concerns.

D. Defendant Roxane Laboratories, Inc.

Defendant Roxane Laboratories, Inc. ("Roxane"), is a generic pharmaceutical company. Roxane filed an Abbreviated New Drug Application ("ANDA") with the FDA seeking approval to market a generic version of Jazz's XYREM® product. Jazz alleges, among other things, that Roxane's generic version of XYREM® would infringe certain claims of the eight patents-in-suit.

[2] Jazz acquired Orphan Medical, Inc. along with XYREM® and the patents-in-suit.

III. LEGAL STANDARD

Claim construction is an issue of law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 970-71 (Fed. Cir. 1995). The Federal Circuit has explained that claim construction starts with the words of the claims. *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298 (Fed. Cir. 2003). Claim terms are deemed to be read "not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). If the patentee has specifically defined a claim term in the specification, that definition controls. *Id.* at 1316 ("[T]he inventor's lexicography governs."). When the patentee has not provided an explicit definition of a claim term, however, the words of a claim are given their plain and ordinary meaning to a person of ordinary skill in the art. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Indeed, "[a]bsent a clear disavowal or contrary definition in the specification or the prosecution history, the patentee is entitled to the full scope of its claim language." *Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1358 (Fed. Cir. 2004).

IV. ARGUMENT

The patents-in-suit generally fall into two categories: (1) pharmaceutical compositions containing sodium oxybate and related methods of making and using the same claimed in the '431 patent family; and (2) methods of treatment through restricted distribution claimed in the '730 patent family. The parties dispute the meaning of thirty-four terms in the asserted claims of the patents-in-suit. Those terms are discussed below, on a patent-by-patent basis, in order based on related subject matter. To the extent a disputed term is found in more than one asserted patent claim, it is discussed below only with respect to the first time it arises.

A. The '431 Patent Family

The '431, '889, '219, and '506 patents claim pharmaceutical compositions containing sodium oxybate and methods of making and using such compositions. The parties dispute nine terms in those patents, as discussed below.

1. Claim 1 of the '431 Patent

Claim 1 states (with emphasis on the disputed claim terms):

> A method of rendering an aqueous medium **resistant to microbial growth**, comprising **adding the gamma-hydroxybutyrate salt to the aqueous medium**, adjusting the concentration of the gamma-hydroxybutyrate **salt** in the aqueous medium to a final concentration of at least **about** 250 mg/ml, and adjusting the pH of the medium to a final pH of **about** 6 to **about** 10, so that the medium is chemically stable and resistant to microbial growth.

(a) "resistant to microbial growth"[3]

The parties' proposed constructions are as follows:

"resistant to microbial growth"	
Jazz's construction	**Roxane's construction**
"the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles"	"formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days, including but not limited to formulations containing greater than about 150 mg/ml GHB to GHB's maximal solubility in an aqueous medium"

[3] The term "resistant to microbial growth" also appears in claim 1 of the '889 patent and claims 1 and 4 of the '219 patent.

The parties' proposed constructions are very similar. As an initial matter, the parties agree that the patentees explicitly defined "resistant to microbial growth" as follows:

> the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles

(Ex. 1 at 3:22-26.) Since the patentees were seeking to make commercial pharmaceutical compositions, it makes sense that they chose to gauge whether their products were "resistant to microbial growth" by the standards for commercial products – i.e., the criteria set by the FDA and U.S. Pharmacopoeia.

The dispute regarding this claim term concerns the second and third portions of Roxane's proposed construction. The second portion of Roxane's proposed construction is as follows:

> which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days

(*Id.* at 3:26-31.) This portion of the specification is a definition of the U.S. Pharmacopoeia criteria. It is not a definition of "resistant to microbial growth," and is therefore not part of the patentee's lexicography. Moreover, it adds nothing to the first portion of Roxane's proposed construction, which already requires that "resistant to microbial growth" meet the U.S. Pharmacopoeia criteria for products made with aqueous bases or vehicles.

The third portion of Roxane's construction is as follows:

> including but not limited to formulations containing greater than about 150 mg/ml GHB to GHB's maximal solubility in an aqueous medium

By Roxane's own proposed words – "including but not limited to" – this is not a claim limitation.[4] Instead, it is merely an example of formulations that can be included in the definition. Examples are not part of constructions. *Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 805 F.2d 1558, 1563 (Fed. Cir. 1986) ("This court has cautioned against limiting the claimed invention to preferred embodiments or specific examples in the specification."). Thus, this Court should adopt the agreed-upon language "the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles" as the construction for the term "resistant to microbial growth."

(b) "adding the gamma-hydroxybutyrate salt to the aqueous medium"

The parties' proposed constructions are as follows:

"adding the gamma-hydroxybutyrate salt to the aqueous medium"	
Jazz's construction	**Roxane's construction**
"including gamma-hydroxybutyrate in a liquid comprising more than 50% water"	"externally adding a pre-made gamma-hydroxybutyrate salt into a pre-existing aqueous medium"

Jazz proposes that the term "adding the gamma-hydroxybutyrate salt to the aqueous medium" means "including gamma-hydroxybutyrate in a liquid comprising more than 50% water." Jazz's proposed construction derives from the meaning of "add" from general dictionaries: "to include as a member of a group." (*See* Ex. 9, Merriam-Webster's Collegiate Dictionary, 10th ed. (1997) at 13.) The Federal Circuit has explained that such general purpose dictionaries should be used for disputed non-technical claim terms:

> In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of

[4] Notably, this portion of Roxane's proposed construction is not found in the specification.

> commonly understood words. . . . In such circumstances, general purpose dictionaries may be helpful.

Phillips, 415 F.3d at 1314 (emphasis added); *see also Vitronics*, 90 F.3d at 1584 n.6 ("[Judges may] rely on dictionary definitions when construing claim terms, so long as the dictionary definition does not contradict any definition found in or ascertained by a reading of the patent documents."). Jazz's proposed definition also derives support from the explicit definition of "aqueous medium" provided in the specification. (Ex. 1 at 3:31-33.)

Moreover, Jazz's construction is consistent with the use of the term in the specification, which focuses on formulations that include GHB in an aqueous medium. (*See, e.g.*, *id.* at 3:37-48, 4:10-13, 4:25-28.) Thus, the intrinsic evidence supports the plain and ordinary meaning of "adding" epitomized by Jazz's proposed definition.

Roxane's construction does not actually provide a definition. Instead, as shown below, Roxane merely attempts to add words to the claim support its non-infringement defense without even pretending to define the claim terms:

Comparison of claim term to Roxane's construction
" adding the gamma-hydroxybutyrate salt to the aqueous medium"
"externally adding a pre-made gamma-hydroxybutyrate salt into a pre-existing aqueous medium"

Thus, Roxane's proposed definition seeks to improperly add limitations of (1) "externally adding;" (2) "pre-made" GHB salt; and (3) "pre-existing aqueous medium." It is a fundamental tenet of claim construction that reading limitations into claims constitutes legal error when those limitations are not found in the claim language. *See McCarty v. Lehigh Valley, R.R.*, 160 U.S. 110, 116 (1895) ("[W]e know of no principle of law which would authorize us to read into a claim an element which is not present . . ."). Ignoring this principle can result in a construction that is too narrow and devoid of any connection to the intrinsic record. *See, e.g.*,

Decisioning.com v. Federated Dep't Stores, Inc., 527 F.3d 1300, 1312 (Fed. Cir. 2008) ("Engrafting the claims with these limitations produces anomalous results, not supported by the specification or the claims themselves"). Here, Roxane has fabricated its proposed construction in a desperate attempt to support its non-infringement position. Unfortunately for Roxane, there is nothing in the intrinsic evidence that supports Roxane's proposed requirements. Thus, Roxane's construction lacks merit, both for failing to encompass the full scope of the claim term and for attempting to read nonexistent limitations into the claims. The Court should reject Roxane's proposal and adopt Jazz's construction of the term "adding the gamma-hydroxybutyrate salt to the aqueous medium."

(c) "salt"[5]

The parties' proposed constructions are as follows:

"salt"	
Jazz's construction	**Roxane's construction**
"a compound formed by the interaction of an acid and a base"	"a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base"

Salts according to the '431 patent are discussed in column 7 of the specification. Both parties draw their constructions from the portion of specification quoted below:

> A "**salt**" is understood herein to mean certain embodiments to mean **a compound formed by the interaction of an acid and a base**, the hydrogen atoms of the acid being replaced by the positive ion of the base. Various salts, including salts of GHB, are also encompassed by the invention, particularly as pH adjusting or buffering agents. Pharmaceutically acceptable salts, include inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as malic, acetic, oxalic, tartaric, mandelic, and the like. Salts formed can also be derived from inorganic bases such as, for example, sodium, potassium, silicates, ammonium, calcium, or ferric hydroxides, and such organic bases

[5] The term "salt" also appears in claim 2 of the '431 patent.

> as isopropylamine, trimethylamine, histidine, procaine and the like. . . . Other salts may comprise ammonium, calcium, magnesium and the like. In one embodiment, a salt of GHB comprising an alkali metal may be combined with an acid to create a composition that achieves the desired pH when admixed with an aqueous medium. In another embodiment, a weak base may be combined with GHB to create a composition that achieves the desired pH when admixed with an aqueous solution. Of course, other salts can be formed from compounds disclosed herein, or as would be known to one of ordinary skill in the art, and all such salts are encompassed by the invention.

(Ex. 1 at 7:2-28 (emphasis added).) Jazz's proposed construction is the first portion of the quotation (underlined above). That portion provides the definition of salt as "a compound formed by the interaction of an acid and a base." The remainder of the quoted portion describes various *examples* of salts. Examples are *not* part of constructions. *See Phillips*, 415 F.3d at 1323 (noting "the danger of reading limitations from the specification into the claim"); *Tex. Instruments*, 805 F.2d at 1563 ("This court has cautioned against limiting the claimed invention to preferred embodiments or specific examples in the specification.").

In a misguided attempt to limit the scope of "salt," Roxane includes one of the examples as part of its proposed construction. Specifically, Roxane's proposed construction includes the example of a salt where "the hydrogen atoms of the acid being replaced by the positive ion of the base." In addition to the inclusion of examples being improper under Federal Circuit case law, Roxane's proposed construction would specifically exclude many of the later examples cited in the quoted portion of the specification. Specifically, Roxane's proposed construction would exclude the scenario where the acid absorbs hydroxide ions from the base. This is described in the specification as follows:

> Salts formed can also be derived from inorganic bases such as, for example, sodium, potassium, silicates, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

(Ex. 1 at 7:10-14.) Thus, Roxane's attempt to limit the scope of "salt" to just one example is improper.[6] Accordingly, Jazz's construction should be adopted.

(d) "about"[7]

The parties' proposed constructions are as follows:

"about"	
Jazz's construction	**Roxane's construction**
"reasonably close to"	"20% of the number modified in the appropriate direction(s)"

The parties agree that the intrinsic evidence for the '431 patent does not provide an explicit definition of "about." The Federal Circuit has explained that in such circumstances, general-purpose dictionaries should be used for disputed non-technical claim terms:

> In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words. . . . In such circumstances, general purpose dictionaries may be helpful.

Phillips, 415 F.3d at 1314 (emphasis added); *see also Vitronics*, 90 F.3d at 1584 n.6 ("[Judges may] rely on dictionary definitions when construing claim terms, so long as the dictionary definition does not contradict any definition found in or ascertained by a reading of the patent documents.").

Here, Jazz proposes that the term "about" means "reasonably close to." This construction is the first definition from Merriam-Webster's Collegiate Dictionary, 10th ed:

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[6] Moreover, Roxane ignores the explicit disclaimer in the specification that "other salts can be formed from compounds disclosed herein . . . and all such salts are encompassed by the invention." (Ex. 1 at 7:24-27.) This indicates that the applicants intended "salt" to have a broad scope. Roxane's proposed construction fails to recognize this fact.

[7] The term "about" also appears in claims 3 and 5 of the '431 patent, claim 1 of the '889 patent, claims 1, 2 and 4 of the '219 patent and claim 1 of the '506 patent.

¹about \ə-'baůt\ *adv* [ME, fr. OE *abūtan*, fr. ¹*a-* + *būtan* outside – more at BUT] (bef. 12c) **1 a :** reasonably close to (~ a year ago)

(Ex. 9 at 3.) There is nothing in the intrinsic evidence that contradicts this ordinary meaning of "about." Accordingly, Jazz Pharmaceutical's proposed construction should be adopted.

In contrast, despite agreeing that there is no explicit definition of "about" in the intrinsic evidence, Roxane does not cite to any dictionary in support of its definition. Instead, Roxane proposes that "about" means "20% of the number modified in the appropriate direction(s)." This is not the ordinary meaning of the term. Roxane's proposed construction appears to be a baseless revision of a line in the specification that "about" "generally means within about 10-20%." (Ex. 1 at 4:8-9.) Roxane's construction lacks merit for at least three reasons. *First*, Roxane is *not* asserting that the patentee acted as his own lexicographer. Instead, Roxane has taken only the "20%" from this portion of the specification and made up the rest of its construction out of whole cloth. Since Roxane's construction is *neither* the patentee's lexicography *nor* the plain and ordinary meaning of the term, it should be rejected.

Second, Roxane's construction would render the specification nonsensical. For example, the '431 patent specification repeatedly uses "about" to describe the amount of GHB in a dosage as "about 0.1, about 0.2, about 0.3, . . . about 9.8, about 9.9, to about 10 grams of GHB." (*Id.* at 9:6-27.) Applying Roxane's "20% of the number modified in the appropriate direction(s)" to, for example, a dose of "about 10" would turn it into "8.0 to 12.0" grams of GHB. This is clearly not what the patentee intended. Accordingly, Roxane's construction is incompatible with the specification.

Third, the use of the word "generally" in the specification means that this proposed meaning for "about" should not apply in all contexts. Indeed, as the Federal Circuit has held, the term "about" does not have a universal meaning in patents and depends on the context of the

claims, including effects of varying parameters on the invention. *See, e.g., Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995). For example, with respect to claim 1 of the '431 patent, Roxane's "20%" definition of "about" would lead to a pH range of 4.8-12. The '431 patent, however, reports a maximal pH of 10.3. (Ex. 1 at 3:57-58, 4:30-36, 20:5-9.) Roxane's construction would cause claim 1 to cover GHB formulations with pHs that lack support in the specification. Such a construction would be improper. *See Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd.*, 476 F.3d 1321, 1327-28 (Fed. Cir. 2007) (citing data points from the specification to construe "about" very close to the claimed ratio).

In addition, Roxane's proposed construction could cause some elements of the claims to read on the prior art. This violates the Federal Circuit maxim that claims should be construed to preserve their validity when possible. *See Harris Corp. v. IXYS Corp.*, 114 F.3d 1149, 1153 (Fed. Cir. 1997) ("[C]laims should be read in a way that avoids ensnaring prior art if it is possible to do so . . ."). For at least the foregoing reasons, Roxane's definition of "about" should be rejected, and Jazz's should be adopted.

2. Claim 4 of the '431 Patent

Claim 4 states (with emphasis on the disputed claim term):

> The method of claim 1 or 2 wherein the medium **does not contain a preservative**.

(a) "does not contain a preservative"; "free of preservatives" [8]

The parties' proposed constructions are as follows:

[8] The term "free of preservatives" appears in claim 1 of the '889 patent and claims 1 and 4 of the '219 patent. The parties have agreed that the construction of the term "does not contain a preservative" will also apply to the term "free of preservatives." *See* Exhibit A to the Revised Joint Claim Construction and Prehearing Statement (D.I. 76) at 2.

"does not contain a preservative"; "free of preservatives"	
Jazz's construction	**Roxane's construction**
"free of conventional exogenous substances that are added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action"	"does not contain any substance added to inhibit chemical change or microbial action"

The parties' proposed constructions of these terms are largely identical and are based on the description of "preservative" in the specification of the '431 patent. (Ex. 1 at 7:42-44.) The only relevant difference (emphasized above) is that Jazz's proposed construction requires that the excluded preservative is a "conventional exogenous substance," while Roxane's proposed construction includes "any substance."[9]

Jazz's proposed construction uses "conventional exogenous substances that are added in addition to the gamma-hydroxybutyrate salt" to make it clear that the excluded substance must be a conventional preservative. In other words, the method of Claim 4 is designed to exclude things that are well known to be preservatives. For example, the specification names exemplary preservatives such as xylitol, sodium benzoate, potassium sorbate, etc. (*Id.* at 7:44-58.) All of these are conventional, outside (or exogenous) substances that could potentially be added to a GHB formulation to prevent chemical degradation or microbial growth. Thus, Jazz's proposed construction is consistent with the specification.

The prosecution history of the '431 patent also supports Jazz's proposed construction. In an August 10, 2001 response to an Office Action, the patentees distinguished the claimed inventions over the prior art's disclosure of "conventional" preservatives:

[9] As described further below, Roxane's proposed constriction includes the "any" substance language because Roxane argues that GHB itself is a preservative in the claimed inventions. This leads to the nonsensical result that a GHB solution can *never* be one that "does not contain a preservative."

> None of the references, including the admitted prior art, teaches or suggests any method of making a solution of GHB salt resistant to microbial growth other than by adding conventional preservatives.

(Ex. 10 at JPI-00000627 (emphasis added).) Similarly, the patentees explained that there would be no motivation to use a GHB formulation free of "conventional" preservatives:

> The references also provide no suggestion or motivation to develop a method of making an aqueous solution of GHB salt resistant to microbial growth, as recited in claims 66-69. Further, if one were to aim to make an aqueous solution of GHB salt resistant to microbial growth, the references provide no suggestion or motivation that this could be done by adjusting the final concentration of GHB salt to at least about 250 mg/ml and adjusting the pH to the range of about 6 to about 10, as recited in claims 66-69. Instead, one would simply add the preservatives disclosed by the references or otherwise conventional in the art, and hope for the best.

(*Id.* at JPI-00000627-8 (emphasis added).) And again in a November 29, 2001 Preliminary Amendment, the patentees explained that:

> [T]here is nothing in the cited art to suggest adjusting the concentration and pH of GHB in an aqueous medium so as to render the resultant composition resistant to microbial growth, so that no conventional preservatives need be used.

(Ex. 11 at JPI-00000644-5 (emphasis added).) Finally, in an April 1, 2002 Response to an Office Action, the patentees make it clear that the claim excludes "exogenous" preservatives:

> However, it is clearly set forth throughout the present specification that the preferred embodiment is a solution of GHB salt that is resistant to microbial growth without the need to add exogenous preservatives.

(Ex. 12 at JPI-00000663.) Thus, the prosecution history confirms that the excluded preservative is a "conventional exogenous substance."

Roxane's proposed construction does not specify that the preservative must be an outside substance other than GHB itself. This is relevant because Roxane has asserted a noninfringement theory based on the argument that GHB itself is a preservative. (*See* Ex. 13,

Roxane's Non-Infringement Contentions at 9-3.) As an initial matter, Roxane's contention that GHB itself is a preservative is nonsensical because it would require a solution containing GHB to also be free of GHB. Roxane's proposed construction is also improper because it would read self-preserving GHB formulations out of the scope of the claims. This is contrary to preferred embodiments identified in the specification of the '431 patent that include examples of self-preserving GHB formulations. (*See* Ex. 1 at 18:1-6, 19:36-20:10.) Roxane ignores that "a construction that would not read on the preferred embodiment . . . would rarely if ever [be] correct and would require highly persuasive evidentiary support." *Chimie v. PPG Indus.*, 402 F.3d 1371, 1377 (Fed. Cir. 2005) (internal quotations omitted). Thus, any construction that even theoretically includes GHB as a potential "preservative" must fail. For these reasons, the Court should construe these terms in accord with Jazz's proposed construction.

3. Claim 6 of the '431 Patent

Claim 6 states (with emphasis on the disputed claim terms):

> The method of claim 1, wherein said **pH-adjusting agent** is an **organic acid**.

(a) "pH-adjusting agent" [10]

The parties' proposed constructions are as follows:

"pH-adjusting agent"	
Jazz's construction	**Roxane's construction**
No construction necessary.	"an agent, which is an acid or base, directly added primarily to alter the pH"

The term "pH-adjusting agent" does not require construction. Instead, Jazz contends that the term means just what it says – an agent that adjusts pH. Indeed, claim construction "is not an

[10] The term "pH-adjusting agent" also appears in claim 1 of the '889 patent and claims 1, 3, and 4 of the '219 patent.

obligatory exercise in redundancy." *U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997). Rather, "[c]laim construction is a matter of resolution of disputed meanings and technical scope, to clarify and when necessary to explain what the patentee covered by the claims, for use in the determination of infringement." *Id.* Thus, it is not necessary for the Court to construe terms with well-understood meanings.

Here, the term "pH-adjusting agent" has a well-understood, ordinary meaning that is consistent with the specification and claims of the patent. The claims refer to "adjusting the pH of the medium." (Ex. 1 at 70:10.) The specification states that pH-adjusting agents are used "to create compositions that achieve a desired pH." (*Id.* at 7:19-24.) The specification also states that a pH-adjusting agent may be used to "help stabilize the composition's pH." (*Id.* at 6:65-67.) Attributing any additional meaning to this term would be superfluous.

Nevertheless, Roxane proposes that the term "pH-adjusting agent" means "an agent, which is an acid or base, directly added primarily to alter the pH." As an initial mater, Roxane's construction does not aid the Court or the parties in understanding the claims and is likely to cause unnecessary confusion. Specifically, the addition of "directly added" and "primarily" only add ambiguity to the claim term. It is unclear what Roxane means by requiring the pH-adjusting agent to be "directly added" (as opposed to indirectly added?). It is also unclear what Roxane means by "primarily to alter the pH," which would appear to add some requirement to determine the relative functional contribution of each component in modifying the pH.

Roxane's attempt to read the phrase "directly added primarily to alter the pH" into the claims also has no support in the intrinsic record. Indeed, those words never appear in the specification or the claims. Likewise, Roxane cannot point to any support in the intrinsic evidence to limit the phrase "pH-adjusting agent" to "an acid or a base." As a result, Roxane has

failed to rebut the heavy presumption that "pH-adjusting agent" carries its ordinary meaning. *See Elbex Video, Ltd v. Sensormatic Electronics Corp.*, 508 F.3d 1366, 1371 (Fed. Cir. 2007). The Court should, therefore, reject Roxane's proposed construction because the term "pH-adjusting agent" requires no construction.

(b) "organic acid"

The parties' proposed constructions are as follows:

"organic acid"	
Jazz's construction	**Roxane's construction**
"a substance containing one or more carbon atoms that is capable of yielding a proton (hydrogen ion) in aqueous solution, turning blue litmus paper red in aqueous solutions, ionizing in solution to yield the positive ion of the solvent, reacting with bases to form salts, or accepting electrons in an acid-base reaction"	"an acid containing at least one carbon atom that directly acidifies a solution"

The parties agree that "organic" means a substance that contains one or more carbon atoms. The parties disagree regarding the proper construction of the term "acid," which is not defined in the specification. When the patentee has not provided an explicit definition of a claim term, the words of a claim are given the full scope of their plain and ordinary meaning to a person of ordinary skill in the art. *See Vitronics*, 90 F.3d at 1582. Here, Jazz has proposed the full scope of the plain and ordinary meaning of "acid." Specifically, acids can be (1) substances that donate a proton in solution; (2) substances that turn blue litmus paper red; (3) substances that ionize in solution; (4) substances that react with bases to form salts; or (5) substances that accept elections in an acid-base reaction (i.e., a Lewis acid). (*See* Ex. 14, Remington's Pharmaceutical Sciences (19th ed.) at 217-221; Ex. 15, McGraw-Hill Dictionary of Scientific and Technical Terms (5th ed.) at 19.) These are all well-accepted, plain and ordinary meanings of "acid" that

must apply because there is nothing in the specification of the '431 patent to limit the full scope of the term. *See Home Diagnostics*, 381 F.3d at 1358 ("Absent a clear disavowal or contrary definition in the specification or the prosecution history, the patentee is entitled to the full scope of its claim language."). Accordingly, the Court should adopt Jazz's construction of "organic acid."

Roxane seeks to define "acid" as something that "directly acidifies a solution." Roxane's definition should be rejected because it improperly seeks to limit the definition of "acid" in a way that is unsupported by the claims. Any such narrowing requires a clear and unmistakable disclaimer of claim scope. *See Cordis Corp. v. Boston Scientific Corp.*, 561 F.3d 1319, 1329 (Fed. Cir. 2009). Here, there is no such disclaimer. Indeed, there is nothing in the specification or prosecution history that requires or suggests that "acid" is limited to things that "directly acidifies a solution." Instead, the specification's description of acids includes substances such as caffeine that do not directly acidify a solution. (*See* Ex. 1 at 6:41-52.) Roxane's construction would therefore improperly *exclude* a preferred embodiment of the patent. *See Chimie*, 402 F.3d at 1377 (Fed. Cir. 2005) ("[A] construction that would not read on the preferred embodiment . . . would rarely if ever [be] correct and would require highly persuasive evidentiary support.") (internal quotations omitted). Thus, Roxane's construction lacks merit for attempting to read a nonexistent limitation into the claims. Therefore, the Court should reject Roxane's proposal and adopt Jazz's construction of the term "organic acid."

4. Claim 1 of the '219 Patent

Claim 1 states (with emphasis on the disputed claim term):

> A pharmaceutical composition, consisting essentially of an aqueous solution of about 350-750 mg/ml sodium gamma-hydroxybutyrate, and a pH adjusting agent, **wherein** the pH adjusting agent **is** malic acid, citric acid, acetic acid, lactic acid, carbonic acid, formic acid, propionic acid or tartaric acid, wherein

> the composition has a pH of about 6-7.5, and wherein the composition is chemically stable and resistant to microbial growth, and wherein the composition is free of preservatives.

(a) "wherein . . . is . . . "[11]

The parties' proposed constructions are as follows:

"wherein . . . is . . . "	
Jazz's construction	**Roxane's construction**
No construction necessary.	"one of the listed components and no others"

The term "wherein . . . is . . . " requires no construction. "Wherein" and "is" are two ordinary English words that mean just what they say. There is nothing in the specification that supports any deviation from these terms' plain and ordinary meaning. Moreover, Roxane's requirement, "and no others," improperly reads nonexistent limitations into the claim term. *See, e.g.*, *Decisioning.com*, 527 F.3d at 1312 ("Engrafting the claims with these limitations produces anomalous results, not supported by the specification or the claims themselves."). Accordingly, Roxane's attempt to use additional, unnecessary language to define this term should be rejected.

5. Claim 1 of the '506 Patent

Claim 1 states (with emphasis on the disputed claim terms):

> A method of treating a condition responsive to sodium gamma-hydroxybutyrate, comprising orally administering to a patient afflicted with the condition an aqueous composition comprising a first **dose** of about 4.5 to about 10 grams of sodium gamma-hydroxybutyrate within an hour prior to initial sleep onset and an aqueous composition comprising a second **dose** of about 4.5 to about 10 grams within 2 to 5 hours following initial sleep onset, wherein the aqueous composition of the first **dose** and the aqueous composition of the second **dose** each comprises a respective concentration of sodium gamma-hydroxybutyrate of greater than about 500 mg/mL, wherein the condition is selected from the group consisting of apnea, sleep time disturbances, narcolepsy,

[11] The term "wherein . . . is . . . " also appears in claims 3 and 4 of the '219 patent.

cataplexy, sleep paralysis, hypnagogic hallucination, sleep arousal, insomnia, and nocturnal myoclonus.

(a) "dose"

The parties' proposed constructions are as follows:

"dose"	
Jazz's construction	**Roxane's construction**
No construction necessary.	"a therapeutic amount of a pharmaceutical composition comprising chemically stable gamma-hydroxybutyrate in an aqueous medium resistant to microbial growth taken by a patient"

The term "dose" requires no construction. As stated above, claim construction "is not an obligatory exercise in redundancy." *U.S. Surgical Corp.*, 103 F.3d at 1568. Despite this, Roxane seeks to include redundant limitations into the otherwise readily understandable term "dose." Specifically, Roxane's construction reads in the limitations "therapeutic amount," "gamma-hydroxybutyrate," and "taken by a patient." But claim 1 of the '506 patent, in which this term appears, already specifies the amount of GHB to be administered to a patient. There is no need to reiterate these limitations by confusingly reading them into the term "dose."

Further, Roxane seeks to incorporate the limitations "chemically stable," "aqueous medium," and "resistant to microbial growth" into the claim without any support in the intrinsic evidence. As stated above, the purpose of claim construction is not to read extraneous limitations into the claims. *See McCarty*, 160 U.S. at 116 ("[W]e know of no principle of law which would authorize us to read into a claim an element which is not present . . ."). Accordingly, Roxane's proposed construction of dose should be rejected.

B. The '730 Patent Family

The '730, '106, '107, and '059 patents claim methods of using drugs such as sodium oxybate under a restricted distribution system. The parties dispute twenty-five separate terms in those patents, as discussed below.

1. "prescription drug"[12]

The parties' proposed constructions are as follows:

"prescription drug"	
Jazz's construction	**Roxane's construction**
"an FDA approved finished dosage form that may be dispensed only upon a prescription"	"a product containing an active pharmaceutical ingredient available by prescription and not based on brand manufacture"

Jazz submits that "prescription drug" should be construed as "an FDA approved finished dosage form that may be dispensed only upon a prescription." Jazz's proposed construction gives this term its plain and ordinary meaning in view of the intrinsic evidence. While the specification does not explicitly define "prescription drug," the intrinsic evidence focuses on drugs that are approved by FDA and must be prescribed. For example, it is understood from the specification of the '730 patent that "drugs are approved for specific uses by the Food and Drug Administration, and must be prescribed by a licensed physician in order to be purchased by customers." (Ex. 5 at 1:10-15.)[13] In addition, in the context of the specification of the '730 patent, the prescribed drug is a drug product that is stored pursuant to FDA regulations. (*Id.* at 3:34-38.) The FDA has defined "drug product" as synonymous with "a finished dosage form."

[12] The term "prescription drug" appears in claims 1, 2, 4, 6, 7, and 11 of the '730 patent, claims 1, 3, 5, and 7 of the '106 patent, claims 1, 2, and 3 of the '107 patent and claims 1, 3, 5-8, 10, and 14-16 of the '059 patent.

[13] The originally filed claims in the application that led to the '730 patent referred to a "sensitive drug." This was changed to "prescription drug" in an Examiner's amendment. (Ex. 16, '730 patent Notice of Allowability at JPI-00002703-2712.)

(Ex. 17, 21 C.F.R. § 314 (2002) at JPI-00358852.) Thus, by looking to the plain and ordinary meaning of the term, informed by the specification and the FDA, "prescription drug" is appropriately construed to mean "an FDA approved finished dosage form that may be dispensed only upon a prescription." Jazz's proposed construction is not contradicted by anything in the intrinsic record. Accordingly, Jazz's proposed construction should be adopted.

Roxane, on the other hand, proposes a construction that seeks to import limitations into the claims that are not supported by the intrinsic record or the plain meaning of the terms. The phrases "an active pharmaceutical ingredient available by prescription" and "not based on brand manufacture" do not appear anywhere in the specification or prosecution history. Accordingly, Roxane can point to nothing in support of adding those limitations. Indeed, the evidence cited by Roxane does not even refer to these two phrases. Thus, Roxane's proposed construction does nothing to clarify the term for the fact finder and is not helpful to the parties or this Court. Moreover, Roxane's attempt to import these phrases as claim limitations is contrary to the intrinsic evidence. Specifically, the '730 patent refers to particular FDA-approved drug products, not to active pharmaceutical ingredients in the abstract, unrelated to any particular drug product. This dooms Roxane's improper effort to import limitations into this term. *See Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1341 (Fed. Cir. 2003) (rejecting a proposed construction that would require the court to import a limitation outside the bounds of the intrinsic evidence). Roxane's proposed construction is nothing but a litigation-contrived interpretation that attempts to read Roxane's proposed ANDA product out of the scope of the claims. Accordingly, this Court should reject Roxane's proposal and adopt Jazz's construction of "prescription drug."

2. "the controls comprising"[14]

The parties' proposed constructions are as follows:

"the controls comprising"	
Jazz's construction	**Roxane's construction**
No construction necessary.	"including all of the recited controls but open to additional controls"

This term does not require construction. As discussed above, claim construction is not an obligatory exercise in redundancy. This term is ordinary English words that mean just what they say. Nothing in the intrinsic record warrants departure from its ordinary meaning.

Roxane argues that term "the controls comprising" should mean "including all of the recited controls but open to additional controls." Roxane's proposed construction ignores the context in which this term appears and would improperly read other limitations out of the claims. Specifically, the phrase "the controls comprising" appears in the following context of claim 1 of the '107 patent:

> A computerized method to control abuse of a prescription drug comprising . . . ***selecting*** with the computer processor ***multiple controls*** for distribution by said exclusive central pharmacy, the ***controls comprising*** communicating prescriptions from a physician to the central pharmacy; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; . . . .

[14] The term "the controls comprising" appears in claims 1 and 4 of the '107 patent.

(Ex. 7 at 8:35-9:25 (emphasis added).) Under Roxane's proposed construction, the requirement that all potential controls listed in the claim must be included would read the "selecting . . . multiple controls" limitation out of the claim. In other words, there is nothing to "select" if everything must be included. Roxane's attempt to strip the phrase "controls comprising" from the context in which it appears is improper. *See ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003) ("[T]he context of the surrounding words of the claim also must be considered in determining the ordinary and customary meaning of those terms."). Further, Roxane's proposed construction violates the claim construction principle that claim language should not be treated as meaningless. *See Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 951 (Fed. Cir. 2006) ("[T]he effect of adopting [the party's] proposed claim construction would be to read limitations . . . out of the claim."). Instead, the word "comprising" in this context needs no construction because it is used to indicate an open-ended list of optional controls, not controls that all must necessarily be included. Accordingly, the Court should reject Roxane's proposed construction of "the controls comprising."

3. The Remaining Terms In Dispute From the '730 Patent Family Do Not Require Further Construction

The remaining disputed terms of the claims of the '730 patent family consist of uncomplicated, non-technical language that do not require further construction:

Term	Jazz's Proposed Construction	Roxane's Proposed Construction
"exclusive"[15]	No construction necessary.	"sole"
"pharmacy"[16]	No construction necessary.	"a place where drugs are compounded or dispensed from a supply stock"
"only"[17]	No construction necessary.	"and no other"
"at"[18]	No construction necessary.	"located at"
"prescription requests"[19]	No construction necessary.	"requests to fill prescriptions"
"all"[20]	No construction necessary.	"every single one, no exceptions"
"database"[21]	No construction necessary.	"database containing all relevant data related to the distribution of the drug and the process of distributing it, including patient, physician and prescription information"
"associated"[22]	No construction necessary.	"located either at or

[15] The term "exclusive" appears in claims 1-3 and 7-11 of the '730 patent, claims 1-8 of the '106 patent, claims 1 and 4 of the '107 patent and claims 1, 2, 6, 7, 9, 10, and 12-15 of the '059 patent.

[16] The term "pharmacy" appears in claims 1-3 and 7-11 of the '730 patent, claims 1, 3, 5, and 7 of the '106 patent, claims 1, 2, and 4-5 of the '107 patent and claims 1, 2, and 6-16 of the '059 patent.

[17] The term "only" appears in claims 1, 2, and 7-11 of the '730 patent, claims 1, 3, 5, and 7 of the '106 patent, claims 1 and 4 of the '107 patent and claims 1, 6, 9 and 12-14 of the '059 patent.

[18] The term "at" appears in claims 1, 2, and 7-11 of the '730 patent, claims 1 and 4 of the '107 patent and claims 1, 6, 9, and 12-14 of the '059 patent.

[19] The term "prescription requests" appears in claims 1, 2, and 7-11 of the '730 patent, claims 1 and 4 of the '107 patent and claims 1, 6, 9, and 12-14 of the '059 patent.

[20] The term "all" appears in claims 1, 2, and 7-11 of the '730 patent, claims 1, 3, 5, and 7 of the '106 patent, claims 1 and 4 of the '107 patent and claims 1, 6, 9, 13, and 14 of the '059 patent.

[21] The term "database" appears in claims 1, 3, and 7-11 of the '730 patent, claims 1, 3, and 5-7 of the '106 patent, claims 1 and 4 of the '107 patent and claims 1, 2, 6, 9, and 12-14 of the '059 patent.

[22] The term "associated" appears in claims 1 and 2 of the '730 patent, claims 1, 3, and 7 of the '106 patent, and claim 1 of the '059 patent.

Term	Jazz's Proposed Construction	Roxane's Proposed Construction
		remote from, but not both"
"control"[23]	No construction necessary.	"write accessibility"
"prescriptions . . . are processed"; "processing . . . prescriptions"[24]	No construction necessary.	"all actions from the receipt of the prescription for the prescription drug through filling of the prescription in a form suitable for providing to the patient"
"confirming . . . patient"[25]	No construction necessary.	"contacting the patient and the patient responding"
"verifying"[26]	No construction necessary.	"contacting another source for affirming"
". . . to . . . patient"[27]	No construction necessary.	"to the patient in a dispensed form"
"dispensed"[28]	No construction necessary.	"prepared in a form suitable for providing to an individual patient"
"therapeutic"[29]	No construction necessary.	"only for approved on-label indications"

[23] The term "control" appears in claims 1, 2, and 7-11 of the '730 patent, claims 1, 6, 9, and 12-14 of the '059 patent.

[24] The terms "prescriptions . . . are processed" or "processing . . . prescriptions" appear in claims 1, 2, and 7-11 of the '730 patent, claims 1 and 4 of the '107 patent and claims 1, 6, 9, and 12-14 of the '059 patent.

[25] The term "confirming . . . patient" appears in claims 1, 2, and 7-11 of the '730 patent, claims 1, 3, 5, and 7 of the '106 patent, claims 1, 2, and 4 of the '107 patent and claims 1, 6, 8-14, and 16 of the '059 patent.

[26] The term "verifying" appears in claims 1-8 of the '106 patent and claims 1, 2, and 4-5 of the '107 patent.

[27] The term ". . . to . . . patient" appears in claims 1, 2, 9, and 10 of the '730 patent, claims 1, 3, 5, and 7 of the '106 patent and claims 1, 6, 7, 9, 10, and 12-15 of the '059 patent.

[28] The term "dispensed" appears in claims 7, 10, and 15 of the '059 patent.

[29] The term "therapeutic" appears in claims 1, 3, 5, and 7 of the '106 patent.

Term	Jazz's Proposed Construction	Roxane's Proposed Construction
"computer system"[30]	No construction necessary.	"a computer system that is located at the exclusive central pharmacy"
"prescriptions . . . processed for authorization"[31]	No construction necessary.	"all actions from receipt of the prescription for the prescription drug up to but not including the filling of the prescription"
"selecting . . . multiple controls"; "places controls"[32]	No construction necessary.	"deciding to select more than one control"
"controls selected from the group consisting of"[33]	No construction necessary.	"selected from the group consisting of the listed controls and no others"
"shipping"; "shipment"[34]	No construction necessary.	"sending of the prescription drug in dispensed form by carrier"
"maintains"[35]	No construction necessary.	"has write access to"
"a separate database"[36]	No construction necessary.	"a database other than the exclusive central database"
"making the	No construction necessary.	"the database includes

[30] The term "computer system" appears in claims 1-5, 7, and 8 of the '106 patent.

[31] The term "prescriptions . . . processed for authorization" appears in claims 1, 3, 5, and 7 of the '106 patent.

[32] The terms "selecting . . . multiple controls" and "places controls" appear in claims 1, 3, 5, and 7 of the '106 patent, claims 1, 2, and 4-5 of the '107 patent and claims 8, 11, and 16 of the '059 patent.

[33] The term "controls selected from the group consisting of" appears in claims 1, 3, 5, and 7 of the '106 patent and claims 8, 11, and 16 of the '059 patent.

[34] The terms "shipping" and "shipment" appear in claims 1, 3, 5, and 7 of the '106 patent and claims 1 and 4 of the '107 patent.

[35] The term "maintains" appears in claims 1 and 4 of the '107 patent.

[36] The term "a separate database" appears in claims 3 and 6 of the '107 patent.

Term	Jazz's Proposed Construction	Roxane's Proposed Construction
database available to the DEA for checking . . . for cash payments and for inappropriate questions"[37]		fields designated for cash payments and for inappropriate questions and the DEA can access the database to check for such payments and questions"

These terms do not require construction. As discussed above, claim construction is not an obligatory exercise in redundancy. These terms are ordinary English words that mean just what they say. Nothing in the intrinsic record warrants departure from their well-understood meanings.

For many of these claim terms, Roxane seeks to import limitations into the claims that cannot be found in the patent specification, file histories, or in any of Roxane's extrinsic evidence. Roxane appears to be attempting to add unsupported limitations to the claims to avoid infringement. This effort to engraft extraneous limitations into the above terms should be rejected. *See Decisioning.com*, 527 F.3d at 1312. Rather, these terms are well understood and require no further construction. Accordingly, Roxane's proposed constructions should be rejected.

V. CONCLUSION

For the foregoing reasons, Jazz respectfully requests that the Court adopt its proposed definitions of the disputed claim terms.

[37] The term "making the database available to the DEA for checking . . . for cash payments and for inappropriate questions" appears in claims 1, 3, 5, and 7 of the '106 patent and claims 1 and 4 of the '107 patent.

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **v.** **ROXANE LABORATORIES, INC.,** **Defendant.**	**Civil Action No. 10-6108 (ES)(CLW)** **(Filed Electronically)**

JAZZ PHARMACEUTICALS, INC.'S RESPONSIVE *MARKMAN* BRIEF

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Plaintiff Jazz Pharmaceuticals, Inc. ("Jazz") submits this responsive brief in support of its proposed constructions of the disputed terms of United States Patent Nos. 6,472,431 (the "'431 patent"), 6,780,889 (the "'889 patent"), 7,262,219 (the "'219 patent") and 7,851,506 (the "'506 patent") (collectively, the "'431 patent family"), and 7,668,730 (the "'730 patent"), 7,765,106 (the "'106 patent"), 7,765,107 (the "'107 patent") and 7,895,059 (the "'059 patent") (collectively, the "'730 patent family") owned by Jazz (collectively, "the patents-in-suit").[1]

I. INTRODUCTION

Roxane's proposed constructions violate a wide range of bedrock principles of claim construction. For example, in its zeal to avoid infringement, Roxane seeks to read examples from the specifications of the patents-in-suit into the claims as limitations. This violates Federal Circuit precedent against encumbering the claims with such extraneous limitations. Roxane also makes up limitations out of thin air that are completely at odds with the intrinsic evidence. This practice is, of course, prohibited by binding case law holding that limitations should never be read into patent claims absent a clear and unequivocal disclaimer of claim scope. In other instances, Roxane insists that the patentees acted as their own lexicographers to explicitly define terms, even where Roxane's proposed constructions do not use the actual language used in the patent specifications. For other terms, Roxane ignores statements made before the Patent and Trademark Office ("PTO") during prosecution of the patents-in-suit that clarify the scope of the claims. Finally, for the majority of the claim terms from the '730 patent family, Roxane takes plain-English words with readily understandable meanings and proposes baseless constructions designed only to further Roxane's noninfringement position. In light of the foregoing, and for the reasons discussed herein, the Court should reject Roxane's proposed constructions.

[1] Exs. 1-17 herein refer to the exhibits to the Declaration of Gabriel P. Brier submitted in support of Jazz's Opening *Markman* Brief. *See* D.I. 80-1 through 80-6. Exs. 18-20 refer to the exhibits to the Supplemental Declaration of Gabriel P. Brier submitted herewith.

II. ARGUMENT

A. The '431 Patent Family

Roxane's proposed constructions for the disputed terms in the '431 patent family violate several tenets of claim construction. For example, Roxane improperly seeks to limit the full scope of several claim terms by importing limitations from the examples of the patents. When the patent's examples are not limiting enough for Roxane, it seeks to engraft completely made-up limitations onto the claims that have no basis in any of the intrinsic or extrinsic evidence. Roxane's proposed limitations consistently seek to limit the scope of the claims absent any clear and unambiguous disclaimer in the patent specifications or file histories. Roxane's proposed constructions are driven by its desire to twist the meaning of the claim terms to avoid infringement. As discussed below, Roxane's desire to avoid infringement is not a valid basis for limiting claim scope.

1. "resistant to microbial growth"

Jazz's construction	Roxane's construction
"the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles"	"formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days, ***including but not limited to*** formulations containing greater than about 150 mg/ml GHB to GHB's maximal solubility in an aqueous medium"

Roxane insists that its proposed construction of this term is correct because "the exact language contained in Roxane's proposed construction" is allegedly the patentees' lexicography. *See* D.I. 77 at 3. This is false. Roxane's construction includes the extraneous phrase "including

but not limited to formulations containing greater than about 150 mg/ml GHB to GHB's maximal solubility in an aqueous medium." This phrase is ***not*** part of the sentence Roxane relies upon as "lexicography," but instead paraphrases from an example located later in the specification.[2] (*See, e.g.*, Ex. 1 at 11:15-26; *id.* at 20:5-10.) Thus, since the phrase is not part of the "exact language" the parties rely upon as lexicography, Roxane's proposed construction fails under its own reasoning.[3] Moreover, as discussed in Jazz's opening brief, Roxane's extraneous phrase starts with the language "including but not limited to," which means that it is a nonlimiting example that should not be part of a claim construction. *See* D.I. 80 at 6-7.

2. "salt"

Jazz's construction	Roxane's construction
"a compound formed by the interaction of an acid and a base"	"a compound formed by the interaction of an acid and a base, ***the hydrogen atoms of the acid being replaced by the positive ion of the base***"

Roxane makes two false and misleading arguments as to why the Court should adopt its proposed construction. *First*, Roxane argues that its proposed construction is the patentee's lexicography. *See* D.I. 77 at 4. This is false. As explained in Jazz's opening brief, the first portion of Roxane's proposed construction, "a compound formed by the interaction of an acid and a base," is the patentee's lexicography. *See* D.I. 80 at 10. The parties agree on this portion. The second portion of Roxane's construction seeks to add the following limitation to the claims: "the hydrogen atoms of the acid being replaced by the positive ion of the base." This is an

[2] The other difference between the parties' constructions concerns the description of the U.S. Pharmacopeia standard in Roxane's proposed construction. As discussed in Jazz's opening brief, this adds nothing to Jazz's proposed construction since it is merely a recitation of the U.S. Pharmacopeia standard. *See* D.I. 80 at 6.

[3] In its opening *Markman* brief, Roxane provides no support for the phrase "including but not limited to formulations containing greater than about 150 mg/ml GHB to GHB's maximal solubility in an aqueous medium." Roxane should not be permitted to sandbag Jazz by belatedly proposed some purported support in its opposition *Markman* brief.

example of a salt, not a definition. The Federal Circuit has "cautioned against limiting the claimed invention to preferred embodiments or specific examples in the specification." *Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 805 F.2d 1558, 1563 (Fed. Cir. 1986).

Moreover, Roxane's proposed construction chooses just one of the many examples of salts from the '431 specification and incorrectly dubs it "lexicography." *See* D.I. 80 at 10. Indeed, the '431 patent specification lists various types of salts encompassed by the invention, and states that "other salts can be formed from compounds disclosed herein, or as would be known to one of ordinary skill in the art . . . ." (Ex. 1 at 7:24-27.) Thus, the specification explicitly states that "salt" is not limited to disclosed examples. Roxane's attempt to impose such a limitation should be rejected.

Second, Roxane argues that Jazz's construction is allegedly wrong because it "defies basic scientific tenets." *See* D.I. 77 at 4. Roxane is mistaken. Specifically, Roxane gives the following example:

HCl	+	NaOH	→	NaCl	+	H_2O
(an acid)		(a base)		(a salt)		(water – not a salt)

See D.I. 77 at 5. While Roxane admits this is an interaction between an acid and a base, and that it forms the salt NaCl, it argues that it does not form just a salt because one of the by-products of the reaction is water. Roxane's argument strains credulity. This reaction forms NaCl—table salt—the most recognizable salt on the planet. The fact that water is also formed is entirely irrelevant; no one of skill in the art would be misled into thinking that water is a "salt" based on Jazz's construction. By contrast, as explained in Jazz's opening brief, by limiting "salt" to just one example in the specification, Roxane's proposed construction would exclude many common salts. *See* D.I. 80 at 10.

3. "adding the gamma-hydroxybutyrate salt to the aqueous medium"

Jazz's construction	Roxane's construction
"including gamma-hydroxybutyrate in a liquid comprising more than 50% water"	"externally adding a pre-made gamma-hydroxybutyrate salt into a pre-existing aqueous medium"

Roxane's primary argument in support of its construction is that certain examples in the '431 patent "***implicitly*** define the term." *See* D.I. 77 at 5. This fails for two reasons. *First*, Roxane's proposal violates one of the most fundamental tenets of claim construction: patent examples should not be used to limit the scope of a claim term absent a clear disclaimer. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (noting "the danger of reading limitations from the specification into the claim"); *Tex. Instruments*, 805 F.2d at 1563. Here, Roxane ***admits*** that there is no explicit limitation on the term "adding" in the specification of the '431 patent. *See* D.I. 77 at 5. Thus, "adding" should retain its full scope, which means "to include as a member of a group." (*See* Ex. 9 at 13.)

Second, Roxane again erroneously attempts to limit the claim term to examples in the specification. This is improper. *See Phillips*, 415 F.3d at 1323; *Tex. Instruments*, 805 F.2d at 1563. Thus, while the specification refers to separately pouring the salt into a solution, this does not exclude adding the salt by making it from its components in a solution—a common chemical technique well known to persons of ordinary skill in the art.

Roxane also argues that its construction should be adopted because the term "adding" was allegedly inserted into the claims during prosecution to overcome a rejection based on patentability. *See* D.I. 77 at 5-6. The term "adding," however, was included as part of an Examiner's amendment in the '431 patent's Notice of Allowability. *See* D.I. 78-9 at ROXGHB002926. Roxane can point to no evidence that the term was added for a reason related

to patentability, and Roxane fails to explain how that amendment limits the scope of the term "adding." Thus, Roxane's argument does not support its constrained construction.

Roxane's opening brief also includes several misguided arguments as to why Jazz's construction is allegedly wrong. Roxane first argues that Jazz's construction is somehow "contrary to claim language" because it allows for the salt components to be formed in an aqueous medium. *See* D.I. 77 at 6. Roxane fails to explain why this would be a problem. As discussed above, a salt can be added by reacting its components in solution. Roxane next argues that Jazz's construction is wrong because a salt is not a salt when it is in solution. *See* D.I. 77 at 6. This is incorrect, as anyone who drinks a salty liquid can attest. In fact, the claims themselves call for adjusting the concentration of "the gamma-hydroxybutyrate salt in the aqueous medium"—in other words, the claims explicitly reference a "salt" existing in a solution. (*See* Ex. 1 at 70:7-9.) Finally, Roxane argues that Jazz "ignores the patent teachings." D.I. 77 at 6. Not so. As discussed above, while Roxane's construction improperly limits the claims to examples, Jazz's construction gives the claims their full scope. Accordingly, this Court should adopt Jazz's construction of "adding the gamma-hydroxybutyrate salt to the aqueous medium."

4. "about"

Jazz's construction	Roxane's construction
"reasonably close to"	"20% of the number modified in the appropriate direction(s)"

Roxane once again argues that its construction adopts the patentees' lexicography. *See* D.I. 77 at 6. And once again, Roxane is mistaken. As an initial matter, contrary to Roxane's representation to the Court, the phrase "20% of the number modified in the appropriate

direction(s)" ***appears nowhere*** in the specification of the '431 patent.[4] This ends Roxane's lexicography argument.

Indeed, here, instead of acting as lexicographers, the patentees used the word "generally" when describing parameters for the term "about." (Ex. 1 at 4:9-10.) The use of the word "generally" means that strict numerical parameters should not be applied to the term "about" in all circumstances. Accordingly, the inventors' use of the term "about" does not support applying a strict 20% numerical limitation. Indeed, if the patentee had meant to include a 20% limitation, or if the Examiner had required such specificity, then the claim would have stated "exactly" instead of "about." As explained in Jazz's opening brief, such a limitation would be inconsistent with the use of "about" to describe the various dosage amounts and pHs that patentees considered within the scope of their inventions. *See* D.I. 80 at 12-13.

Roxane also argues that Jazz's construction will leave interpretation of this term for another day. *See* D.I. 77 at 7. Roxane is incorrect. Jazz's construction of "reasonably close to" gives the disputed claim term its full scope and is consistent with how that term is used in the specification in accordance with Federal Circuit precedent. *See, e.g., Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995) (holding that "about" does not have a universal meaning in patent claims but depends upon the fact of a particular case). Indeed, the Federal Circuit has previously construed "about" to mean "approximately" without including some specific numeric range. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1369 (Fed. Cir. 2005). Roxane's construction, on the other hand, represents an improper attempt to import a limitation into the claim without any valid basis for doing so. *See, e.g., Decisioning.com, Inc. v. Federated Dep't Stores, Inc.*, 527 F.3d 1300, 1312 (Fed. Cir. 2008)

[4] While Roxane relies on a statement in the specification that "about" "generally means within about 10-20%," its proposed construction reads "generally" and "10%" out of the claims.

("Engrafting the claims with these limitations produces anomalous results, not supported by the specification or the claims themselves."). Accordingly, this Court should reject Roxane's construction of "about" and adopt Jazz's proposed construction.

5. "does not contain a preservative"; "free of preservative"

Jazz's construction	Roxane's construction
"free of conventional exogenous substances that are added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action"	"does not contain any substance added to inhibit chemical change or microbial action"

Roxane accuses Jazz of baselessly importing the words "conventional" and "exogenous" into this construction. *See* D.I. 77 at 7-8. Roxane ignores that Jazz included these words in its proposed construction because the patentees clarified the terms during prosecution. There, the patentees explicitly described the invention as "a solution of GHB salt that is resistant to microbial growth without the need to add ***exogenous*** preservatives." (Ex. 12 at JPI-663 (emphasis added).) This was not an isolated incident. Rather, the patentees repeatedly explained that their invention referred to GHB solutions that did not require conventional preservatives. (*See* Ex. 11 at JPI-644-5 ("no ***conventional*** preservatives need be used" (emphasis added)); Ex. 10 at JPI-627-8 (similar).) Thus, during prosecution, the patentees clearly and unambiguously limited the scope of these claim terms through explicit statements in which they described their invention to the PTO. Jazz's construction is supported by these explicit statements.

Roxane again resurrects its lexicography argument to defend its position. *See* D.I. 77 at 8. Roxane ignores, however, the clear statements in the prosecution history that further define the meaning of those terms. Thus, Roxane's lexicography argument does not help its case.

Further, as stated in Jazz's opening *Markman* brief, Roxane's proposed construction is part of a misguided attempt to construe the claims so that GHB itself could be deemed a

preservative. *See* D.I. 80 at 15-16. Indeed, Roxane would construe the claims to require a solution containing GHB that is also free of GHB. Such a litigation-contrived, nonsensical construction does not merit consideration. Instead, when the patentees referred to preservatives in the specification, they described conventional, exogenous preservatives, such as xylitol and sodium benzoate, that can be added to the GHB solution. (*See* Ex. 1 at 7:42-62.)

In sum, the intrinsic record establishes that when the patentees referred to being "free of preservatives," they meant that the GHB solutions claimed are free of conventional, exogenous substances other than GHB itself. Thus, Roxane's proposed construction must be rejected.

6. "pH-adjusting agent"

Jazz's construction	Roxane's construction
No construction necessary.	"an agent, which is an acid or base, directly added primarily to alter the pH"

Roxane again seeks to import limitations into the claims that are not supported by the intrinsic evidence. As an initial matter, Roxane argues that the use of "***said*** pH-adjusting agent" in claim 6 means that the term must be "construed in connection with claim 1." *See* D.I. 77 at 8 (emphasis added). This cuts against Roxane's construction. Specifically, claim 1 recites "adjusting the pH of the medium to a final pH of about 6 to about 10 . . . ." (Ex. 1 at 70:5-12.) The use of "adjusting the pH" in claim 1 does not include any of Roxane's baseless limitations of (1) ***an acid or base***; (2) ***directly added***; and (3) ***primarily*** to alter the pH. In other words, claim 1 encompasses anything that somehow adjusts the pH. Thus, Roxane's argument confirms that its own proposed construction of "pH-adjusting agent" cannot be correct.[5]

[5] In any event, the lack of antecedent basis would not render claim 6 invalid as suggested by Roxane. Instead, the claim is valid so long as the scope of the claim is ascertainable to a person of skill in the art. *See Energizer Holdings, Inc. v. Int'l Trade Comm'n*, 435 F.3d 1366, 1370-71 (Fed. Cir. 2006) (finding that a claim term lacking antecedent basis was not invalid because its meaning was reasonably ascertainable in context).

Roxane also attempts to read examples from the specification into "pH-adjusting agent." *See* D.I. 77 at 8-9. As stated above, it is improper to read limitations into the claims from the examples absent a clear disclaimer by the patentee. *See Phillips*, 415 F.3d at 1323 (noting "the danger of reading limitations from the specification into the claim"); *Tex. Instruments*, 805 F.2d at 1563 ("This court has cautioned against limiting the claimed invention to preferred embodiments or specific examples in the specification."). Here, Roxane can identify no clear disclaimer of claim scope that would limit the term "pH-adjusting agent" to an acid or a base. *See Cordis Corp. v. Boston Scientific Corp.*, 561 F.3d 1319, 1329 (Fed. Cir. 2009) (holding that a narrowing construction requires a clear and unmistakable disclaimer of claim scope). Nor can Roxane identify any reason to import the words "directly added" and "primarily" into this term. Accordingly, this Court should reject Roxane's proposed construction.

There is nothing ambiguous about the term "pH-adjusting agent," and there is nothing in the intrinsic record that changes its readily understood meaning. Roxane has failed to rebut the "heavy presumption" that the term retains its "ordinary and customary meaning." *See Elbex Video, Ltd. v. Sensormatic Elecs. Corp.*, 508 F.3d 1366, 1371 (Fed. Cir. 2007). Therefore, this term does not require construction.

7. "organic acid"

Jazz's construction	Roxane's construction
"a substance containing one or more carbon atoms that is capable of yielding a proton (hydrogen ion) in aqueous solution, turning blue litmus paper red in aqueous solutions, ionizing in solution to yield the positive ion of the solvent, reacting with bases to form salts, or accepting electrons in an acid-base reaction"	"an acid containing at least one carbon atom that directly acidifies a solution"

Here, it appears that Roxane has simply made up a definition that it believes will aid its noninfringement position. The phrase "directly acidifies a solution" is not lexicography. It is not the full scope of the ordinary meaning. It is not even derived from examples in the specification or language in the prosecution history. Rather, Roxane seems to be arguing that because there are organic acids named in the specification, when those organic acids are directly added to a solution, they will function to make the solution more acidic. *See* D.I. 77 at 9. Roxane, however, provides no basis for this contrived attorney argument.[6]

Roxane accuses Jazz of importing limitations into its proposed construction of "organic acid." D.I. 77 at 10. Jazz has done no such thing. In fact, Jazz has done the exact opposite by incorporating into its proposed constructions the standard definitions of "acid" to give the term "organic acid" the full scope of its ordinary meaning. Indeed, Roxane's limited construction is encompassed within Jazz's proposed construction. It is well known in chemistry that acids function in other ways besides merely to "acidify," as Roxane would limit this term. Instead, as described by the technical treatises cited in Jazz's opening *Markman* brief, an acid is a substance capable either donating a proton in solution, turning blue litmus paper red, ionizing in solution, reacting with a base to form a salt, or accepting electrons in an acid-base reaction. (*See, e.g.*, Ex. 14 at 217-221; Ex. 15 at 19.) Such technical dictionaries can be helpful towards understanding how a term would be understood by a person of ordinary skill in the art, so long as they do not contradict the teachings of the patent. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584 n.6 (Fed. Cir. 1996) (noting that "technical treatises . . . are worthy of special note"). Only the "yielding a proton" and "ionizing in solution" portions of the definition of "acid" arguably go

[6] Again, to the extent that Roxane attempts to introduce a new justification for its proposed construction in its opposition brief, that argument should be stricken as sandbagging.

towards acidifying. Therefore, Roxane's proposed definition is improperly narrower than the full scope of this disputed claim term's ordinary and customary meaning.

Also, to define "acid" to mean "acidify" would be circular and add nothing towards understanding the scope of the term. Instead of using Roxane's narrow, circular construction, this Court should adopt Jazz's proposed construction of "organic acid."

8. "wherein . . . is . . . "

Jazz's construction	Roxane's construction
No construction necessary.	"one of the listed components and no others"

Roxane cites the Manual of Patent Examining Procedure ("MPEP") in support of its proposed construction. *See* D.I. 77 at 10. Yet Roxane fails to explain why the parties must resort to the PTO's procedural guidelines to understand this clear and unambiguous phrase. There is nothing about this term that renders it difficult to understand on its face. If anything, Roxane's attempt to rephrase this term only renders it less clear.

Also, Roxane cannot cite to the MPEP or any other source for its gratuitous use of the phrase "and no others." This is yet another example of Roxane seeking to import limitations into a claim term without any basis for doing so. As discussed above at length, this is improper. *See Cordis*, 561 F.3d at 1329 (Fed. Cir. 2009). Accordingly, this Court should reject Roxane's proposed definition because this term does not require construction.

9. "dose"

Jazz's construction	Roxane's construction
No construction necessary.	"a therapeutic amount of a pharmaceutical composition comprising chemically stable gamma-hydroxybutyrate in an aqueous medium resistant to microbial growth taken by a patient"

Roxane concedes that the term "dose" is not given any specialized meaning in the '506 patent. *See* D.I. 77 at 11. Nevertheless, Roxane still insists that the term requires construction because the '506 patent allegedly "consistently discusses" the term in the context of administering GHB to a patient. It is not clear why Roxane feels the need to clarify that "dose" refers to GHB taken by a patient when the very claim in which this term appears separately requires administering GHB to a patient. (*See* Ex. 4 at 72:19-33.) Rather than clarifying the meaning of "dose"—a term that requires no clarification—Roxane seeks to import unnecessarily redundant limitations into the claim.

Roxane also attempts to read in the phrases "chemically stable," "aqueous medium," and "resistant to microbial growth." Those limitations, however, are made from whole cloth. Yet again, Roxane seeks to narrow the meaning of a readily understandable claim term without any basis in the intrinsic evidence. Again, this is improper.

Finally, Roxane attempts to rely on a dictionary definition to support its construction. *See* D.I. 77 at 11. But Roxane's dictionary merely reiterates that a dose is the amount of drug taken by a patient. Again, the claim already requires administering the drug to a patient, so it is difficult to see what Roxane's proposed construction adds to this easily understood term besides extraneous, unsupported limitations. Accordingly, this Court should reject Roxane's proposed construction. The term "dose" is readily understandable and requires no construction.

B. The '730 Patent Family

Before addressing each of its proposed claim constructions for the disputed terms in the '730 patent family, Roxane provides a lengthy but misguided description of the prosecution history. Specifically, Roxane points to two claim amendments made during prosecution and asserts that they "inform[] the claim constructions for all the terms in the '730 patent family." D.I. 77 at 12. Roxane follows this assertion with several bald, conclusory allegations about what

the disputed terms "must" mean, despite failing to provide any actual connection between the claim amendments and "all the terms in the '730 patent family."[7] *See id.*

In other words, Roxane seeks to wield the prosecution history as a magic wand that it can wave over all of the disputed claim terms to convert their plain and ordinary meanings into Roxane's proposed constructions. Of course, Roxane ignores that "[a]bsent a clear disavowal or contrary definition in the specification or the prosecution history, the patentee is entitled to the full scope of its claim language." *Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1358 (Fed. Cir. 2004). To narrow the plain language of a claim, a "disclaimer must be clear and unmistakable, and unclear prosecution history cannot be used to limit claims." *Cordis*, 561 F.3d at 1329 (Fed. Cir. 2009) (internal quotations omitted). Here, as discussed below in the context of the disputed claim terms, there is no such disclaimer.

Moreover, the majority of the disputed terms—ordinary words like "pharmacy," "only," "at," "all," and "dispensed"—do not require construction. They are not complicated or technical in nature, and have simple meanings apparent to persons of ordinary skill in the art. The law with respect to those terms is equally simple: "[O]rdinary, simple English words whose meaning is clear and unquestionable," absent any indication that their use in a particular context changes their meaning, are construed to "mean exactly what they say." *Chef Am., Inc. v. Lamb-Weston,*

[7] For example, after baldly alleging what the claims "must" require in light of the prosecution history, Roxane argues that "[i]t would be contrary to the patent's teachings and applicants' representations to the Patent Office to construe the claims to include a situation where the exclusive central pharmacy sends a bulk stock to another pharmacy to keep as inventory for later dispensing to a patient." D.I. 77 at 12. But several claims of the patents-in-suit recite precisely such a "situation." (*See, e.g.*, Ex. 6 at 9:22-23 ("shipping to another pharmacy for delivery"); *id.* at 10:39-40 (same); Ex. 8 at 9:52-55 ("7. The computerized method of claim 6, wherein providing the prescription drug to the patient comprises the central pharmacy authorizing the prescription drug to be dispensed to the patient by another pharmacy.").) This undermines Roxane's prosecution-history argument.

Inc., 358 F.3d 1371, 1373 (Fed. Cir. 2004). For these terms, no construction is necessary because the ordinary English words in the claims mean exactly what they say.

For the remaining few of these terms, Roxane has proposed litigation-contrived constructions that are unsupported by any intrinsic or extrinsic evidence, and that improperly seek to add unsupported limitations to the claims or to deny the claims their full scope. This is improper. Accordingly, this Court should reject Roxane's proposed constructions.

1. "prescription drug"

Jazz's construction	Roxane's construction
"an FDA approved finished dosage form that may be dispensed only upon a prescription"	"a product containing an active pharmaceutical ingredient available by prescription and not based on brand manufacture"

Roxane's construction is driven not by the intrinsic evidence, but by its noninfringement position. Here, Roxane is trying to argue that its ANDA product and Jazz's Xyrem® product are the same "prescription drug" by defining that term by active ingredient. This would ostensibly help Roxane's argument that its proposed distribution system would not meet the "exclusive central pharmacy" limitation of the claims. However, as discussed below and in Jazz's opening brief, Roxane's zeal to support its noninfringement position has caused it to completely disregard established canons of claim construction.

Roxane disagrees with Jazz's construction for three reasons. *See* D.I. 77 at 13-14. *First*, Roxane argues that because the '730 patent identifies sodium oxybate as "one example" of a "sensitive drug," the definition of "prescription drug" must be limited to "a product containing an active pharmaceutical ingredient available by prescription and not based on brand manufacture." *Id.* at 13. Roxane ignores that it is improper to read examples into the claims. *See Tex. Instruments*, 805 F.2d at 1563 ("This court has cautioned against limiting the claimed

invention to preferred embodiments or specific examples in the specification."). Thus, Roxane's first argument lacks merit.

Second, Roxane argues that because Jazz has filed a continuation application that specifically claims a prescription drug based on its manufacturer or trademark, that the term "prescription drug" ***must*** mean something different in the patents-in-suit. D.I. 77 at 13. In other words, Roxane would have this Court believe that later claims in a different patent application that is not part of the intrinsic record somehow define the scope of the claims at issue here. They do not. In fact, "two claims with different terminology can define the exact same subject matter." *Curtiss-Wright Flow Control Corp. v. Velan, Inc.*, 438 F.3d 1374, 1380 (Fed. Cir. 2006). The claims are defined in the context of the patent in which they appear, not in the context of another pending patent application.

Third, Roxane takes issue with Jazz's inclusion of the phrase "FDA approved" because some prescription drugs have been on the market since before the FDA began approving drugs. D.I. 77 at 13-14. This makes no sense. In the United States, all drug prescription drugs must be approved before they can be sold. Indeed, Roxane's alleged counter-examples are only active ingredients, not prescription drugs. Roxane also ignores the explicit disclosures of the '730 patent, which explain that prescription drugs "are approved for specific uses by the Food and Drug Administration . . . ." (Ex. 5 at 1:12-14.) Notably, Roxane relies on this exact language from the specification in arguing for its proposed construction of "therapeutic," D.I. 77 at 25, but conveniently ignores it here. Roxane cannot have it both ways. Jazz's proposed construction, including the phrase "FDA approved," gives the term "prescription drug" its plain and ordinary meaning in view of the intrinsic evidence.

For these reasons, and those stated in Jazz's opening *Markman* brief, this Court should adopt Jazz's proposed construction of "prescription drug." *See* D.I. 80 at 22-23.

2. "exclusive"

Jazz's construction	Roxane's construction
No construction necessary.	"sole"

Roxane argues that the applicants "assigned a special definition to 'exclusive'" during prosecution. *See* D.I. 77 at 14. On the contrary, the applicants argued during prosecution that the "broadest reasonable interpretation must be limited by the ***ordinary meaning*** of the word at issue," not some special definition. *See* D.I. 78-15 at Ex. L at ROXGHB004733 (emphasis added). Indeed, during prosecution, the patentees looked to an online Merriam-Webster dictionary in stating that "the term 'exclusive' means 'single' or 'sole.'" *Id.* Roxane, however, did not propose the Merriam-Webster dictionary definition, nor did it propose "single or sole." Instead, it cherry-picked a single word from the "ordinary meaning" sought by the patentees.

Thus, it is Roxane that seeks a "special definition" by insisting that the Court make unnecessary efforts to hold that the word "exclusive" should actually be swapped with the word "sole." This approach makes little sense. If the inventors wanted to say "sole," they could have easily done so. It is not this Court's task to adopt what Roxane considers to be a synonym that the inventors opted not to use when drafting their claims. Moreover, doing so accomplishes nothing but creating a confusing circle of definitions. When the time comes to analyze the term "exclusive" against the accused product and the prior art, the trier of fact—if Roxane's approach is adopted—will be left to decide what "sole" means, and will have committed an error if it reads it as anything other than "exclusive," as already stated in the claims.

3. "pharmacy"

Jazz's construction	Roxane's construction
No construction necessary.	"a place where drugs are compounded or dispensed from a supply stock"

Roxane again seeks to construe an ordinary English word. Roxane argues that the '730 patent specification and "dictionary references" agree with its proposed construction. D.I. 77 at 15. This is false. The portion of the specification cited by Roxane actually recites as follows:

> The inventory is owned by a company, and is managed by a central pharmacy, which maintains the consignment inventory. Xyrem® is distributed and dispensed through a primary and exclusive central pharmacy . . . .

D.I. 80 at 5 at 3:38-42. This is not a definition, and even if it were, it does not support Roxane's proposed construction. Indeed, it does not even mention "compounding" or any "supply stock." Roxane's dictionary is similarly unsupportive, as it too fails to refer to any "supply stock." Moreover, despite having failed to substantiate the need to construe this common, nontechnical word, Roxane cites only to a technical dictionary—"Dorland's Pocket Medical Dictionary"—that also fails to mention the phrase "supply stock." *See* D.I. 77 at 15.

Indeed, rather than making the term "pharmacy" more clear through construction, Roxane's proposal makes this ordinary English word complicated and inaccessible. For example, the term "supply stock" in Roxane's proposed construction is not from the '730 patent, nor does it have an ordinary, well-understood meaning. This defeats the purpose of claim construction. This Court should therefore reject Roxane's construction.

4. "only"

Jazz's construction	Roxane's construction
No construction necessary.	"and no other"

Yet again, Roxane seeks to construe a nontechnical term that needs no construction. Roxane cites to various portions of the '730 patent specification and prosecution history that allegedly support its construction, D.I. 77 at 15-16, but neither the specification nor the prosecution history contain the phrase "and no other." Roxane also cites to extrinsic evidence in the form of two Webster's dictionaries, but neither contains the phrase "and no other." *See* D.I. 77 at 15-16. Roxane has simply made up a construction that it likes, and alleged support where none exists. "Only" is an ordinary, well-understood word that needs no construction.

5. "at"

Jazz's construction	Roxane's construction
No construction necessary.	"located at"

Roxane again seeks to construe a nontechnical term that requires no construction. As an initial matter, Roxane's proposed construction circularly defines the term "at" by using the word "at." This is not helpful to the parties or the Court. Roxane also seeks to add the word "located" to the definition of "at." *See* D.I. 77 at 16-17. Specifically, Roxane wants to construe "at" to require that the claimed computer processor must be ***physically located*** "at" the claimed pharmacy. *Id.* As an initial matter, Roxane has admitted that the specification contemplates a computer database that is "remote from" the pharmacy in connection with its proposed construction of "associated." *See* D.I. 77 at 19-20. (*See also* Ex. 5 at 2:55-3:13; 3:46-4:6.) Thus, its proposed construction would exclude embodiments in the specification. This is improper. *See Chimie v. PPG Indus.*, 402 F.3d 1371, 1377 (Fed. Cir. 2005). Roxane's proposed construction lacks merit for this reason alone.

Roxane's construction also lacks merit because it fails to identify any disavowal of claim scope that supports its proposed limiting of "at" to "located at." Any such narrowing requires a

clear and unmistakable disclaimer of claim scope. *See Cordis*, 561 F.3d at 1329. Here, no such disclaimer exists. Roxane's construction fails for this additional reason.

[redacted] For these reasons, this Court should reject Roxane's attempt to construe this ordinary, nontechnical term.

6. "prescription requests"

Jazz's construction	Roxane's construction
No construction necessary.	"requests to fill prescriptions"

This term is composed of nothing more than ordinary, nontechnical terms, but Roxane again seeks construction. *See* D.I. 77 at 17. Here, however, Roxane's proposed construction simply rearranges the words in the term, which does nothing to clarify the meaning for the Court or the parties. Roxane also cites to dictionary definitions of "request" and "prescription," but its proposed construction does not include either definition. *Id.* In short, Roxane has failed to provide any reason to construe this term.

7. "all"

Jazz's construction	Roxane's construction
No construction necessary.	"every single one, no exceptions"

"All" does not require construction. It is an ordinary English word that means just what it says. Nothing in the intrinsic record warrants departure from its well-understood meaning. Nevertheless, Roxane argues that construction is proper because the inventors amended the claims to add the word "all" during prosecution. *See* D.I. 77 at 18. The addition of the word "all," however, has nothing to do with Roxane's proposed construction. Indeed, the inventors

did not ascribe any special meaning to "all," or use it in a manner inconsistent with its ordinary meaning to one of skill in the art, nor does Roxane allege that they did.

While Roxane lists a string of seven citations to the record, not one of these supports Roxane's proposed construction, "every single one, no exceptions." Similarly, Roxane relies upon a dictionary that defines "all" as "every," not as "every single one, no exceptions." *See* D.I. 77 at 18. Accordingly, Roxane has not provided any evidence to support the need for any construction, let alone its proposed construction. This Court should reject Roxane's proposal.

8. "database"

Jazz's construction	Roxane's construction
No construction necessary.	"database containing all relevant data related to the distribution of the drug and the process of distributing it, including patient, physician and prescription information"

Roxane argues that Board of Patent Appeals "found that applicants acted as their own lexicographers with respect to this term . . . ." D.I. 77 at 19. Roxane is mistaken. The portion of the prosecution history that Roxane relies upon states as follows:

> Given its ordinary and customary meaning, an "***exclusive computer database***" would mean a database exclusive of other databases in "containing all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information."

See D.I. 78-15 at Ex. L at ROXGHB004759 (emphasis added). The term discussed in this portion of the prosecution history is "exclusive computer database," not "database," the term at issue here. Roxane's argument fails for this reason alone.

"Database" is a commonly understood term that requires no construction. Moreover, the patentees made clear that the term at issue during prosecution—"exclusive computer database"—has its "ordinary and customary meaning." *Id.* Roxane has provided no support for

construing this term at all, let alone for equating its definition with that of "exclusive computer database." This Court should therefore reject Roxane's proposed construction.

9. "associated"

Jazz's construction	Roxane's construction
No construction necessary.	"located either at or remote from, but not both"

Like so many of the terms Roxane seeks to construe, "associated" is a nontechnical term that requires no construction. Yet again, however, Roxane seeks to add narrowing limitations regarding physical location that are unsupported by the intrinsic evidence. *See* D.I. 77 at 19-20. Roxane cites to a figure and embodiments in the '730 patent specification in support of its proposed construction. *Id.* As an initial matter, Roxane's proposal—"located either at or remote from, but not both"—does not appear anywhere in the intrinsic record. Roxane simply made up some words—without any support—to read its misguided definition of "at" into the term "associated." And even if its proposal were supported by the specification—it is not—Roxane again ignores that it is improper to read embodiments into the claims. *See Tex. Instruments*, 805 F.2d at 1563. Finally, Roxane's proposed construction seeks to improperly narrow the scope of the claims without any clear and unmistakable disavowal of claim scope. *See Cordis*, 561 F.3d at 1329. This Court should reject Roxane's attempt to construe this ordinary, nontechnical term.

10. "control" 22. "maintains"[8]

	Jazz's construction	Roxane's construction
"control"	No construction necessary.	"write accessibility"
"maintains"	No construction necessary.	"has write access to"

[8] Jazz has combined its arguments for "control" and "maintains," but, for ease of reference, has retained consistency with the numbering of claim terms in Roxane's Opening *Markman* Brief.

Once again, Roxane seeks to construe nontechnical terms that require no construction. Roxane cites to a lengthy portion of the '730 patent specification—more than three full columns—that allegedly supports its proposed constructions of both terms, but nothing in the specification contains the phrase "write accessibility" or "has write access to." *See* D.I. 77 at 20 & 28. Indeed, neither "access" nor "accessibility" appears anywhere in the '730 patent or anywhere else in the intrinsic record. And Roxane fails to cite to any dictionaries or other extrinsic evidence in support of its proposed constructions of these terms.

Moreover, Roxane's proposed constructions make no sense. For example, Roxane would replace the term "control" with the words "write accessibility." This would result in the following nonsensical claim preambles in the '730 and '059 patents:

> A computerized method of distributing a prescription drug under [write accessibility] of an exclusive central pharmacy, the method comprising:

(*See, e.g.*, Ex. 5 at 8:37-39; Ex. 8 at 9:13-15.) Roxane's proposed constructions fail for this additional reason.

Finally, to the extent that Roxane argues that its constructions derive from examples in the specification, Roxane again improperly seeks to read embodiments into the claims. *See Tex. Instruments*, 805 F.2d at 1563. [redacted] Of course, there exists nothing to support a reading of "control" and "maintains" that is

limited to "write access." Roxane ignores that these terms are ordinary, well-understood words that need no construction. This Court should reject Roxane's proposals.

11. "prescriptions . . . are processed"; "processing . . . prescriptions"

Jazz's construction	Roxane's construction
No construction necessary.	"all actions from the receipt of the prescription for the prescription drug through filling of the prescription in a form suitable for providing to the patient"

Roxane again seeks to construe a term composed of nothing more than ordinary, nontechnical words. *See* D.I. 77 at 21. Here, Roxane cites to the figures and a lengthy passage of the specification—nearly two full columns—that recites various embodiments of the claimed inventions, and argues that, "[b]ecause the '730 patent describes the prescription processing as encompassing all of these steps, Roxane's construction is correct." *Id.* In other words, Roxane concedes that it seeks to read the specification into the claims. This is improper. *See Tex. Instruments*, 805 F.2d at 1563. Accordingly, this Court should reject Roxane's construction.

12. "prescriptions . . . processed for authorization"

Jazz's construction	Roxane's construction
No construction necessary.	"all actions from receipt of the prescription for the prescription drug up to but not including the filling of the prescription"

As described above in connection with the other "prescriptions" terms, Roxane's proposed construction is improper because it seeks to read the figures and embodiments from the specification into the claims. *See Tex. Instruments*, 805 F.2d at 1563. Roxane also adds an argument pertaining to claim differentiation, but misapplies the doctrine in at least three ways. *First*, claim differentiation applies to entire claims, not claim elements. *See Andersen Corp. v. Fiber Composites, LLC*, 474 F.3d 1361, 1370 (Fed. Cir. 2007) ("A further reason for not

applying the doctrine of claim differentiation in this case is that the [claims] are not otherwise identical but for the [limitations in question]."). Here, the claims in which the "prescriptions" terms appear are not identical but for those terms, so Roxane's focus on these specific claim elements is misplaced and irrelevant. *Second*, claim differentiation does not apply to claims in different patents.[9] *See Curtiss-Wright*, 438 F.3d at 1380 (defining claim differentiation as "the presumption that each claim in a patent has a different scope"). *Third*, Roxane incorrectly states that claim differentiation requires one term to be narrower than another. This is false. Rather, as the Federal Circuit has observed, "two claims with different terminology can define the exact same subject matter." *Id.* Accordingly, Roxane's claim-differentiation argument lacks merit, and its proposed construction should be rejected for this additional reason.

13. "confirming . . . patient"

Jazz's construction	Roxane's construction
No construction necessary.	"contacting the patient and the patient responding"

Roxane again seeks a tortured construction of ordinary English words. *See* D.I. 77 at 22. Here, Roxane improperly seeks to read unsupported limitations into the claims; namely "contacting the patient" and "the patient responding." Roxane provides nothing but bald, conclusory assertions that its proposed limitations are supported by the intrinsic record. *Id.* In fact, Roxane's proposed construction is unsupported by the claims, the specification, or the prosecution history, and is, therefore, improper. Moreover, Roxane's proposed construction ignores the full scope of the claim language. For example, several of the asserted claims require "confirming receipt by the patient of the prescription drug." Roxane insists that this requires "contacting the patient and the patient responding." But this is clearly not the case: if a

[9] This term appears in the claims of the '106 patent, while the other "prescriptions" terms appear in the '730, '107, and '059 patents.

pharmacist hands the drug to the patient, receipt is confirmed without "the patient responding"; if the drug is shipped directly to the patient, receipt is confirmed by tracking the shipment without "contacting the patient." As the Federal Circuit has explained, "[a]bsent a clear disavowal or contrary definition in the specification or the prosecution history, the patentee is entitled to the full scope of its claim language." *Home Diagnostics*, 381 F.3d at 1358. For these reasons, this Court should reject Roxane's construction.

14. "verifying"

Jazz's construction	Roxane's construction
No construction necessary.	"contacting another source for affirming"

Yet again, Roxane seeks construction where none is required. *See* D.I. 77 at 23. This time, Roxane argues that its construction is mandated by the doctrine of claim differentiation when compared to the "confirming . . . patient" term. As discussed above, however, Roxane does not understand that doctrine and continues to misapply it here. To recap: (1) claim differentiation applies to entire claims, not claim elements; (2) it does not apply between claims in different patents; and (3) it does not require that claims with different language be construed to have different scope. *See Andersen*, 474 F.3d at 1370; *Curtiss-Wright*, 438 F.3d at 1380.

Roxane also argues that its "another source" limitation is supported by the specification's reference to the NTIS (National Technical Information Service), and because "whenever [the patent] uses the term 'verifying,' a second source of affirmance of the act of information is required." D.I. 77 at 23. Once again, however, Roxane simply seeks to read limitations from the specification into the claims. And again, this is improper. *See Cordis*, 561 F.3d at 1329.

Moreover, Roxane seeks to substitute the inventors' choice of "verifying" with its own arbitrarily selected word, "affirming." Roxane ignores that if the inventors wanted to say

"affirming," they would have done so. They did not. Instead, they opted to use the ordinary term "verifying." To adopt Roxane's proposed construction would accomplish nothing besides creating a confusing circle of definitions. This Court should reject Roxane's construction.

15. "dispensed"

Jazz's construction	Roxane's construction
No construction necessary.	"prepared in a form suitable for providing to an individual patient"

Roxane again seeks to construe an ordinary English word that requires no construction. *See* D.I. 77 at 23-24. Roxane concedes that the claims include the phrase "dispensed to the patient," but ignores the redundancy created by reading "to an individual patient" into the definition of "dispensed." As the Federal Circuit has held, claim construction is not an "exercise in redundancy." *U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997).

Additionally, the phrase "a form suitable" is nowhere in the intrinsic or extrinsic evidence, nor does it have any ordinary meaning. Accordingly, Roxane's proposed addition of this phrase is unsupported and renders the term more confusing than "dispensed" alone.

Moreover, despite having failed to rebut the presumption that this nontechnical term is entitled to its ordinary meaning, and thus does not require construction, Roxane cites only to a medical dictionary. *See* D.I. 77 at 23. And the definition of "dispense" in Roxane's medical dictionary does not comport with the language of Roxane's proposed construction. Finally, Roxane alleges that the nontechnical dictionaries cited by Jazz support Roxane's proposal. *Id.* at 23-24. Roxane is mistaken. None of the nontechnical dictionaries cited by Jazz support Roxane's proposed "in a form suitable" or "individual patient" limitations. For these reasons, this Court should reject Roxane's attempt to construe this ordinary word.

16. ". . . to . . . patient"

Jazz's construction	Roxane's construction
No construction necessary.	"to the patient in a dispensed form"

Yet again, Roxane seeks to construe ordinary, nontechnical English words that require no construction. Roxane cites to various portions of the '730 patent specification that allegedly support its construction, D.I. 77 at 24, but the specification does not contain the phrase "in a dispensed form." Roxane next argues that its proposed construction is consistent with its definition of "dispensed," but as discussed above, that construction is also unsupported and unnecessary. Roxane has simply made up a construction that suits its purpose, and alleged support where none exists. This Court should reject Roxane's construction.

17. "shipping"; "shipment"

Jazz's construction	Roxane's construction
No construction necessary.	"sending of the prescription drug in dispensed form by carrier"

Roxane again seeks to construe nontechnical terms that require no construction. Here, Roxane cites to a few lines of the specification that refer to shipping a drug product, and seeks to read those portions of the specification into the claims. As explained above, this is improper. *See Tex. Instruments*, 805 F.2d at 1563. This Court should reject Roxane's construction.

18. "therapeutic"

Jazz's construction	Roxane's construction
No construction necessary.	"only for approved on-label indications"

As with most of the preceding terms, "therapeutic" does not require construction. It is an ordinary English word that means just what it says. Nothing in the intrinsic record warrants departure from its well-understood meaning. Indeed, there is no support whatsoever, intrinsic or

extrinsic, for Roxane's proposed construction. And the phrase "on-label indications" does not appear anywhere in the intrinsic record. Roxane has conjured this out of thin air.

Nevertheless, Roxane insists that construction is proper because the specification discusses "sensitive drugs" that are "approved for specific uses by the Food and Drug Administration." *See* D.I. 77 at 25. Jazz does not dispute that the specification discusses FDA-approved uses.[10] Roxane, however, incorrectly asserts that "the only FDA-approved indications for a drug are listed on the drug's label." *Id.* Roxane cannot seriously dispute, however, that many FDA-approved drugs possess therapeutic uses that are ***not*** listed on the drug's label. In other words, the fact that a drug is approved by the FDA for certain specific uses does not rule out the fact that physicians can prescribe the drug for whatever conditions they deem appropriate for therapeutic off-label uses. There is nothing in the intrinsic record to support reading such uses out of the scope of the term "therapeutic," yet that is precisely what Roxane seeks to do. And, of course, absent some clear and unmistakable disavowal of claim scope, the claims are entitled to their full scope. *See Cordis*, 561 F.3d at 1329. Accordingly, this Court should reject Roxane's proposed construction.

19. "computer system"

Jazz's construction	Roxane's construction
No construction necessary.	"a computer system that is located at the exclusive central pharmacy"

Roxane has not proposed a construction for this term. Instead, Roxane has taken the claim term "computer system," without defining it, and simply tagged on an unsupported physical-location limitation: "located at the exclusive central pharmacy." Roxane's proposal, however, does not provide any elucidation of the meaning of "computer system," since it

[10] In fact, as discussed above, the specification's reference to FDA-approved uses supports Jazz's construction of "prescription drug" while undermining Roxane's construction of that term.

proposes to define that term using those same exact words. This means that Roxane agrees that the actual words "computer system" do not require construction. The analysis should end here.

In any event, there is nothing in the claims, the specification, or the prosecution history to support reading a physical-location limitation into the claims. That limitation is therefore improper. *See Cordis*, 561 F.3d at 1329. Moreover, as described above, the specification explicitly contemplates remote access, rendering Roxane's limitations contrary to the intrinsic evidence. *See supra* at §§ II.B.5 & II.B.9. [redacted] Finally, to the extent that Roxane relies solely on the figures and embodiments in the specification to support its proposed construction, Roxane once again ignores that it is improper to read embodiments into the claims. *See Tex. Instruments*, 805 F.2d at 1563. This Court should reject Roxane's construction.

20. "selecting . . . multiple controls"; "places controls"

Jazz's construction	Roxane's construction
No construction necessary.	"deciding to select more than one control"

Roxane again insists that the Court construe ordinary, nontechnical English words. *See* D.I. 77 at 27. This time, Roxane argues that the plural form of a word—in this case "controls"—is not sufficient to convey its plural meaning to those of skill in the art. Rather, according to Roxane, the Court must construe the word to mean "more than one control." This is a waste of the Court's time and resources, and the Court should reject it as such.

Next, Roxane demands that the Court make unnecessary efforts to hold that the words "selecting" and "places" should actually be swapped with the word "deciding." This approach makes little sense. If the inventors wanted to say "deciding," they could have easily done so. It

is inappropriate to construe these terms using what Roxane considers to be a synonym that the inventors opted not to use when drafting their claims. Doing so accomplishes nothing besides create a confusing circle of definitions, where the trier of fact will ultimately have to decide what "deciding" means, and will have committed an error if it reads it as anything other than "selecting" and "places," as already stated in the claims. For these reasons, this Court should reject Roxane's construction.

21. "controls selected from the group consisting of"

Jazz's construction	Roxane's construction
No construction necessary.	"selected from the group consisting of the listed controls and no others"

This term does not require construction. As discussed above, claim construction is not an obligatory exercise in redundancy. This term is composed of ordinary English words that mean just what they say. Nothing in the intrinsic record warrants departure from the ordinary meaning. Ultimately, Roxane aims to construe "consisting of" so that it can contrast it with the "comprising" claim terms discussed below. Notably, however, Roxane recognizes the claim context here, and includes the preceding phrase "controls selected from the group" in its analysis of "consisting of." This is in stark contrast to Roxane's treatment of the similar claim term, "the controls comprising," for which Roxane ignores the preceding phrase "selecting with the computer processor multiple controls for distribution." In other words, Roxane includes the claim context here, where it does not impact its proposed construction, but ignores the claim context, in particular the word "selecting," where inconvenient and unsupportive of its proposed construction of "the controls comprising." Roxane's dissimilar treatment of these similar claim terms undermines its proposed constructions.

23. "the controls comprising"

Jazz's construction	Roxane's construction
No construction necessary.	"including all of the recited controls but open to additional controls"

Like the previous term, this term does not require construction. It too is composed of ordinary English words that mean just what they say. Nevertheless, Roxane argues that it should mean "including all of the recited controls but open to additional controls." *See* D.I. 77 at 28-29. Roxane ignores the context in which this term appears, namely "***selecting with the computer processor multiple controls for distribution*** . . . the controls comprising." (Ex. 7 at 8:60-62 (emphasis added).) Specifically, Roxane seeks to read the word "selecting" out of the claims. Roxane does so because its construction would make no sense if it acknowledged the presence of that word. Indeed, according to Roxane, "the plain and ordinary meaning of 'selecting' . . . ha[s] a decision component." *See* D.I. 77 at 27. Roxane's proposed construction, on the other hand, allows for no decisions; it requires that ***all*** controls listed in the claim ***must*** be included. *Id.* at 28-29. Of course, there is nothing to "select" if everything must be included.

As explained in Jazz's opening brief, Roxane's attempt to strip the phrase "controls comprising" from the context of the claims is improper, and violates the claim construction principle that claim language should not be treated as meaningless. *See* D.I. 80 at 24-25 (citing *ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003) and *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 951 (Fed. Cir. 2006). Instead, the word "comprising," in this context, needs no construction because it is used in combination with "selecting . . . multiple controls" to indicate an open-ended list of optional controls, not a list of required controls.

Roxane also seeks to rely on the prosecution history of the '107 patent in support of its proposed construction. *See* D.I. 77 at 29. Specifically, Roxane places great weight on the fact

that the claims were amended during prosecution from "consisting of" to "comprising." *Id.* Roxane misstates the record, however, when it alleges that the amendment was made to overcome a rejection. In fact, the applicants submitted more than eight pages of "Remarks" with their amendments, but they did not mention the amendment from "consisting of" to "comprising" at all, let alone in a way that supports Roxane's assertion that the amendment was made to overcome a rejection. *See* D.I. 78-17 at Ex. N at ROXGHB005269-77.

Finally, the doctrine of claim differentiation, which Roxane consistently misapplies in its brief in connection with other claim terms, actually applies here and renders Roxane's proposed construction of this term nonsensical and contrary to law. Specifically, "[u]nder the doctrine of claim differentiation, ***dependent claims are presumed to be of narrower scope than the independent claims from which they depend***." *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1242 (Fed. Cir. 2003) (emphasis added); *see also Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1334 (Fed. Cir. 2010) (same); 35 U.S.C. § 112, ¶ 4 ("[A] claim in dependent form shall contain a reference to a claim previously set forth and then specify ***a further limitation*** of the subject matter claimed.") (emphasis added). Moreover, "the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." *Phillips*, 415 F.3d at 1314-15; *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 910 (Fed. Cir. 2004).

Here, Claim 2 of the '107 patent depends from Claim 1, and adds a further limitation to Claim 1 that requires selecting 14 of the 23 controls recited in Claim 1. *See* D.I. 80 at Ex. 7 at 9:26-44. Roxane argues that Claim 1 requires all 23 of the claimed controls, including the 14 controls required in Claim 2. Roxane ignores, however, the presumption created by Claim 2, namely that the limitation of Claim 2—***14 required controls***—is not present in Claim 1. *See*

Phillips, 415 F.3d at 1314-15; *Liebel-Flarsheim*, 358 F.3d at 910. Roxane has offered nothing to rebut that presumption. It therefore controls, and dooms Roxane's proposed construction.

[redacted] This is not a reason to read words out of a claim and to adopt Roxane's tortured construction of this term.

For the foregoing reasons, and those set forth in Jazz's opening brief, this Court should reject Roxane's proposed construction of "the controls comprising."

24. "a separate database"

Jazz's construction	Roxane's construction
No construction necessary.	"a database other than the exclusive central database"

The parties' dispute regarding the term "database" is summarized above. *See supra* at § II.B.8. "Separate" is an ordinary English word that means exactly what it says. Roxane agrees to the extent that it argues that the "plain meaning of 'separate' further supports Roxane's proposed construction." *See* D.I. 77 at 29. This term is yet another example of Roxane seeking construction where none is required. The plain English words of the term speak for themselves. This Court should reject Roxane's proposal.

25. "making the database available to the DEA for checking . . . for cash payments and for inappropriate question"

Jazz's construction	Roxane's construction
No construction necessary.	"the database includes fields designated for cash payments and for inappropriate questions and the DEA can access the database to check for such payments and questions"

Once again, Roxane seeks to construe ordinary English words that require no construction. *See* D.I. 77 at 30. Moreover, Roxane's proposed construction finds no support in the intrinsic or extrinsic record. In fact, every part of Roxane's proposed construction here is made up from whole cloth, and improperly seeks to narrow the scope of the claims without any clear and unmistakable disavowal of claim scope. *See Cordis*, 561 F.3d at 1329. For example, Roxane insists that the DEA must have "access" to the database. But the claim term only requires "making the database available." This can be accomplished in many ways, including by printing out a hard copy of the relevant information from the database and sending it to the DEA. Roxane's proposed construction would improperly exclude that option from the claims. Roxane also insists that the database must "include[] fields designated for cash payments and for inappropriate questions," but again, the claims are not so limited. They simply require that the DEA be able to check for such payments and questions. This too can be accomplished in many ways, for example through the use of a general, catch-all field designed to obtain information regarding potential abuse, misuse, and diversion of the drug product. Again, however, Roxane's proposed construction would exclude this option. In the end, Roxane simply seeks the narrowest possible construction of this term to bolster its noninfringement theory. This is no reason to construe ordinary English words that require no construction. The Court should reject Roxane's proposal.

III. CONCLUSION

For the foregoing reasons, and those set forth in Jazz's Opening *Markman* Brief, Jazz respectfully requests that this Court reject Roxane's proposed constructions and adopt Jazz's proposed definitions of the disputed claim terms.

Respectfully submitted,

Dated: February 21, 2012

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **v.** **ROXANE LABORATORIES, INC.,** **Defendant.**	**Civil Action No. 10-6108 (ES)(CLW)** **Civil Action No. 11-660 (ES)(CLW)** **Civil Action No. 11-2523 (ES)(CLW)** **(Filed Electronically)**

JOINT CLAIM CONSTRUCTION AND PREHEARING STATEMENT

Plaintiff Jazz Pharmaceuticals, Inc. ("Jazz Pharmaceuticals") and Defendant Roxane Laboratories, Inc. ("Roxane") hereby submit their Joint Claim Construction and Prehearing Statement in accordance with Local Patent Rule 4.3.

I. BACKGROUND

This case arises out of Roxane's filing of ANDA No. 202-090 with the U.S. Food and Drug Administration ("FDA"), which seeks approval to market a generic version of Jazz Pharmaceuticals' XYREM® product. The active ingredient in XYREM® is sodium oxybate. Jazz Pharmaceuticals alleges, among other things, that Roxane's submission of ANDA No. 202-090 to the FDA constitutes infringement of certain claims of United States Patent Nos. 6,472,431 (the "'431 patent"), 6,780,889 (the "'889 patent"), 7,262,219 (the "'219 patent") and 7,851,506 (the "'506 patent") (collectively, the "'431 patent family"), and 7,668,730 (the "'730 patent"), 7,765,106 (the "'106 patent"), 7,765,107 (the "'107 patent") and 7,895,059 (the "'059 patent") (collectively, the "'730 patent family") owned by Jazz Pharmaceuticals (collectively, "the patents-in-suit") under 35 U.S.C. §271(e)(2). Roxane alleges, among other things, that certain of the asserted claims are invalid, not infringed, and/or improperly listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book").

Pursuant to Local Patent Rules 4.2(a)-(b), on September 21, 2011, the parties exchanged preliminary claim constructions and identified intrinsic as well as extrinsic evidence in support of their proposed preliminary constructions. Pursuant to Local Patent Rule 4.2(c), on October 17, 2011, counsel for the parties met and conferred for the purposes of narrowing the issues and preparation of the Joint Claim Construction and Prehearing Statement.

II. CONSTRUCTION OF PATENT TERMS

A. Agreed Upon Claim Constructions

Pursuant to Local Patent Rule 4.3(a), the parties identify the following phrase on which the parties agree:

Term (Patent Claims)	Definition
"another pharmacy" ('106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 4; '059 patent, claims 7-8, 10-11, 15-16)	"a pharmacy different than the exclusive central pharmacy"

B. Disputed Claim Terms

Pursuant to Local Patent Rule 4.3(b), attached hereto as Exhibit A is a series of claim charts identifying the claim terms and phrases in dispute and the parties' proposed constructions. Additionally, attached hereto as Exhibit B is a series of claim charts providing the evidence, including intrinsic and extrinsic evidence, that each party intends to rely upon either to support its proposed construction or to oppose the other party's proposed construction.

C. Claim Terms Whose Construction Will Be Most Significant

Pursuant to Local Patent Rule 4.3(c), the parties were unable to agree that there are any terms "whose construction will be most significant to the resolution of the case." Likewise, the parties were unable to agree that there are any terms "whose construction will be case or claim dispositive or substantially conducive to promoting settlement."

D. Anticipated Length of Time Necessary for the Claim Construction Hearing

Pursuant to Local Patent Rule 4.3(d), the parties anticipate that the Court will be able to conduct a hearing on the meaning of the disputed terms in less than one day.

E. Identification of Witnesses For The Claim Construction Hearing

Pursuant to Local Patent Rule 4.3(e), Jazz Pharmaceuticals has identified Dr. Jeffrey Winkler as a potential expert for the claim construction hearing to testify regarding the meaning of the disputed claim terms "organic acid," "pH-adjusting agent," "resistant to microbial growth," "salt," "adding the gamma-hydroxybutyrate salt to the aqueous medium," "about," "chemically stable," "does not contain a preservative," "free of preservatives," and "wherein .. is …" to one of ordinary skill in the art at the time of the invention in the context of the patents in rebuttal to Roxane's proposed definitions.

Roxane Laboratories, pursuant to Local Patent Rule 4.3(e), identifies Dr. Ronald Kluger as a potential expert to testify in rebuttal to Jazz Pharmaceuticals' proposed constructions of "resistant to microbial growth," "salt," "adding the gamma-hydroxybutyrate salt to the aqueous medium," "about," "chemically stable," "does not contain a preservative," "free of preservatives," "pH-adjusting agent," "organic acid," and "wherein .. is …".

Dated: October 21, 2011

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Exhibit A

Disputed Claim Terms

'431 PATENT FAMILY

Term (Patent Claims)	Jazz Pharmaceuticals' Proposed Definition	Roxane's Proposed Definition
"resistant to microbial growth" ('431 patent, claim 1; '889 patent, claim 1; '219 patent, claims 1, 4)	The formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles.	"formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days, including but not limited to formulations containing greater than about 150 mg/ml GHB to GHB's maximal solubility in an aqueous medium"
"salt" ('431 patent, claims 1-2)	A compound formed by the interaction of an acid and a base.	"a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base"
"adding the gamma-hydroxybutyrate salt to the aqueous medium" ('431 patent, claim 1)	Including gamma-hydroxybutyrate in a liquid comprising more than 50% water.	"externally adding a pre-made gamma-hydroxybutyrate salt into a pre-existing aqueous medium"
"about" ('431 patent, claims 1, 3, 5; '889 patent, claim 1; '219 patent, claims 1, 2, 4; '506 patent claim 1)	Reasonably close to.	"20% of the number modified in the appropriate direction(s)"

Exhibit A

Disputed Claim Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Proposed Definition	Roxane's Proposed Definition
"chemically stable" ('431 patent, claim 1; '889 patent, claim 1; '219 patent, claims 1, 4)	Resistant to degradation of GHB into its known or unknown decomposition elements.	"resistant to degradation of gamma-hydroxybutyrate into its known or unknown decomposition elements, including GBL"
"does not contain a preservative"; "free of preservatives" ('431 patent, claim 4; '889 patent, claim 1; '219 patent, claims 1, 4)	Free of conventional exogenous substances that are added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action.	"does not contain any substance added to inhibit chemical change or microbial action" "
"pH-adjusting agent"[1] ('431 patent, claim 6; '889 patent, claim 1; '219 patent, claims 1, 3, 4)	No construction necessary.	"an agent, which is an acid or base, directly added primarily to alter the pH"
"organic acid" ('431 patent, claim 6)	A substance containing one or more carbon atoms that is capable of yielding a proton (hydrogen ion) in aqueous solution, turning blue litmus paper red in aqueous solutions, ionizing in solution to yield the positive ion of the solvent, reacting with bases to form salts, or accepting electrons in an acid-base reaction.	"an acid containing at least one carbon atom that directly acidifies a solution"
"wherein .. is …"	No construction necessary.	"one of the listed components and

[1] Roxane maintains that the term "pH-adjusting agent" is contained within claim 1 of the '431 patent as the required antecedent basis for the use of the term in claim 6.

Exhibit A

Disputed Claim Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Proposed Definition	Roxane's Proposed Definition
('219 patent, claims 1, 3, 4)		no others"
"dose" ('506 patent, claim 1)	No construction necessary.	"a therapeutic amount of a pharmaceutical composition comprising chemically stable gamma-hydroxybutyrate in an aqueous medium resistant to microbial growth taken by a patient"

'730 PATENT FAMILY

Term (Patent Claims)	Jazz Pharmaceuticals' Proposed Definition	Roxane's Proposed Definition
"prescription drug" ('730 patent, claims 1, 2, 4, 6, 7, 11; '106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 2, 3; '059 patent, claims 1, 3, 5, 6, 7, 8, 10, 14, 15, 16)	An FDA approved finished dosage form that may be dispensed only upon a prescription.	"a product containing an active pharmaceutical ingredient available by prescription and not based on brand manufacture"
"exclusive" ('730 patent, claims 1-3, 7-11; '106 patent, claims 1-8; '107 patent, claims 1, 4; '059 patent, claims 1-2, 6, 7, 9-10, 12-15)	No construction necessary.	"sole"

Exhibit A

Disputed Claim Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Proposed Definition	Roxane's Proposed Definition
"pharmacy" ('730 patent, claims 1-3, 7-11; '106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 2, 4-5; '059 patent, claims 1, 2, 6-16)	No construction necessary.	"a place where drugs are compounded or dispensed from a supply stock"
"only" ('730 patent, claims 1-2, 7-11; '106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 12-14)	No construction necessary.	"and no other"
"at" ('730 patent, claims 1-2, 7-11; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 12-14)	No construction necessary.	"located at"
"prescription requests" ('730 patent, claims 1-2, 7-11; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 12-14)	No construction necessary.	"requests to fill prescriptions"
"all" ('730 patent, claims 1, 2, 7-11; '106 patent,	No construction necessary.	"every single one, no exceptions"

Exhibit A

Disputed Claim Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Proposed Definition	Roxane's Proposed Definition
claims 1, 3, 5, 7; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 13-14)		
"database" ('730 patent, claims 1-3, 7-11; '106 patent, claims 1, 3, 5-7; '107 patent, claims 1, 4; '059 patent, claims 1, 2, 6, 9, 12-14)	No construction necessary.	"database containing all relevant data related to the distribution of the drug and the process of distributing it, including patient, physician and prescription information"
"associated" ('730 patent, claims 1-2; '106 patent, claims 1, 3, 7; '059 patent, claim 1)	No construction necessary.	"located either at or remote from, but not both"
"control" ('730 patent, claims 7-11; '059 patent, claims 6, 9, 12-14)	No construction necessary.	"write accessibility"
"prescriptions . . . are processed"; "processing . . . prescriptions" ('730 patent, claims 1, 2, 7-11; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 12-14)	No construction necessary.	"all actions from the receipt of the prescription for the prescription drug through filling of the prescription in a form suitable for providing to the patient"
"confirming . . .	No construction necessary.	"contacting the patient and the

Exhibit A

Disputed Claim Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Proposed Definition	Roxane's Proposed Definition
patient" ('730 patent, claims 1, 2, 7-19; '106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 2, 4, 5; '059 patent, claims 1, 6, 8-14, 16)		patient responding"
"verifying" ('106 patent, claims 1-8; '107 patent claims 1-2, 4-5)	No construction necessary.	"contacting another source for affirming"
". . . to . . . patient" ('730 patent, claims 1, 2, 9-10; '106 patent, claims 1, 3, 5, 7; '059 patent, claims 1, 6, 7, 9-10, 12-15)	No construction necessary.	"to the patient in a dispensed form"
"dispensed" ('059 patent, claims 7, 10, 15)	No construction necessary.	"prepared in a form suitable for providing to an individual patient"
"therapeutic" ('106 patent, claims 1, 3, 5, 7)	No construction necessary.	"only for approved on-label indications"
"computer system" ('106 patent, claims 1-5, 7-8)	No construction necessary.	"a computer system that is located at the exclusive central pharmacy"

Exhibit A

Disputed Claim Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Proposed Definition	Roxane's Proposed Definition
"prescriptions . . . processed for authorization" ('106 patent, claims 1, 3, 5, 7)	No construction necessary.	"all actions from receipt of the prescription for the prescription drug up to but not including the filling of the prescription"
"selecting . . . multiple controls"; "places controls" ('106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 2, 4-5; '059 patent, claims 8, 11, 16)	No construction necessary.	"deciding to select more than one control"
"controls selected from the group consisting of" ('106 patent, claims 1, 3, 5, 7; '059 patent, claims 8, 11, 16)	No construction necessary.	"selected from the group consisting of the listed controls and no others"
"shipping"; "shipment" ('106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 4)	No construction necessary.	"sending of the prescription drug in dispensed form by carrier"
"maintains" ('107 patent, claims 1, 4)	No construction necessary.	"has write access to"
"the controls	No construction necessary.	"including all of the recited

Exhibit A

Disputed Claim Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Proposed Definition	Roxane's Proposed Definition
comprising" ('107 patent, claim 1, 4)		controls but open to additional controls"
"a separate database" ('107 patent, claims 3, 6)	No construction necessary.	"a database other than the exclusive central database"
"making the database available to the DEA for checking . . . for cash payments and for inappropriate questions" ('106 patent, claims 1, 3, 5, 7; '107 patent claims 1, 4)	No construction necessary.	"the database includes fields designated for cash payments and for inappropriate questions and the DEA can access the database to check for such payments and questions"

Exhibit B

Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

'431 PATENT FAMILY

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
"resistant to microbial growth" ('431 patent, claim 1; '889 patent, claim 1; '219 patent, claims 1, 4)	'431 patent at col. 3:22-31, Tables 18, 19, 20, 21, 22, 23, 24, 27; '431 file history, 8/10/01 Response at JPI-00000623, 11/29/01 Preliminary amendment at JPI-00000644-645, 3/6/02 Response at JPI-00000663-664; '889 file history, 3/18/04 Notice of Allowability at JPI-00001011; '219 file history, 2/21/07 Response at JPI-00001652. Jazz Pharmaceuticals may also rely on rebuttal expert testimony from Dr. Winkler.	'431 patent, col. 3, lns. 22-31; col. 3, lns. 37-40 Roxane may also rely on rebuttal expert testimony from Dr. Kluger.
"salt" ('431 patent, claims 1-2)	'431 patent at col. 7:2-28; '431 file history, 8/10/01 Response at JPI-00000626-628, 3/6/02 Response at JPI-00000663-666, 4/16/02 Notice of Allowability at JPI-00000673. Jazz Pharmaceuticals may also rely on rebuttal expert testimony from Dr. Winkler.	'431 patent, col. 7, lns. 2-5 Roxane may also rely on rebuttal expert testimony from Dr. Kluger.
"adding the gamma-hydroxybutyrate salt to the aqueous medium" ('431 patent, claim 1)	'431 patent at col. 3:31-40, 3:46-48, 4:10-13, 4:25-28, 8:45-49, 32:40-43, 32:48-51; '431 file history, 3/6/02 Response at JPI-00000664, 666, 4/16/02 Notice of Allowability at JPI-	'431 patent, col. 3, lns. 37-40, 46-48; col. 4, lns. 25-28; col. 8, lns. 45-49, 63-67; col. 10, lns. 14-16; col. 10, lns. 20-23; col. 10, lns. 28-29; '431 patent prosecution history,

Exhibit B

Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
	00000673; Merriam Webster's Collegiate Dictionary (10th ed.) at JPI-00358838. Jazz Pharmaceuticals may also rely on rebuttal expert testimony from Dr. Winkler.	Notice of Allowability dated April 16, 2002 at p. 2 (Examiner's Amendment) Roxane may also rely on rebuttal expert testimony from Dr. Kluger.
"about" ('431 patent, claims 1, 3, 5; '889 patent, claim 1; '219 patent, claims 1, 2, 4; '506 patent claim 1)	'431 patent at col. 4:8-9, 20:29-31, 33:1-7; '431 file history, 8/10/01 Response at JPI-00000624, 3/6/02 Response at JPI-00000666; Merriam Webster's Collegiate Dictionary (10th ed.) at JPI-00358835. Jazz Pharmaceuticals may also rely on rebuttal expert testimony from Dr. Winkler.	'431 patent, col. 4, lns. 8-9; col. 22, lns. 5-49 Roxane may also rely on rebuttal expert testimony from Dr. Kluger.
"chemically stable" ('431 patent, claim 1; '889 patent, claim 1; '219 patent, claims 1, 4)	'431 patent at col. 1:23-29, 3:18-20; '431 file history, 8/10/01 Response at JPI-00000627; '219 file history, 2/21/07 Response at JPI-00001652. Jazz Pharmaceuticals may also rely on rebuttal expert testimony from Dr. Winkler.	'431 patent, col. 2, lns. 46-49; col. 3, lns. 18-22; col. 13, lns. 2-5 Roxane may also rely on rebuttal expert testimony from Dr. Kluger.
"does not contain a preservative"; "free of preservatives"	'431 patent at col. 2:48-51, 7:42-62; '431 file history, 8/10/01 Response at JPI-00000623, 626-628),	'431 patent, col. 7, lns. 42-44 '219 patent prosecution history, Amendment dated February 21,

Exhibit B

Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
('431 patent, claim 4; '889 patent, claim 1; '219 patent, claims 1, 4)	11/29/01 Preliminary amendment at JPI-00000644-645, 3/6/02 Response at JPI-00000663, 664; '889 file history, 3/18/04 Notice of Allowability at JPI-00001011; '219 file history, 2/21/07 Response at JPI-00001652. Jazz Pharmaceuticals may also rely on rebuttal expert testimony from Dr. Winkler.	2007 at p. 4 (Remarks) Roxane may also rely on rebuttal expert testimony from Dr. Kluger.
"pH-adjusting agent" ('431 patent, claim 6; '889 patent, claim 1; '219 patent, claims 1, 3, 4)	'431 patent at col. 6:36-67, 7:4-27, 8:37-44, 8:49-50, 8:60-62, 12:59-62; '431 file history, 8/10/01 Response at JPI-00000626, 3/6/02 Response at JPI-00000663; '219 file history, 5/25/07 Notice of Allowability at JPI-00001741. Jazz Pharmaceuticals may also rely on rebuttal expert testimony from Dr. Winkler.	'431 patent, col. 6, lns. 36-39; col. 8, lns. 45-59; col. 12, lns. 50-63; '431 patent prosecution history, Notice of Allowability dated March 23, 2004 at 2 (Reasons for Allowance) Roxane may also rely on rebuttal expert testimony from Dr. Kluger.
"organic acid" ('431 patent, claim 6)	'431 patent at col. 6:63-67, 6:39-53, 7:5-11; Remington's Pharmaceutical Sciences (19th ed.) at JPI-00358844-848, McGraw-Hill Dictionary of Scientific and Technical Terms (5th ed.) at JPI-00358841. Jazz Pharmaceuticals may also rely on rebuttal expert testimony from	'431 patent, col. 6, lns. 39-51 Roxane may also rely on rebuttal expert testimony from Dr. Kluger.

Exhibit B

Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
	Dr. Winkler.	
"wherein .. is …" ('219 patent, claims 1, 3, 4)	'431 patent at col. 6:36-53; '219 file history, 5/25/07 Notice of Allowability at JPI-00001741. Jazz Pharmaceuticals may also rely on rebuttal expert testimony from Dr. Winkler.	MPEP §§ 2111.03-.04 Roxane may also rely on rebuttal expert testimony from Dr. Kluger.
"dose" ('506 patent, claim 1)	'431 patent at col. 9:32-44, 14:65-67; '506 file history, 4/2/09 Response at JPI-00010754-756, 1/11/10 Response at JPI-00010791-793. McGraw-Hill Dictionary of Scientific and Technical Terms (5th ed.) at JPI-00358882; Merriam Webster's Collegiate Dictionary (10th ed.) at JPI-00358879; Stedman's Medical Dictionary (26th Ed. 1995) at JPI-00358874.	'431 patent, col. 9, lns. 1-44 Prosecution history for United States Patent Application Serial No. 12/913,644, Preliminary Amendment dated January 10, 2011 at pp. 31-32 Merriam-Webster's Collegiate Dictionary, 10th ed., 346 (1996) defines "dose" as "the measured quantity of a therapeutic agent to be taken at one time"

'730 PATENT FAMILY

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
"prescription drug" ('730 patent, claims 1, 2, 4, 6, 7, 11; '106 patent, claims 1, 3, 5,	'730 patent at col. 1:10-15, 1:24-28, 1:38-40, 3:34-40; '730 file history, 12/31/2009 Notice of Allowance at JPI-00002703-	'730 patent, col. 1, lns. 38-42; col. 3, lns. 14-24 Prosecution history for United States Patent application Serial No.

Exhibit B

Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
7; '107 patent, claims 1, 2, 3; '059 patent, claims 1, 3, 5, 6, 7, 8, 10, 14, 15, 16)	2712; '106 file history, 3/11/2010 Response at JPI-00004420-4421; '107 file history, 3/10/2010 Notice of Allowance at JPI-00006561-6565; 21 C.F.R. § 314 (2002) at JPI-00358852.	13/013,680, claims as filed
"exclusive" ('730 patent, claims 1-3, 7-11; '106 patent, claims 1-8; '107 patent, claims 1, 4; '059 patent, claims 1-2, 6, 7, 9-10, 12-15)	'730 patent at col. 2:10-15, 3:34-45, 7:38-52, 7:65-8:3, Abstract, FIG. 7; '730 file history, 3/10/2005 Response at JPI-00002381-2382, 3/29/2006 Response at JPI-00002412, 2415, 1/17/2007 Response, at JPI-00002520-2521, 5/21/2007 Appeal Brief at JPI-00002556, 2561, 7/18/2007 Substitute Appeal Brief at JPI-00002600, 12/3/2007 Reply Brief at JPI-00002638-2639, 9/2/09 BPAI Decision at JPI-00002661, 2665; 11/2/2009 Response at JPI-00002685-2690, 12/31/2009 Notice of Allowance at JPI-00002703-2712; '107 file history, Petition to Make Special at JPI-00006450-6451, 11/3/2009 Response at JPI-00006507-6513, 3/10/2010 Notice of Allowance at JPI-00006564-6565; '059 file history, 12/21/2010 Notice of Allowance at JPI-00011582-583.	'730 patent, col. 1, lns. 38-42; col. 2, lns. 10-12; col. 3, lns. 40-45 '730 patent prosecution history, Proposed Interview Agenda filed July 31, 2006 at pp. 6-11 '730 patent prosecution history, Office Action dated October 18, 2006 at pp. 4-7 '730 patent prosecution history, Amendment filed January 17, 2007 at pp. 9-10, 13-14 '730 patent prosecution history, Advisory Action dated February 5, 2007 at p. 3 '730 patent prosecution history, Substitute Appeal Brief filed July 18, 2007 at pp. 16-23 '730 patent prosecution history, Examiner's Answer dated October 3, 2007 at pp. 4-8, 15-16 '730 patent prosecution history, Reply Brief filed December 3,

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Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
		2007 at pp. 2-3. '730 patent prosecution history, Decision on Appeal decided August 31, 2009 at pp. 5-6, 8-11 '730 patent prosecution history, Amendment filed November 2, 2009 at pp. 9-14 '730 patent prosecution history, Notice of Allowability dated December 31, 2009 at pp. 10-11 '106 patent prosecution history, Office Action dated November 17, 2009 at pp. 5-7 '106 patent prosecution history, Notice of Allowability dated April 30, 2010 at pp. 2-3 '107 patent prosecution history, Office Action dated September 14, 2009 at pp. 6-7 '107 patent prosecution history, Amendment filed November 3, 2009 at pp. 2, 4, 6-9, 12-13 '107 patent prosecution history, Notice of Allowability dated March 10, 2010 at pp. 5-6 '059 patent prosecution history, Notice of Allowability dated December 21, 2010 at pp. 2-3
"pharmacy" ('730 patent, claims 1-3, 7-11; '106 patent,	'730 patent at col. 2:10-15, 3:34-45, 7:38-52, 7:65-8:3, Abstract, FIG. 7; '730 file history, 3/10/2005	'730 patent, col. 3, lns. 35-42 Dorland's Pocket Medical Dictionary, 25th ed., p. 627 (1995)

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Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
claims 1, 3, 5, 7; '107 patent, claims 1, 2, 4-5; '059 patent, claims 1, 2, 6-16)	Response at JPI-00002381-2382, 3/29/2006 Response at JPI-00002412, 2415, 1/17/2007 Response, at JPI-00002520-2521, 5/21/2007 Appeal Brief at JPI-00002556, 2561, 7/18/2007 Substitute Appeal Brief at JPI-00002600, 12/3/2007 Reply Brief at JPI-00002638-2639, 9/2/09 BPAI Decision at JPI-00002661, 2665; 11/2/2009 Response at JPI-00002685-2690, 12/31/2009 Notice of Allowance at JPI-00002703-2712; '107 file history, Petition to Make Special at JPI-00006450-6451, 11/3/2009 Response at JPI-00006507-6513, 3/10/2010 Notice of Allowance at JPI-00006564-6565; '059 file history, 12/21/2010 Notice of Allowance at JPI-00011582-583. McGraw-Hill Dictionary of Scientific and Technical Terms (5th ed.) at JPI-00358871; Merriam Webster's Collegiate Dictionary (10th ed.) at JPI-00358868; Stedman's Medical Dictionary (26th Ed. 1995) at JPI-00358865.	defines "pharmacy" as "a place where drugs are compounded or dispensed"
"only" ('730 patent, claims 1-2, 7-11; '106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 4; '059 patent, claims 1,	'730 patent at col. 2:10-15, 3:34-45, 7:38-52, 7:65-8:3, Abstract, FIG. 7; '730 file history, 3/10/2005 Response at JPI-00002381-2382, 3/29/2006 Response at JPI-00002412, 2415, 1/17/2007 Response, at JPI-00002520-2521,	'730 patent, Figs. 2A-2C; col. 3, lns. 35-45, 62-64; col. 3, ln. 66-col. 4, ln. 1; col. 4, ln. 7-col. 5, ln. 58; col. 7, lns. 37-45 '730 patent prosecution history, Proposed Interview Agenda filed

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Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
6, 9, 12-14)	5/21/2007 Appeal Brief at JPI-00002556, 2561, 7/18/2007 Substitute Appeal Brief at JPI-00002600, 12/3/2007 Reply Brief at JPI-00002638-2639, 9/2/09 BPAI Decision at JPI-00002661, 2665; 11/2/2009 Response at JPI-00002685-2690, 12/31/2009 Notice of Allowance at JPI-00002703-2712; '107 file history, Petition to Make Special at JPI-00006450-6451, 11/3/2009 Response at JPI-00006507-6513, 3/10/2010 Notice of Allowance at JPI-00006564-6565; '059 file history, 12/21/2010 Notice of Allowance at JPI-00011582-583.	July 31, 2006 at p. 6 '730 patent prosecution history, Amendment filed August 8, 2006 at p. 2 '730 patent prosecution history, Office Action dated October 18, 2006 at pp. 2, 4 '730 patent prosecution history, Amendment filed November 2, 2009 at pp. 2-13 '730 patent prosecution history, Notice of Allowability dated December 31, 2009 at pp. 10-11 '106 patent prosecution history, Amendment filed March 11, 2010 at pp. 2, 4, 6, 8, 11-12 '106 patent prosecution history, Notice of Allowability dated April 30, 2010 at p. 2 '107 patent prosecution history, Amendment filed November 3, 2009 at pp. 2, 4, 6, 8-10 '107 patent prosecution history, Notice of Allowability dated March 10, 2010 at pp. 5, 6 '059 patent prosecution history, Notice of Allowability dated December 21, 2010 at pp. 2, 3 Webster's New Universal Unabridged Dictionary, p. 1250 (1983) defines "only" as "solely;

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Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
		no other than"
"at" ('730 patent, claims 1-2, 7-11; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 12-14)	'730 patent at col. 2:10-15, 3:34-45, 7:38-52, 7:65-8:3, Abstract, FIG. 7; '730 file history, 3/10/2005 Response at JPI-00002381-2382, 3/29/2006 Response at JPI-00002412, 2415, 1/17/2007 Response, at JPI-00002520-2521, 5/21/2007 Appeal Brief at JPI-00002556, 2561, 7/18/2007 Substitute Appeal Brief at JPI-00002600, 12/3/2007 Reply Brief at JPI-00002638-2639, 9/2/09 BPAI Decision at JPI-00002661, 2665; 11/2/2009 Response at JPI-00002685-2690, 12/31/2009 Notice of Allowance at JPI-00002703-2712; '107 file history, Petition to Make Special at JPI-00006450-6451, 11/3/2009 Response at JPI-00006507-6513, 3/10/2010 Notice of Allowance at JPI-00006564-6565; '059 file history, 12/21/2010 Notice of Allowance at JPI-00011582-583.	Webster's Ninth New Collegiate Dictionary, p. 111 (1991) defines "at" as "used as a function word to indicate presence or occurrence in, on, or near <staying ~ a hotel> <~ a party> <sick ~ heart>"
"prescription requests" ('730 patent, claims 1-2, 7-11; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 12-14)	'730 patent at col. 2:3-6, 2:28-30, 6:9-14, 6:33-37, 6:47-51, 6:64-67, 4:7-25, FIGS. 4A, 4B.	Webster's Ninth New Collegiate Dictionary, p. 1001 (1991) defines "request" as "the act or instance of asking for something" and "something asked for" Dorland's Pocket Medical Dictionary, 25th ed., p. 660 (1995) defines "prescription" as "a written directive for the preparation and

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Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
		administration of a
"all" ('730 patent, claims 1, 2, 7-11; '106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 13-14)	'730 patent at col. 2:10-15, 3:34-45, 7:38-52, 7:65-8:3, Abstract, FIG. 7; '730 file history, 3/10/2005 Response at JPI-00002381-2382, 3/29/2006 Response at JPI-00002412, 2415, 1/17/2007 Response, at JPI-00002520-2521, 5/21/2007 Appeal Brief at JPI-00002556, 2561, 7/18/2007 Substitute Appeal Brief at JPI-00002600, 12/3/2007 Reply Brief at JPI-00002638-2639, 9/2/09 BPAI Decision at JPI-00002661, 2665; 11/2/2009 Response at JPI-00002685-2690, 12/31/2009 Notice of Allowance at JPI-00002703-2712; '107 file history, Petition to Make Special at JPI-00006450-6451, 11/3/2009 Response at JPI-00006507-6513, 3/10/2010 Notice of Allowance at JPI-00006564-6565; '059 file history, 12/21/2010 Notice of Allowance at JPI-00011582-583.	'730 patent, col. 7, lns. 62-67 '730 patent prosecution history, Proposed Interview Agenda filed July 31, 2006 at p. 6 '730 patent prosecution history, Amendment filed January 17, 2007 at p. 2 '730 patent prosecution history, Examiner's Answer dated October 3, 2007 at p. 5 '730 patent prosecution history, Amendment filed November 2, 2009 at pp. 2, 7, 9-13 '730 patent prosecution history, Notice of Allowability dated December 31, 2009 at pp. 10, 11 '106 patent prosecution history, Amendment filed March 11, 2010 at pp. 2, 4, 6, 8, 11, 12 '106 patent prosecution history, Notice of Allowability dated April 30, 2010 at p. 2 '107 patent prosecution history, Amendment filed November 3, 2009 at pp. 2, 4, 6, 8, 11 '107 patent prosecution history, Notice of Allowability dated March 10, 2010 at pp. 5, 6 '059 patent prosecution history, Notice of Allowability dated

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Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
		December 21, 2010 at pp. 2, 3 Webster's Ninth New Collegiate Dictionary, pp. 70-71 (1991) defines "all" as "EVERY <~ manner of hardship>"
"database" ('730 patent, claims 1-3, 7-11; '106 patent, claims 1, 3, 5-7; '107 patent, claims 1, 4; '059 patent, claims 1, 2, 6, 9, 12-14)	'730 patent at col. 2:10-15, 3:34-45, 7:38-52, 7:65-8:3, Abstract, FIG. 7; '730 file history, 3/10/2005 Response at JPI-00002381-2382, 3/29/2006 Response at JPI-00002412, 2415, 1/17/2007 Response, at JPI-00002520-2521, 5/21/2007 Appeal Brief at JPI-00002556, 2561, 7/18/2007 Substitute Appeal Brief at JPI-00002600, 12/3/2007 Reply Brief at JPI-00002638-2639, 9/2/09 BPAI Decision at JPI-00002661, 2665; 11/2/2009 Response at JPI-00002685-2690, 12/31/2009 Notice of Allowance at JPI-00002703-2712; '107 file history, Petition to Make Special at JPI-00006450-6451, 11/3/2009 Response at JPI-00006507-6513, 3/10/2010 Notice of Allowance at JPI-00006564-6565; '059 file history, 12/21/2010 Notice of Allowance at JPI-00011582-583. McGraw-Hill Dictionary of Scientific and Technical Terms (5th ed.) at JPI-00358862; Merriam Webster's Collegiate Dictionary	'730 patent, col. 1, lns. 37-43; col. 2, lns. 10-12 '730 patent prosecution history, Decision on Appeal decided August 31, 2009 at p. 9

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Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
	(10th ed.) at JPI-00358859.	
"associated" ('730 patent, claims 1-2; '106 patent, claims 1, 3, 7; '059 patent, claim 1)	'730 patent at col. 2:10-15, 3:34-45, 7:38-52, 7:65-8:3, Abstract, FIG. 7; '730 file history, 3/10/2005 Response at JPI-00002381-2382, 3/29/2006 Response at JPI-00002412, 2415, 1/17/2007 Response, at JPI-00002520-2521, 5/21/2007 Appeal Brief at JPI-00002556, 2561, 7/18/2007 Substitute Appeal Brief at JPI-00002600, 12/3/2007 Reply Brief at JPI-00002638-2639, 9/2/09 BPAI Decision at JPI-00002661, 2665; 11/2/2009 Response at JPI-00002685-2690, 12/31/2009 Notice of Allowance at JPI-00002703-2712; '107 file history, Petition to Make Special at JPI-00006450-6451, 11/3/2009 Response at JPI-00006507-6513, 3/10/2010 Notice of Allowance at JPI-00006564-6565; '059 file history, 12/21/2010 Notice of Allowance at JPI-00011582-583.	'730 patent, Fig. 1; col. 3, ln. 46-col. 4, ln. 1
"control" ('730 patent, claims 7-11; '059 patent, claims 6, 9, 12-14)	'730 patent at col. 2:10-15, 3:34-45, 7:38-52, 7:65-8:3, Abstract, FIG. 7; '730 file history, 3/10/2005 Response at JPI-00002381-2382, 3/29/2006 Response at JPI-00002412, 2415, 1/17/2007 Response, at JPI-00002520-2521, 5/21/2007 Appeal Brief at JPI-00002556, 2561, 7/18/2007	'730 patent, Figs. 2A-2C, 4A-5; col. 4, ln. 7-col. 7, ln. 18 '730 patent prosecution history, original application filed December 17, 2002 at p. 16

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Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
	Substitute Appeal Brief at JPI-00002600, 12/3/2007 Reply Brief at JPI-00002638-2639, 9/2/09 BPAI Decision at JPI-00002661, 2665; 11/2/2009 Response at JPI-00002685-2690, 12/31/2009 Notice of Allowance at JPI-00002703-2712; '107 file history, Petition to Make Special at JPI-00006450-6451, 11/3/2009 Response at JPI-00006507-6513, 3/10/2010 Notice of Allowance at JPI-00006564-6565; '059 file history, 12/21/2010 Notice of Allowance at JPI-00011582-583.	
"prescriptions . . . are processed"; "processing . . . prescriptions" ('730 patent, claims 1, 2, 7-11; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 12-14)	'730 patent at col. 2:10-12, 5:15-26, 6:47-54, 6:58-67, FIGS 2A-2C.	'730 patent, Fig. 2A-2C; col. 2, lns. 21-23; col. 4, ln. 7-col. 5, ln. 67
"confirming . . . patient" ('730 patent, claims 1, 2, 7-19; '106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 2, 4, 5; '059 patent, claims 1, 6, 8-14, 16)	'730 patent at col. 1:53-64, 3:25-31, 4:62-5:1, 5:27-41; '730 file history, 3/10/2005 Response at JPI-00002380-2381, 1/17/2007 Response at JPI-00002518.	'730 patent, Fig. 2C; col. 5, lns. 27-41, 61-63

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Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
"verifying" ('106 patent, claims 1-8; '107 patent claims 1-2, 4-5)	'730 patent at col. 1:53-64, 3:25-31, 4:62-5:1, 5:27-41; '730 file history, 3/10/2005 Response at JPI-00002380-2381, 1/17/2007 Response at JPI-00002518.	'730 patent, col. 1, lns. 38-52; col. 5, lns. 27-41
". . . to . . . patient" ('730 patent, claims 1, 2, 9-10; '106 patent, claims 1, 3, 5, 7; '059 patent, claims 1, 6, 7, 9-10, 12-15)	'730 patent at col. 1:53-64, 3:40-45, 5:42-63, 6:23-32.	'730 patent, Fig. 2C; col. 1, lns. 65-66; col. 3, lns. 40-42; col. 5, lns. 27-62 Dorland's Medical Dictionary, 28th ed., p. 496 (1994) defines "dispense" as "to prepare and distribute medicines to those who are to use them"
"dispensed" ('059 patent, claims 7, 10, 15)	'730 patent at col. 1:53-64, 3:40-45, 5:42-63, 6:23-32. Merriam Webster's Collegiate Dictionary (10th ed.) at JPI-00358856; Stedman's Medical Dictionary (26th Ed. 1995) at JPI-00358853.	'730 patent, col. 3, lns. 40-42 Dorland's Medical Dictionary, 28th ed., p. 496 (1994) defines "dispense" as "to prepare and distribute medicines to those who are to use them"
"therapeutic" ('106 patent, claims 1, 3, 5, 7)	'730 patent at col. 1:21-24, 6:37-39.	'730 patent, col. 1, lns. 11-15, 21-24
"computer system" ('106 patent, claims 1-5, 7-8)	'730 patent at col. 3:46-4:6, FIGS 1.	'730 patent, Fig. 2A; col. 4, lns. 8-12 '106 patent prosecution history, Amendment filed March 11, 2010 at p. 2-9, 11-12

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Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
"prescriptions . . . processed for authorization" ('106 patent, claims 1, 3, 5, 7)	'730 patent at col. 5:15-26, 6:47-7:2, FIGS 2B, 4B; '730 file history, 11/2/2009 Response at JPI-00002685-2690, 12/31/2009 Notice of Allowance at JPI-00002703-2712.	'730 patent, Figs. 2A, 2B; col. 2, lns. 22-24; col. 4, ln. 7-col. 5, ln. 26
"selecting . . . multiple controls"; "places controls" ('106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 2, 4-5; '059 patent, claims 8, 11, 16)	'730 patent at col. 1:11-12, 1:50-52, 3:21-24, 8:30-34, Abstract; '730 file history, 10/4/2004 Petition to Make Special at JPI-00002310-2311; '106 file history, 11/17/2009 Office Action at JPI-00004393.	'730 patent, col. 1, lns. 49-51 '730 patent prosecution history, original application filed December 17, 2002 at p. 15-16 '106 patent prosecution history, Office Action dated November 17, 2009 at pp. 6-9 '107 patent prosecution history, Office Action dated September 14, 2009 at pp. 6-7, 11-12 Webster's Ninth New Collegiate Dictionary, p. 779 (1991) defines "multiple" as "consisting of, including, or involving more than one" Webster's Ninth New Collegiate Dictionary, p. 1064 (1991) defines "select" as "to take by preference from a number or group : pick out : CHOOSE" Webster's Ninth New Collegiate Dictionary, p. 897 (1991) defines "place" as "to put in or as if in a particular place : SET," "to put in a particular state," and "to direct to a desired spot" The noun "controls" is the plural

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Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
		form of the singular noun "control."
"controls selected from the group consisting of" ('106 patent, claims 1, 3, 5, 7; '059 patent, claims 8, 11, 16)	'730 patent at col. 1:11-12, 1:50-52, 3:21-24, 3:29-33, 4:7-25, 4:62-5:8, 5:27-67, 8:30-34, Abstract; '730 file history, 10/4/2004 Petition to Make Special at JPI-00002310-2311; '106 file history, 11/17/2009 Office Action at JPI-00004393.	'106 patent prosecution history, Office Action dated November 17, 2009 at pp. 6-9 The transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. *In re Gray*, 53 F.2d 520 (CCPA 1931). MPEP § 2111.03 Seventh edition, July 1998
"shipping"; "shipment" ('106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 4)	'730 patent at col. 1:65-2:1, 5:35-44, 6:9-7:2.	'730 patent, col. 1, lns. 53-66; col. 3, lns. 42-45; col. 5, lns. 42-63
"maintains" ('107 patent, claims 1, 4)	'730 patent at col. 2:10-15, 3:34-45, 7:38-52, 7:65-8:3, Abstract, FIG. 7; '730 file history, 3/10/2005 Response at JPI-00002381-2382, 3/29/2006 Response at JPI-00002412, 2415, 1/17/2007 Response, at JPI-00002520-2521, 5/21/2007 Appeal Brief at JPI-00002556, 2561, 7/18/2007 Substitute Appeal Brief at JPI-00002600, 12/3/2007 Reply Brief at JPI-00002638-2639, 9/2/09 BPAI Decision at JPI-00002661, 2665; 11/2/2009 Response at JPI-00002685-2690, 12/31/2009 Notice of Allowance at JPI-00002703-	'730 patent, Figs. 2A-2C, 4A-5; col. 4, ln. 7-col. 7, ln. 25 '730 patent prosecution history, original application filed December 17, 2002 at p. 16

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Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
	2712; '107 file history, Petition to Make Special at JPI-00006450-6451, 11/3/2009 Response at JPI-00006507-6513, 3/10/2010 Notice of Allowance at JPI-00006564-6565; '059 file history, 12/21/2010 Notice of Allowance at JPI-00011582-583.	
"the controls comprising" ('107 patent, claim 1, 4)	'730 patent at col. 1:11-12, 1:50-52, 3:21-24, 3:29-33, 4:7-25, 4:62-5:8, 5:27-67, 8:30-34, Abstract; '730 file history, 10/4/2004 Petition to Make Special at JPI-00002310-2311; '106 file history, 11/17/2009 Office Action at JPI-00004393.	'107 patent prosecution history, Office Action dated September 14, 2009 at pp. 6-7; 11-12 '107 patent prosecution history, Amendment dated November 3, 2009 at pp. 2, 4 "Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim. *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997). MPEP § 2111.03 Eighth edition Aug 2001
"a separate database" ('107 patent, claims 3, 6)	'730 patent at col. 1:44-50, Abstract.	'730 patent, col. 1, lns. 38-51; col. 2, lns. 10-12 Webster's Ninth New Collegiate Dictionary, p. 1073 (1991) defines "separate" as "existing by itself: AUTOMATOUS," "dissimilar in nature or identity," and "syn see

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Evidence Supporting / Opposing Proposed Constructions for Disputed Terms

Term (Patent Claims)	Jazz Pharmaceuticals' Evidence	Roxane's Evidence
		DISTINCT"
"making the database available to the DEA for checking . . . for cash payments and for inappropriate questions" ('106 patent, claims 1, 3, 5, 7; '107 patent claims 1, 4)	'730 patent at col. 1:24-28, 6:37-40. McGraw-Hill Dictionary of Scientific and Technical Terms (5th ed.) at JPI-00358862; Merriam Webster's Collegiate Dictionary (10th ed.) at JPI-00358859	'730 patent, col. 6, lns. 33-40; col. 7, lns. 41-52 and Fig. 7. '730 patent prosecution history, original application filed December 17, 2002 at p. 16 "What's a database? A database is a collection of related information, or data, which you can sort, search through, and print as needed. Using a database, you can organize and analyze information in various ways so that you understand its significance. These are the elements that make up a database. Each category of information is a *field* The information in each field is a value; values can be text, numbers, dates, times, pictures, references to movies, or formulas that calculate values A set of fields is a *record*" (AppleWorks 5 User's Manual (1998), p. 8-2)

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October 14, 2010

Patent Notice Pursuant to § 505(b)(3)(B) [21 USC § 355(b)(3)(B)]

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Dear Mr. Cozadd:

Roxane Laboratories, Inc., hereby notifies you that it has filed, and the FDA has received and accepted abbreviated new drug application (ANDA) No. 202090 which seeks approval for sodium oxybate oral solution. The ANDA contains any required bioequivalence or bioavailability data or information and a Paragraph IV certification that U.S. Patent Nos. 6,780,889 and 7,262,219, each expiring on July 4, 2020; U.S. Patent No. 7,668,730, expiring on March 7, 2024; and U.S. Patent Nos. 7,765,106, and 7,765,107, each expiring on June 16, 2024, are not infringed, are invalid, and/or are unenforceable. The detailed statement of the factual and legal basis as to why the aforementioned Orange Book patents are not infringed, are invalid and/or are unenforceable is set forth below. It will be understood that the following statement may not be exhaustive of the grounds on which the patents are invalid, not infringed, and/or is unenforceable, and that Roxane Laboratories, Inc. expressly reserves the right to assert additional grounds in any litigation commenced against it asserting patent infringement pursuant to 35 U.S.C. § 271.

Discussion

Proposed Product

Roxane's sodium oxybate oral solution product will contain 500 mg/ml sodium oxybate and water. Roxane's label will otherwise correspond to the approved labeling for the approved indication for treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.

Roxane's sodium oxybate oral solution product will be distributed and controlled through a central pharmacy using computer databases and computer aided management protocols

substantially the same as those used in connection with the distribution and control of the reference listed drug as required by any applicable FDA guidelines or requirements for approval.

I. U.S. Patent No. 6,780,889:

The '889 patent expires July 4, 2020 due to a 195 day extension under 35 U.S.C. §154. The patent contains only one claim, claim 1, which is directed to a pharmaceutical composition consisting essentially of an aqueous solution of 500 mg/ml sodium gamma-hydroxybutyrate (GHB), and malic acid as a pH adjusting agent, wherein the composition has a pH of about 7.5, and wherein the composition is chemically stable and resistant to microbial growth, and wherein the composition is free of preservatives.

Roxane's proposed product will not infringe the sole claim of the '889 patent. As noted above, Roxane's proposed product contains only sodium oxybate (also referred to as sodium gamma-hydroxybutyrate or GHB) and water. Because Roxane's product will not include malic acid as required by the claim, the proposed product will not literally infringe the claim. The proposed product also will not infringe the sole claim of the '889 patent under the doctrine of equivalents. To read the sole claim of the '889 patent on a formulation that does not contain a pH adjusting agent, let alone malic acid in particular, would require the complete vitiation of an essential claim element, which is not allowed under the doctrine of equivalents. Further, according to the '889 specification, malic acid is employed as a pH adjusting agent because compositions of GHB pH adjusted with malic acid are resistant to both microbial growth and chemical degradation of GHB. As such, one of ordinary skill in the art would not consider a formulation that does not contain malic acid or any other pH adjusting agent to be performing substantially the same function, in substantially the same way to achieve the same result as the claimed formulation containing malic acid as a pH adjusting agent.

For at least the foregoing reasons, Roxane's proposed product will not infringe the claim of the '889 patent either literally or equivalently.

II. U.S. Patent No. 7,262,219:

The '219 patent, which will expire July 4, 2020, contains two independent claims, claims 1 and 4. Claim 1 is directed to a pharmaceutical composition, consisting essentially of an aqueous solution of about 350-750 mg/ml sodium GHB, and a pH adjusting agent, wherein the pH adjusting agent is malic acid, citric acid, acetic acid, lactic acid, carbonic acid, formic acid, propionic acid or tartaric acid, wherein the composition has a pH of about 6-7.5, and wherein the composition is chemically stable and resistant to microbial growth, and wherein the composition is free of preservatives. Claim 4 is substantially the same as claim 1, except for reciting hydrochloric acid, phosphoric acid, sulphuric acid, boric acid or nitric acid as the pH adjusting agent.

The proposed product will not infringe the claims of the '219 patent literally or equivalently for at least the reasons discussed above with respect to the '889 patent. Specifically, the proposed product will not include malic acid, citric acid, acetic acid, lactic acid, carbonic acid, formic acid, propionic acid, tartaric acid, hydrochloric acid, phosphoric acid,

sulphuric acid, boric acid, or nitric acid as claimed, or any other pH adjusting agent. As such, the proposed product will not literally infringe claims 1 and 4 of the '219 patent. With respect to equivalents, to read the claims on the proposed product that does not contain a pH adjusting agent, let alone one of the specifically claimed pH adjusting agents, would require the complete vitiation of an essential claim element of each claim and its attendant function. The complete vitiation of essential claim elements is not allowed under the doctrine of equivalents. Further, as discussed above, one of ordinary skill in the art would not consider the proposed formulation without a pH adjusting agent to be substantially the same as the claimed formulation requiring a pH adjusting agent. Accordingly, Roxane's proposed product will not infringe independent claims 1 or 4 of the '219 patent and, because the independent claims are not infringed, neither will any of the remaining claims, all of which depend from and include all of the limitations of a dependent claims.

In view of the foregoing, no claim of the '219 patent will be infringed by Roxane's proposed product either literally or under the doctrine of equivalents.

III. U.S. Patent No. 7,668,730:

The '730 patent, which expires March, 7, 2024, contains 11 claims, of which claims 1, 2 and 7-11 are independent. As discussed below, the claims of the '730 patent do not read on the distribution of sodium oxybate from multiple sources employing distinct computer based distribution systems, regardless of the details of the particular system used. Accordingly, Roxane's use of substantially the same computerized system as that used for the reference listed drug to distribute its proposed sodium oxybate product will not infringe any claim of the '730 patent.

A. Claim Construction:

As noted, of the eleven claims in the '730 patent, claims 1, 2 and 7-11 are the only independent claims. Each claim is directed to a computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy. The prescription drug in claims 8-10 is specifically defined as GHB (sodium oxybate). Although the claims differ in scope and detail, each independent claim requires that the method of distribution comprises the steps of:

"receiving in a computer processor ***all prescription requests****, for* ***any and all patients*** *being prescribed the prescription drug, only at the exclusive central pharmacy from* ***any and all medical doctors*** *allowed to prescribe the prescription drug; and...*

requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, such that ***all prescriptions*** *for the prescription drug are processed* ***only*** ***by*** *the exclusive central pharmacy* ***using only*** *the exclusive computer database..."*[emphasis added].

Construing the meaning of terms in a claim begins and ends with the language of the claims. *Bell Commun. Research, Inc. v. Vitalink Commun. Corp.*, 55 f.3d 615, 619-20 (Fed. Cir.

1995). Any questioned terms should be given their plain and ordinary meaning as understood by one of ordinary skill in the art, unless the inventor used the terms differently, and that difference is clearly expressed in the patent's specification or prosecution history. *Nike, Inc. v. Wolverine Word Wide, Inc.*, 43 F.3d 644, 646 (Fed. Cir. 1994). Extrinsic sources, such as a dictionary, for example, may not be used to contradict claim meaning that is unambiguous in light of the specification and prosecution history. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1324 (Fed. Cir. 2005).

In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words. *Phillips*, at 1314. The plain language of the '730 claims requires that "***all*** prescription requests" for "***any and all patients*** being prescribed the prescription drug" from "***any and all doctors*** allowed to prescribe the prescription drug" be received "**only**" at the exclusive central pharmacy such that "***all prescriptions*** for the prescription drug" are processed "**only**" by an exclusive computer database. Regardless of how one might want to characterize the person of ordinary skill in the art, the foregoing claim language is unambiguous, and its interpretation is a matter of plain English. The claims require that *all* prescriptions, for *all* patients, from *all* doctors for a given prescription drug are to be received and processed *only* by the claimed exclusive central pharmacy and *only* in its claimed exclusive database. Thus, based on the unambiguous plain language of the claims themselves, the receipt of prescriptions for a given prescription drug by a pharmacy other than the claimed exclusive central pharmacy, and the processing thereof a database other than the claimed exclusive computer database necessarily falls outside the scope of the '730 claims because *all* prescriptions for the prescription drug, for *all* patients, from *all* doctors would no longer be received exclusively by the claimed central pharmacy for processing only by the claimed exclusive central database.

Nothing in the specification supports a contrary interpretation to the plain language of the claims as requiring a singular administration point - that *all* prescriptions for a given drug for *all* patients from *all* doctors be received and processed *only* by an exclusive central pharmacy for processing *only* by the claimed exclusive central database. To the contrary, the specification reaffirms the meaning of the plain language. For example, not only is the specification devoid of any suggestion to use multiple exclusive pharmacies or multiple exclusive databases, the specification discloses problems associated with the use of such distribution systems, at least to the extent that they fail to share information with each other. In particular, the specification teaches that some drugs may be the object of abuse and illegal schemes to distribute for profit, such as obtaining prescriptions from multiple doctors, filling prescriptions at multiple pharmacies or obtaining multiple prescriptions from an unscrupulous physician. Col. 1, ll. 10-30. To address such abuses, the patent teaches a distribution system utilizing a central pharmacy and database to track all prescriptions for a drug from all physicians allowed to prescribe the drug and all patients receiving the drug. Col. 1, ll. 38-41. Thus, the specification teaches away from and waives any claim to the use of multiple exclusive pharmacies and databases to process prescriptions for a given prescription drug. Of note, the fact that the specification does not support an interpretation of the claims that is contrary to the plain language of the claims of course does not mean that the specification provides an adequate written description for the exceedingly narrow invention that the patentee ultimately claimed and, indeed, as discussed

below, the specification does not provide an adequate written description to support the claims that were ultimately granted.

That the claimed method requires *all* prescriptions, for *all* patients, from *all* doctors for the prescription drug to be processed *only* through an exclusive central pharmacy and *only* by its exclusive central database is further supported by arguments made by the patentee during prosecution of the '730 patent. For example, in an amendment dated July 31, 2006, the patentee distinguished prior art to Moradi et al., by arguing that "many different pharmacies may or may not use the system of Moradi et al. In the current claims, the use of a single central database is required for *all* distribution of the sensitive drug." Amdt. 7/31/06, p. 11 [emphasis added]. Clearly, according to the patentee's method, it is not sufficient that only some pharmacies use the claimed system. Rather, they must all use the claimed system, again affirming the plain language of the claims that *all* prescriptions, for *all* patients must be processed through the claimed exclusive central pharmacy.

Still further, in an amendment dated November 2, 2009, the patentee amended the claims to even further emphasize the exclusive nature of the claimed method as requiring *all* prescriptions to be processed *only* by an exclusive central pharmacy and *only* in its exclusive central database. More specifically, the claims were amended to further specify that all prescription requests as originally claimed means "for any and all patients" from "any and all" medical doctors allowed to prescribe the drug such that "all prescriptions for the sensitive drug" are processed by the exclusive central pharmacy. As if the plain language of these amendments were not enough, the patentee went on to again distinguish the prior art on the bases that "Moradi does not disclose that all prescriptions for a sensitive drug, or all prescriptions for any other drug for that matter, are processed ***only*** by the central pharmacy" and that "there is no disclosure in Lilly that all prescriptions for a particular drug use ***only*** the database." Amdt. 11/2/09, p. 11 [italics in original, underlining added]. These amendments and arguments resulted in the allowance of the claims, with the Examiner stating in her Reasons for Allowance that the prior art "does not teach or fairly suggest that *all* prescriptions for the prescription drug are processed only by the exclusive central pharmacy using *only the exclusive computer database.*" Notice of Allowability dated 12/16/09 [emphasis in original]. Patentee chose not to dispute, rebut or reply to the Examiner's Reasons for Allowance.

In view of the foregoing, there can be no dispute that the claimed method requires *all* prescriptions, for *all* patients, from *all* doctors for the prescription drug to be processed *only* through an exclusive central pharmacy and *only* by its exclusive central database in accordance with the plain language of the claims.

B. Non-Infringement:

It will be apparent from the foregoing that Roxane's implementation of its own computerized distribution system for its proposed sodium oxybate product will not infringe the claims of the '730 patent as properly construed. Because Roxane's prescriptions all will be processed solely through Roxane's exclusive central pharmacy and data base, while at the same time other prescriptions for the reference listed drug will be processed solely through that exclusive central pharmacy and database, clearly not *all* prescriptions for sodium oxybate, for *all*

patients being prescribed sodium oxybate, from *all* doctors allowed to prescribe it will be received and processed only at an exclusive central pharmacy, such that *all* prescriptions for sodium oxybate are processed only by the exclusive central pharmacy using only the exclusive central database, as required by the claims. Rather, some prescriptions for some patients will be received and processed through Roxane's database, and others will, in accordance with the claims, be received and processed by the database associated with the distribution of the reference listed drug. Accordingly, no claim of the '730 patent will be literally infringed by Roxane's separate and independent distribution of its sodium oxybate oral solution product, regardless of the details or configuration of Roxane's system.

The implementation of Roxane's computerized distribution system also will not infringe any claim of the '730 patent under the doctrine of equivalents. As discussed above, the language of the claims clearly limits the distribution method to one pharmacy, one computer database. Regardless of the level of ordinary skill in the art, no person could seriously consider the situation in which two different sources for the prescription drug distribute the drug under two different distribution systems, to be substantially the same as the claimed process requiring that "*all* prescription requests" for "*any and all patients* being prescribed the prescription drug" from "*any and all doctors* allowed to prescribe the prescription drug" be received *only* at the exclusive central pharmacy such that "*all prescriptions* for the prescription drug" are processed *only* by an exclusive computer database. Further, in light of the fact that the patentee amended the claims for purposes of patentability to require "*all* prescription requests" for "*any and all*" patients and from "*any and all*" doctors be processed through the claimed exclusive central pharmacy and database, and distinguished the claimed method from prior art on the that the prior art "does not disclose that all prescriptions for a sensitive drug, or all prescriptions for any other drug for that matter, are processed *only* by the central pharmacy" and provides no disclosure "that all prescriptions for a particular drug use *only* the database," the patentee will be estopped from arguing that Roxane's distribution of sodium oxybate oral solution through a distribution system substantially the same as, but separate from, the distribution system for the reference listed drug would be equivalent under the doctrine of equivalents.

In view of the foregoing, no independent claim of the '730 patent will be infringed by the distribution of Roxane's sodium oxybate oral solution either literally or under the doctrine of equivalents. Because the independent claims are not infringed, neither are any of the remaining claims which depend from and include all of the limitations of an independent claim.

IV. U.S. Patent No. 7,765,106:

The '106 patent contains 8 claims, of which claims 1, 3, 5 and 7 are independent. All of the independent claims are variously directed, *inter alia*, to a method for treating a patient, in the case of claim 3 a narcoleptic patient, with a prescription drug. Although variously worded, each independent claim, and thus all claims of the '106 patent, require the essential elements that *all* prescriptions, for *all* patients, from *all* doctors for a prescription drug covered by the claims to be received into an exclusive computer database in an exclusive computer system, such that *all* prescriptions for the drug are processed for authorization *only* using the exclusive central computer system and the exclusive computer database. As will be apparent from the discussion of the '730 patent above, and as elaborated upon below, because the necessary result of treating

patients with Roxane's sodium oxybate oral solution is that all prescriptions, for all patients, from all doctors for a sodium oxybate will not be received into an exclusive computer database in an exclusive computer system as claimed, such that all prescriptions for the drug are processed for authorization only using the exclusive central computer system and the exclusive computer database as claimed, the method of treating patients with Roxane's proposed product will not infringe any claim of the '106 patent either literally or under the doctrine of equivalents.

In the present case, Roxane will implement its own computerized distribution system for its proposed sodium oxybate product, separate from that of the reference listed drug. Because Roxane's prescriptions all will be processed solely through Roxane's exclusive database, but prescriptions for the reference listed drug will be processed through the reference listed drug's database, clearly not *all* prescriptions for sodium oxybate, for *all* patients being prescribed sodium oxybate, from *all* doctors allowed to prescribe it will be received into an exclusive computer database, such that *all* prescriptions for sodium oxybate are processed only by the exclusive central computer system and the exclusive central database, as required by the claims. Rather, some prescriptions for some patients will be received and processed through Roxane's database, and others will be received and processed by the database associated with the distribution of the reference listed drug.

Notably, the claim requirements that all prescriptions, for all patients, from all doctors for a prescription drug be received into an exclusive computer database in an exclusive computer system, such that all prescriptions for the drug are processed for authorization only using the exclusive central computer system and the exclusive computer database, were added by amendment during prosecution of the '106 patent for purposes of patentability. Moreover, these elements correspond substantially to the elements on which non-infringement of the above-noted '730 patent, which shares the same specification as the '106 patent and from which the '106 patent is a divisional, is established. In each case, both the specification and prosecution history establish that the above-identified claim language means what it plainly says, that no less than all prescriptions, for all patients, from all doctors must be processed only by the exclusive central computer system and database. In other words, all means all. Although it is well established that arguments made during prosecution with respect to like claim terms of related patents apply equally to both, such that the arguments establishing the meaning of these terms during prosecution of the '730 patent apply equally here, we need not reiterate those here because the prosecution of the '106 patent itself also reemphasizes that all means all, and that the claims do not contemplate or read on the processing of any less than all prescriptions, from all doctors, for all patients through only the exclusive central computer system and database.

For example, as was the case with the '730 patent, in order to overcome a rejection over prior art to, *inter alia*, Moradi et al. and Lilly et al., the applicant amended the claims of the '106 patent to require that all prescriptions, for all patients, from all doctors for a prescription drug be received into an exclusive computer database in an exclusive computer system, such that all prescriptions for the drug are processed for authorization only using the exclusive central computer system and the exclusive computer database. Amdt. 3/11/10. In order to emphasize the distinction, the applicant argued that "none of the prior art discloses the features of receiving *all* prescription requests *only* into an exclusive central computer system or an exclusive computer database..." Id. at 11-12 (emphasis added). As a result, the Examiner allowed the

claims, specifically relying on the distinction that the prior art did not teach or suggest "receiving only into an exclusive central computer system/exclusive computer database, *all* prescriptions for any and all patients being prescribed the prescription drug..." as her reasons for allowance. Notice of Allowance dated 4/20/10 (emphasis in original). Thus, there is no doubt that the claims do not read on the processing of prescriptions by multiple computer systems and databases, or of only some prescriptions, from some doctors, for some patients through one exclusive computer system and database, while others are processed by a different computer system and database. Accordingly, because Roxane will implement its own computerized distribution system, no claim of the '106 patent will be literally infringed, regardless of the details or configuration of Roxane's system. Moreover, because these claim requirements were added by amendment for purposes of patentability, the patentee will be estopped from reading the claims on the implementation and use of Roxane's system under the doctrine of equivalents.

For at least the foregoing reasons, no claim of the '106 patent will be infringed by Roxane's proposed product either literally or under the doctrine of equivalents.

V. U.S. Patent No. 7,765,107:

The '107 patent contains 6 claims, of which claims 1 and 4 are independent. Like the '106 patent, the '107 patent also is a divisional if the '730 patent and shares an identical specification. In the case of the '107 patent, however, the claims are directed to a method to control the abuse of a prescription drug, such as GHB. Notably, although the claims are drawn to a method to control abuse, they contain the same essential requirements as the claims of the '730 and '106 patents, namely receiving in a computer processor all prescription requests, for any and all patients being prescribed the drug, only at an exclusive central pharmacy, from any and all medical doctors allowed to prescribe the drug, and processing with the computer processor all prescriptions for the drug only by the exclusive central pharmacy using only a central database maintained by the exclusive central pharmacy.

Although the language varies slightly, there can be no doubt that, like the '730 and '106 patents, the claims require that all prescriptions, for any and all patients, from any and all doctors must be processed only by an exclusive central database at an exclusive central pharmacy and that, again consistent with the intrinsic record, all means all as the plain language suggests. Also like the '730 and '106 patents, the requirement that all prescriptions, for any and all patients, from any and all doctors must be processed only by an exclusive central database at an exclusive central pharmacy was added by amendment during prosecution and argued by the applicant to distinguish the prior art over which the claims were rejected. Amdt. 11/3/09. Based thereon, the Examiner's reasons for allowance once again cited the failure of the prior art to "teach or suggest receiving in the computer processor all prescription requests, for any and all patients being prescribed the drug, only at the exclusive central pharmacy, from any and all medical doctors allowed to prescribe the prescription drug and processing with the computer processor all prescriptions for the prescription drug only by the exclusive central pharmacy using only the central database." Notice of Allowance mailed 3/10/10 at 5.

In view of the foregoing, it is once again the case that the claims do not read on a method to control abuse that involves the processing of prescriptions by multiple computer systems and

databases, or of only some prescriptions, from some doctors, for some patients through one exclusive computer database or central pharmacy, while others are processed by a different computer system and database at a different central pharmacy. Accordingly, because Roxane will implement its own computerized distribution system, no claim of the '107 patent will be literally infringed, regardless of the details or configuration of Roxane's system. Moreover, because these claim requirements were added by amendment for purposes of patentability, the patentee will be estopped from reading the claims on the implementation and use of Roxane's system under the doctrine of equivalents. Accordingly, no claim of the '107 patent will be infringed by the distribution, use or sale of Roxane's proposed sodium oxybate oral solution either literally or under the doctrine of equivalents.

VI. Invalidity

Although the manufacture, sale, offer for sale, distribution and use of Roxane's proposed sodium oxybate oral solution product will not infringe any claim of U.S. Patent Nos. 6,780,889, 7,262,219, 7,668,730, 7,765,106 or 7,765,107 for the reasons above, it is also the case that each of the claims of the '730, '106, and '107 patents is invalid based on lack of adequate written description.

Each claim of the '730 patent is invalid for lack of adequate written description because the patentee added to all of the claims during prosecution the limitation that "all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database" but the '730 specification, including the claims, as originally filed, does not describe to a person of ordinary skill in the art any invention including this limitation. The Patent Statute provides in relevant part that "[t]he specification shall contain a written description of the invention." 35 U.S.C. § 112, para. 1. With regard to limitations to claims added during prosecution, the standard for adequate written description is whether the specification, including claims, as originally filed, describes to a person of ordinary skill in the art the invention later claimed. As discussed at length above, the patentee added the limitation that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database, among other limitations, during prosecution in order to overcome a rejection of the claims for obviousness over the prior art of record, and indeed the examiner specifically stated that this limitation was the basis for withdrawal of the obviousness rejection. However, this limitation is without support in the specification, including claims, as originally filed.

Specifically, the patentee cited as support for this limitation two passages from the specification, Amendment dated November 2, 2009, at 11, the first being "[a] drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug," specification at page 1, lines 27-28, and the second being "Xyrem(R) is distributed and dispensed through a primary and exclusive central pharmacy, and is not stocked in retail pharmacy outlets," specification at page 4, line 29-page 5, line 1. As can be seen, neither passage describes an invention which requires all prescriptions for a prescription drug to be processed only by an exclusive central pharmacy using only an exclusive computer database, and the patentee provided no further explanation as to why one of ordinary skill would understand either statement to otherwise describe such a limited invention. In fact, a review of

the specification, including claims, as originally filed, indicates that the word "only" appears only one time, and never in relation to subject matter directed to requiring that all prescriptions for a prescription drug are processed only by an exclusive central pharmacy, let alone using only an exclusive computer database. Accordingly, neither passage could be legitimately argued to describe to a person of ordinary skill in the art the invention later claimed. Moreover, one of ordinary skill would of course not have understood the purpose of the disclosed invention, identification of abuses by monitoring data in a database for prescription patterns by physicians and prescriptions obtained by patients, to in any way require processing of prescriptions only by an exclusive central pharmacy using only an exclusive computer database. As the prior art of record establishes, effective systems for identifying abuses and controlling distribution need not, in fact, employ only an exclusive central pharmacy and only an exclusive central database and, as admitted by the patentee, the embodiment exemplified in the specification and figures is only illustrative and should not be taken in a limited sense. Col. 2, ll. 55 *et seq*. Although the limitation proved convenient with respect to obtaining withdrawal of the obviousness rejection, it is without support in the specification. Because the specification, including claims, as originally filed, fail to describe to a person of ordinary skill in the art the invention later claimed, all claims of the '730 patent are invalid for lack of adequate written description.

For essentially the same reasons as indicated above regarding the '730 claims, each claim of the '106 and '107 patents are also invalid for lack of adequate written description. Specifically, as discussed above, with respect to the '106 patent again the patentee added the limitations that "all prescriptions for the prescription drug [e.g. sodium oxybate] are processed for authorization only using the exclusive central computer system and the exclusive computer database" or "all prescriptions for the prescription drug are processed for authorization only via the exclusive computer database" to each claim during prosecution to overcome an obviousness rejection over the prior art of record, and again the Examiner withdraw the rejection specifically based on this limitation. Similarly, as also discussed above, with respect to the '107 patent the patentee added the limitation of processing "all prescriptions for the prescription drug [e.g. GHB] only by the exclusive central pharmacy using only the central database" to each claim during prosecution to overcome an obviousness rejection over the prior art of record, and again the Examiner withdraw the rejection specifically based on this limitation. In these cases the patentee did not even offer specific support for the limitations. As the '106 and '107 patents are based on divisionals of the application on which the '730 patent is based, for the reasons indicated above regarding the '730 patent, the specification, including claims, as originally filed for the '106 and '107 patents also fails to describe to a person of ordinary skill in the art the invention later claimed, and thus all claims of the '106 and '107 patents are also invalid for lack of adequate written description.

For at least the foregoing reasons, the manufacture, sale, offer for sale, distribution and use of Roxane's proposed sodium oxybate oral solution product will not infringe any claim of U.S. Patent Nos. 6,780,889, 7,262,219, 7,668,730, 7,765,106 or 7,765,107, either literally or under the doctrine of equivalents. Moreover, for at least the foregoing reasons, all claims of the '730, '106 and '107 patents are also invalid for lack of adequate written description. However, by this certification Roxane Laboratories is in no way limiting its defenses and expressly reserves the right to assert additional claims, including invalidity and unenforceability, under all relevant sections of the patent laws or other applicable laws in the United States.

Finally, Roxane hereby makes its offer of confidential disclosure pursuant to 21 U.S.C. §355(j)(5)(C)(i)(1)(cc). This offer of confidential access to Roxane's ANDA is specifically restricted to Jazz Pharmaceuticals' outside legal counsel and to one in-house counsel who does not have any responsibility for procurement of patents relating to and/or development of any Jazz Pharmaceuticals products, and is for the sole and limited purpose of evaluating whether the aforementioned patents will be infringed, and for no other purpose. This offer of confidential access is also subject to Jazz Pharmaceuticals' agreement to (i) treat Roxane's documents and the information contained therein with the same degree of care that Jazz Pharmaceuticals accords its own confidential documents, (ii) not to disclose any of Roxane's documents or the information contained therein to anyone excepting the persons identified above, and (iii) if Roxane elects to provide copies of documents to Jazz Pharmaceuticals, then upon Jazz Pharmaceuticals' determination on the question of infringement, to return to Roxane all of Roxane's documents and all copies thereof, and to destroy all notes, summaries or other documents concerning the information contained in Roxane's documents (excepting that the individuals identified above may retain a summary of the reasons for Jazz Pharmaceuticals' determination of no infringement). If Jazz Pharmaceuticals accepts this offer of confidential access, Roxane reserves the right to redact from its documents information not of relevance to the question of patent infringement.

If you have any reason to disagree with Roxane's position, please contact me by phone at 614-272-4799 or by telefax at 614-308-3559. In my absence, please contact Julie Economou at 614-241-4118.

Respectfully,

Randall S. Wilson

Randall S. Wilson
Vice President, Scientific, Medical and Regulatory Affairs
Roxane Laboratories, Inc.

CC: Senior Vice President, General Counsel and Corporate Secretary, Jazz Pharmaceuticals
CEO, Orphan Medical, Inc.
CEO, Twist Merger Sub, Inc.
CEO, JPI Commercial, LLC
General Counsel, Silicon Valley Bank
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February 27, 2012

Via ECF and Overnight Delivery
The Honorable Cathy L. Waldor
United States Magistrate Judge
M.L. King, Jr. Federal Bldg. & Courthouse, Room 4C
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Fax: (973) 776-7865

Re: *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*
Civil Action No. 2:10-cv-06108 (ES)(CLW)

Dear Judge Waldor:

We along with Locke Lord LLP represent defendant Roxane Laboratories, Inc. ("Roxane") in this action. We respectfully request that this Court grant Roxane leave to supplement its Initial Invalidity and Noninfringement Contentions.

Roxane's request is proper because the new material prior art with which Roxane seeks to supplement its Initial Invalidity Contentions was only recently discovered, despite earlier diligent searching. In addition, the business records Roxane seeks to cite to in supplementing its Initial Noninfringement Contentions were generated after the Initial Contentions were served. Roxane's requested supplementation pursuant to Local Patent Rule 3.7, furthermore, will not lead to an enlargement of time or impact other scheduled deadlines and will not cause prejudice to Jazz Pharmaceuticals, Inc. ("Jazz"). However, Roxane will be materially prejudiced if the Court denies Roxane's request.

A. Background

As this Court is familiar, Jazz initiated this and two other actions now consolidated with the present action (Civil Action Nos. 11-660 and 11-2523) pursuant to the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act and to Title 35 of the United States Code ("Hatch-Waxman Act"), asserting eight patents against Roxane—(a) four related to the

product: U.S. Patent Nos. 6,472,431 ("the '431 patent"), 6,780,889 ("the '889 patent"), 7,262,219 ("the '219 patent"), and 7,851,506 ("the '506 patent"); and (b) four related to a method of distributing the product: U.S. Patent Nos. 7,668,730 ("the '730 patent"), 7,765,106 ("the '106 patent"), 7,765,107 ("the '107 patent") and 7,895,059 ("the '059 patent")—based on Roxane's filing of its Abbreviated New Drug Application ("ANDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to market and distribute a generic sodium oxybate product that is bioequivalent to Jazz's XYREM® product. Thus, this is an eight-patent infringement action with 56 claims, *some of which are over 500 words long.* (*See, e.g.*, Ex. A, '106 patent, claims 1, 3, 5, 7.)

This case was filed on November 22, 2010. Consequently, the parties have operated under the N.J. Local Patent Rules that were in existence at the time of the filing, *i.e.*, the 2008 Local Patent Rules. Magistrate Judge Arleo held the first Rule 16 scheduling conference on February 11, 2011. But a scheduling order was not put in place at that time because Jazz complained that it would not be able to prepare its Infringement Contentions without additional information it sought pursuant to a third party subpoena of Roxane's raw material supplier. At a second Rule 16 conference on March 22, 2011, Judge Arleo instructed Roxane to serve its Initial Invalidity and Noninfringement Contentions on April 14, 2011. Roxane timely served both sets of contentions. Due to the large number and length of the patent claims, Roxane's contentions, including claim charts, *totaled over 400 pages*.

No pretrial scheduling order was entered in this case until September 1, 2011 (D.I. 60), due to other issues, including Jazz's refusal to enter into a discovery confidentiality order with a patent prosecution bar. This issue was finally resolved in Roxane's favor on June 7, 2011.

Because of the parties' disputes concerning whether expert discovery could commence before or after a *Markman* claim construction order is entered, the current scheduling order for this case contemplated dates only up through the proposal to the Court of a date for the Claim Construction hearing (February 28, 2012) and the close of fact discovery (March 30, 2012). (*See* D.I. 60, D.I. 96 (submitting proposed Amended Scheduling Order).) The Court has not yet set a schedule for expert discovery, summary judgment briefing or the final pretrial conference.

B. Roxane's Proposed Supplementation of its Initial Contentions

Roxane respectfully requests leave to:

(1) supplement its Initial Invalidity Contentions to add new bases for invalidity of the '730, '106, '107 and '059 patents (collectively "distribution patents") based on publicly available FDA materials and public presentations dated more than a year before the earliest filing date for the distribution patents; and

(2) supplement its Initial Noninfringement Contentions to add citations to business records produced after the submission of the Initial Contentions.

C. Roxane's Attempts to Meet and Confer With Jazz

On January 30, 2012 and February 3, 2012, Roxane requested to meet and confer with Jazz's counsel to discuss Roxane's proposed supplementations to its Initial Contentions that are the subject of this letter. (*See* Ex. B, 1/30/2012 Goodin ltr.; Ex. C, 2/3/2012 Goodin ltr.) In response to both requests, and under the guise of seeking additional information regarding Roxane's supplementations, Jazz would not agree to provide a time and date for meeting and conferring with Roxane. To date, Jazz has still refused to agree to a date to meet and confer with Roxane on this issue. These meritless refusals have required Roxane to submit this letter requesting leave to supplement its contentions. Roxane notes that Jazz previously requested permission from this Court to amend Jazz's infringement contentions without even seeking a meet and confer on the issue with Roxane so as to proceed by way of a joint letter. (*See*D.I. 82.) Despite Jazz's unilateral actions, this Court granted Jazz's request.

D. Ongoing Investigation Has Uncovered Material Prior Art For Which Supplementation of Roxane's Initial Invalidity Contentions Should Be Permitted

1. Roxane Recently Discovered New, Material Prior Art

As noted above, three months before Jazz made any production of documents in response to Roxane's production requests, Roxane served its Initial Invalidity and Noninfringement Contentions setting forth detailed bases as to why it or its proposed ANDA product does not infringe the asserted claims of the patents-in-suit and detailed bases for Roxane's contention that the asserted claims are invalid. (*See* Ex. D, April 14, 2011 Initial Contentions (attaching, by way of example, Initial Contentions regarding claim 1 of the '730 patent).) During approximately the next ten months, while the parties engaged in discovery and discovery disputes, Roxane continued to investigate and further develop its invalidity defenses to Jazz's claims of infringement. As part of its investigation, Roxane independently searched for publicly available documents and other materials relating to Jazz's restricted distribution system. In doing so, Roxane uncovered, *e.g.*, several documents and other materials that were made publicly available by the FDA relating to Jazz's restricted distribution system that were not part of Jazz's document production. Roxane also discovered related prior art references in Jazz's document production.

Roxane continued its due diligence, evaluating these documents and other materials, and determined that these materials are prior art to the distribution patents and that they, alone or in combination with other prior art references, render the asserted claims of the distribution patents invalid as anticipated or obvious. Roxane's analysis was no small undertaking given the number of patents, patent claims and the extreme wordiness and length of these patent claims. Specifically, the four distribution patents combined have claims totaling about fifteen columns or *over 7500 words*. In order to make certain that the prior art Roxane found anticipated or rendered obvious each claim of Jazz's distribution patents, Roxane had to painstakingly compare the prior art to each patent claim. Roxane anticipates that the supplemental invalidity claim

charts for these four patents based on the new prior art will total at least a few hundred pages, and has worked as diligently as possible to bring this matter to Jazz's and the Court's attention.

Based on prior correspondence with Jazz, Roxane expects Jazz to argue that the references Roxane relies on were cited in the file histories of the distribution patents and, therefore, Roxane has not been diligent in seeking to amend the contentions. But Jazz's assertion rings hollow, because many of the references on which Roxane relies were not cited in the prosecution history of the distribution patents. While Roxane may combine one or more of the newly-discovered prior-art publications with documents from the prosecution histories, Roxane is not relying solely on the prosecution-history documents. Together, these documents establish that Jazz's predecessor, Orphan Medical, was publicly promoting its restricted distribution system more than one year prior to the filing date of the distribution patents.

To find these new, material prior art references, Roxane was required to undertake significant additional searching and investigations to determine whether the documents relied upon were publicly available and, thus, qualify as "prior art" (for it was not discernible, let alone readily apparent, from the prosecution histories that these documents were in fact publicly available). Roxane was also required to obtain one of the materials (Orphan Medical's video discussing the restricted distribution system) from a separate public source even though it may have been produced by Jazz, because Jazz produced it in an unreadable format. Roxane requested that Jazz reproduce the CD containing the video and other materials that Orphan Medical submitted to the FDA, which were made public, in native format (*see* Ex. E, 2/3/2012 Goodin ltr.), but Jazz has thus far ignored Roxane's request.

2. Jazz Will Not Be Unfairly Prejudiced By Roxane's Supplementation of Its Invalidity Contentions

Further, Roxane's request to supplement its contentions poses no possible unfair prejudice to Jazz. First, the documents are, or should be, well-known to Jazz. All relate to activities involving Orphan Medical while it sought FDA approval for its (and now Jazz's) distribution system for XYREM®. Second, Roxane seeks to amend its invalidity contentions while fact discovery is ongoing. Currently, fact discovery is not scheduled to close until March 30, 2012. It appears, however, that this Court-mandated deadline will need to be extended in light of Jazz's delinquency in providing Roxane with deposition dates for the inventors of the patents-in-suit and 30(b)(6) corporate representatives. Roxane originally subpoenaed the patent inventors for deposition in this case on December 29, 2011. Despite repeated requests for Jazz to provide deposition dates for the inventors (*see*, *e.g.*, Ex. F, 1/30/2012 Goodin ltr.; Ex. G, 2/15/2012 Goodin email; Ex. H, 2/21/2012 Abramowitz ltr.), it was not until February 22, 2012 that Jazz provided Roxane with dates, some of which proposed dates extend into May 2012—well after the currently scheduled close of fact discovery. (Ex. I, 2/22/2012 Brier ltr.) Moreover, Roxane has yet to receive a single response to the 30(b)(6) deposition notice Roxane served on Jazz several weeks ago.

As for fact depositions to be taken by Jazz, to date, Jazz has not requested any depositions from Roxane. Therefore, there can be no prejudice to Jazz in that regard. All documents that Roxane plans to rely on for the supplementation of its Invalidity Contentions have been produced to Jazz. And, as this Court has previously ruled, there is no requirement under the Local Patent Rules governing this action for Jazz to submit responsive validity contentions. Thus, Jazz also is not prejudiced in that regard. *See TFHPubl'ns, Inc. v. Doskocil Mfg. Co., Inc.*, 705 F. Supp. 2d 361, 366-67 (D.N.J. 2010) (permitting amendment of contentions despite an amendment of the opposing party's contentions were required, as a result stating,

> "Rule 3.7 'is not a straitjacket into which litigants are locked from the moment their contentions are served,' … Therefore, while the Local Patent Rules strive to have a party establish their contentions early on, it is important to recognize that 'preliminary infringement contentions are still preliminary.' (internal citation omitted)");

see also Int'l Dev. LLC v. Richmond, 2010 WL 3946714, *3-4 (D.N.J. Oct. 4, 2010).

Additionally, Markman briefing was only just finished last week and the parties are to submit their Local Patent Rule 4.6 Request for Markman Hearing paper to the Court on February 28, 2012. Thus, there has been no *Markman* ruling on claim construction, after which supplementation of the contentions may again be needed, as the meaning of the claim terms may change. And there has been no expert report dates set, so Jazz will have Roxane's supplemental contentions well in advance of having to submit an expert report in response to Roxane's experts' reports on invalidity.

In summary, it is plain that there will be no unfair prejudice to Jazz based on Roxane's submission of its supplemental Invalidity Contentions.

E. Roxane Should Be Permitted To Supplement Its Initial Noninfringement Contentions With Business Records Generated After the Contentions Were Initially Served

1. Roxane's Business Records Were Recently Generated

As this Court is aware from Jazz's recent request to supplement its infringement contentions (D.I. 82), Roxane's ANDA is currently undergoing FDA review and Roxane continues to generate business records relating to its ANDA. After it served its Initial Contentions to Jazz, Roxane generated documents that relate to and describe Roxane's proposed restricted distribution system that Jazz accuses of infringement.

Jazz requested and Roxane agreed that Jazz should be entitled to supplement its Infringement Contentions based on these documents submitted to the FDA. In response to Jazz's infringement assertions, Roxane intends to rely on the same documents to show noninfringement and, therefore, requests leave to cite to them in its Noninfringement Contentions.

As Jazz bears the burden of proof on infringement and now seeks to rely on these documents as proof of infringement, Roxane plainly should have the right to rely on them in response. Any ruling to the contrary would lead to the illogical result that Jazz and its experts could rely on Roxane's own documents in their expert reports to prove infringement, but Roxane's experts would not be allowed to comment on them. Instead of any prejudice to Jazz, this would unfairly prejudice Roxane.

2. Jazz Will Not Be Unfairly Prejudiced By Roxane's Supplementation of Its Noninfringement Contentions

There is no unfair prejudice to Jazz in allowing Roxane to supplement its noninfringement contentions with these documents because: (1) Jazz is now aware that Roxane plans on relying on these documents (and Jazz itself plans to rely on them as well), (2) there is the possibility that there will be further communications with the FDA regarding Roxane's distribution system as FDA review is ongoing; (3) Jazz has yet to take a deposition in this action, (4) fact discovery is not yet closed and likely will need to be extended based on Jazz's delay in providing deposition dates, (5) Jazz requested and received additional time for its *Markman* opposition briefing to consider these documents (some of which Jazz even cited to in its *Markman* opposition brief), (6) there has not been a *Markman* hearing or ruling yet setting forth the claim constructions that will govern the infringement analysis in this case, and (7) the time for Jazz to submit its infringement expert report has not even been set and is likely months away.

F. Roxane's Proposed Supplementation of Its Initial Contentions Will Not Lead To An Enlargement Of Time Or Impact Other Scheduled Deadlines

As explained above, the date for a *Markman* hearing has not been set (and accordingly there has been no *Markman* ruling), nor have dates for expert discovery been set. For these reasons as well, Roxane's proposed supplementation of its Initial Invalidity and Noninfringement Contentions will not in any way unfairly prejudice Jazz or adversely affect any of the scheduled deadlines on the current case schedule.

* * *

For the foregoing reasons, Roxane respectfully requests this Court's leave to amend its initial invalidity and noninfringement contentions pursuant to Local Patent Rule 3.7.

Respectfully submitted,

s/ Theodora McCormick
Theodora McCormick

cc: USDJ Hon. Esther Salas
All Counsel of Record (via ECF)

EXHIBIT A

US007765106B2

(12) United States Patent
Reardan et al.

(10) Patent No.: US 7,765,106 B2
(45) Date of Patent: *Jul. 27, 2010

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

(75) Inventors: **Dayton T. Reardan**, Excelsior, MN (US); **Patti A. Engel**, Eagan, MN (US); **Bob Gagne**, St. Paul, MN (US)

(73) Assignee: **JPI Commercial, LLC**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1645 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/979,665**

(22) Filed: **Nov. 2, 2004**

(65) **Prior Publication Data**

US 2005/0090425 A1 Apr. 28, 2005

Related U.S. Application Data

(62) Division of application No. 10/322,348, filed on Dec. 17, 2002, now Pat. No. 7,668,730.

(51) **Int. Cl.**
G06Q 10/00 (2006.01)

(52) **U.S. Cl.** **705/2**; 705/3

(58) **Field of Classification Search** 705/2, 705/3

See application file for complete search history.

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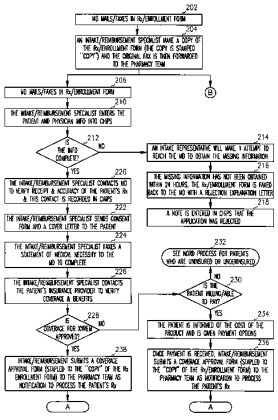
(57) **ABSTRACT**

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in the database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database, and optionally whether any actions are taken against the physician. Multiple controls beyond those for normal drugs are imposed on the distribution depending on the sensitivity of the drug.

8 Claims, 16 Drawing Sheets



cessed at **466**. At **468**, the pharmacy technician contacts the patient to schedule shipment. The process of filling the order is continued at **470** by following the process beginning at **240**.

A process, referred to as a NORD process in one embodiment is used to determine whether donated, third party funds are available for paying for prescriptions where neither insurance will, nor the patient can pay. The process begins at **510** upon determining that a patient is uninsured or underinsured. A reimbursement specialist explains the NORD program to the patient and faxes an application request form to NORD for the patient. At **515**, the intake reimbursement specialist documents in the database that an application has been received through NORD. At **520**, NORD mails an application to the patient within one business day.

A determination is made at **525** by NORD whether the patient is approved. If not, at **530**, NORD sends a denial letter to the patient, and it is documented in the database at **540** that the patient was denied by NORD. If the patient is approved, NORD sends an acceptance letter to the patient and faxes a voucher to the central pharmacy (SDS in one embodiment) to indicate the approval at **545**. At **550**, an intake reimbursement specialist submits a coverage approval form to the pharmacy team as notification that the patient has been approved for coverage. The process of filling the order is continued at **555** by following the process beginning at **240**.

An inventory control process is illustrated in FIG. **6** beginning at **610**. Each week, a responsible person at the central pharmacy, such as the director of the pharmacy transfers inventory for the week's shipments to a segregated warehouse location for production inventory. At **620**, a purchase order is generated for the inventory transferred to the production location and is sent, such as by fax, to a controller, such as the controller of the company that obtained approval for distribution and use of the sensitive drug. At **630**, the controller invoices the central pharmacy for the product moved to production. The process ends at **640**.

The central database described above is a relational database running on the system of FIG. **1**, or a server based system having a similar architecture coupled to workstations via a network, as represented by communications **160**. The database is likely stored in storage **140**, and contains multiple fields of information as indicated at **700** in FIG. **7**. The organization and groupings of the fields are shown in one format for convenience. It is recognized that many different organizations or schemas may be utilized. In one embodiment, the groups of fields comprise prescriber fields **710**, patient fields **720**, prescription fields **730** and insurance fields **740**. For purposes of illustration, all the entries described with respect to the above processes are included in the fields. In further embodiments, no such groupings are made, and the data is organized in a different manner.

Several queries are illustrated at **800** in FIG. **8**. There may be many other queries as required by individual state reporting requirements. A first query at **810** is used to identify prescriptions written by physician. The queries may be written in structured query language, natural query languages or in any other manner compatible with the database. A second query **820** is used to pull information from the database related to prescriptions by patient name. A third query **830** is used to determine prescriptions by frequency, and a n^{th} query finds prescriptions by dose at **840**. Using query languages combined with the depth of data in the central database allows many other methods of investigating for potential abuse of the drugs. The central database ensures that all prescriptions, prescribers and patients are tracked and subject to such investigations. In further embodiments, the central database may be distributed among multiple computers provided a query operates over all data relating to such prescriptions, prescribers and patients for the drug.

An example of one prescription and enrollment form is shown at **900** in FIG. **9**. As previously indicated, several fields are included for prescriber information, prescription information and patient information.

FIG. **10** is a copy of one example NORD application request form **1000** used to request that an application be sent to a patient for financial assistance.

FIG. **11** is a copy of one example application **1100** for financial assistance as requested by form **1000**. The form requires both patient and physician information. Social security number information is also requested. The form provides information for approving the financial assistance and for tracking assistance provided.

FIG. **12** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**. In addition to patient and physician information, prescription information and diagnosis information is also provided.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**. The activities grouped by sales, regulatory, quality assurance, call center, pharmacy, inventory, reimbursement, patient care and drug information. Each report has an associated frequency or frequencies. The reports are obtained by running queries against the database, with the queries written in one of many query languages.

While the invention has been described with respect to a Schedule III drug, it is useful for other sensitive drugs that are DEA or Federally scheduled drugs in Schedule II-V, as well as still other sensitive drugs where multiple controls are desired for distribution and use.

The invention claimed is:

1. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and from any and all doctors allowed to prescribe the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is prescribing the prescription drug;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using said exclusive central computer system, the controls selected

from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug.

2. The method of claim **1** , wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

3. A therapeutic method for treating a narcoleptic patient with sodium oxybate for daytime cataplexy comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed sodium oxybate and from any and all medical doctors allowed to prescribe sodium oxybate, the prescriptions containing information relating to the patient, sodium oxybate, and various credentials of the medical doctor who is prescribing the sodium oxybate;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion, such that all prescriptions for sodium oxybate are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of sodium oxybate using the exclusive central computer system that tracks all prescriptions of sodium oxybate and analyzes for the potential abuse, misuse, or diversion by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of sodium oxybate from periodic reports generated by the exclusive central computer system based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, sodium oxybate as the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using said exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe sodium oxybate by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for sodium oxybate that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the sodium oxybate to the patient in order to treat the patient with the sodium oxybate.

4. The method of claim **3**, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the

patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

5. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive computer database in a computer system, from any and all medical doctors allowed to prescribe the prescription drug and any and all patients being prescribed the prescription drug, all prescriptions for the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is prescribing the prescription drug;

requiring entering of the information into the exclusive computer database for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only via the exclusive computer database;

controlling the distribution of said prescription drug with the computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the computer system based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution of the prescription drug, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive computer database; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing the release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive computer database, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug.

6. The method of claim **5**, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive computer database; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

7. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and any and all medical doctors allowed to prescribed the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is writing the prescription;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using the exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information;

verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials;

verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug.

8. The method of claim **7**, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,765,106 B2
APPLICATION NO. : 10/979665
DATED : July 27, 2010
INVENTOR(S) : Dayton T. Reardan et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

ln column 12, lines 20-67, column 13, lines 1-20, column 14, lines 1-7, in Claim 7, delete "7. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and any and all medical doctors allowed to prescribed the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is writing the prescription;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using the exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information;

verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug;

Signed and Sealed this

Twenty-third Day of November, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug." and

insert -- 7. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and any and all medical doctors allowed to prescribed the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is writing the prescription;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using the exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical lnformation Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of

an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug. --, therefor.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,765,106 B2
APPLICATION NO. : 10/979665
DATED : July 27, 2010
INVENTOR(S) : Dayton T. Reardan et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Delete the Title Page showing an illustrative figure, and substitute the attached Title Page therefor.

Delete Sheet 2 of 16 showing Fig. 2A, and substitute the attached sheet therefor.

On Sheet 10 of 16, in Figure 9, line 23, after "ESTABLlSHED" insert -- . --.

ln column 1, line 27, delete "buterate" and insert -- butyrate --, therefor.

ln column 1, line 28, delete "theraputic" and insert -- therapeutic --, therefor.

ln column 4, line 65, delete "coveral" and insert -- coverage --, therefor.

Signed and Sealed this
Fifteenth Day of February, 2011

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

CERTIFICATE OF CORRECTION (continued)

(12) **United States Patent**
Reardan et al.

(10) **Patent No.: US 7,765,106 B2**
(45) **Date of Patent: *Jul. 27, 2010**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

(75) Inventors: **Dayton T. Reardan**, Excelsior, MN (US); **Patti A. Engel**, Eagan, MN (US); **Bob Gagne**, St. Paul, MN (US)

(73) Assignee: **JPI Commercial, LLC**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1645 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/979,665**

(22) Filed: **Nov. 2, 2004**

(65) **Prior Publication Data**

US 2005/0090425 A1 Apr. 28, 2005

Related U.S. Application Data

(62) Division of application No. 10/322,348, filed on Dec. 17, 2002, now Pat. No. 7,668,730.

(51) **Int. Cl.**
G06Q 10/00 (2006.01)

(52) **U.S. Cl.** **705/2**; 705/3

(58) **Field of Classification Search** 705/2, 705/3

See application file for complete search history.

(56) **References Cited**

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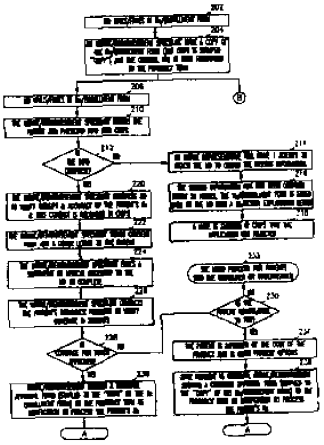
(Continued)

Primary Examiner—Gerald J. O'Connor
Assistant Examiner—Lena Najarian
(74) *Attorney, Agent, or Firm*— Schwegman, Lundberg & Woessner, P.A.

(57) **ABSTRACT**

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in the database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database, and optionally whether any actions are taken against the physician. Multiple controls beyond those for normal drugs are imposed on the distribution depending on the sensitivity of the drug.

8 Claims, 16 Drawing Sheets



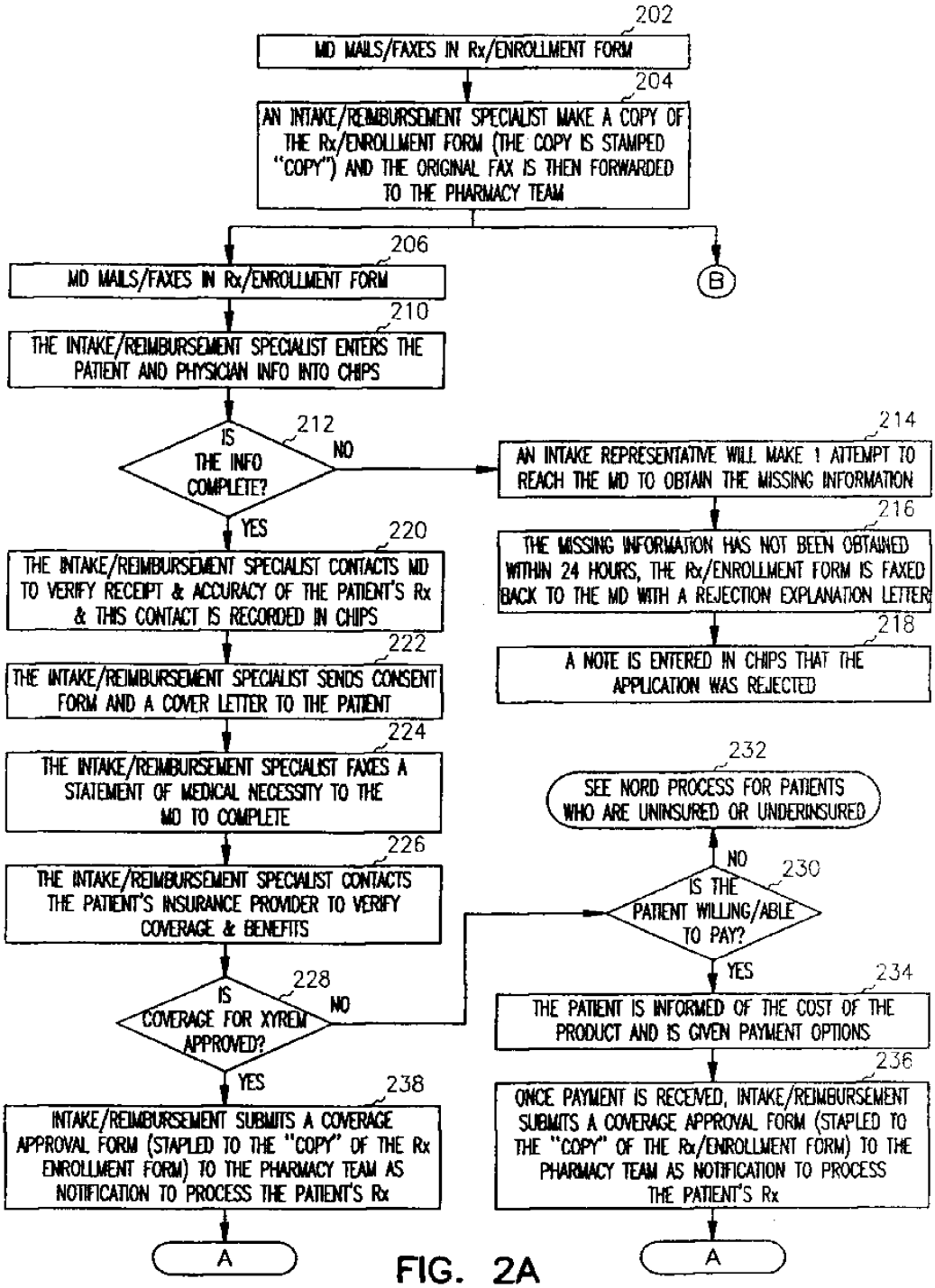

202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHIPS
212
IS THE INFO COMPLETE?
NO
214
AN INTAKE REPRESENTATIVE WILL MAKE 1 ATTEMPT TO REACH THE MD TO OBTAIN THE MISSING INFORMATION
216
THE MISSING INFORMATION HAS NOT BEEN OBTAINED WITHIN 24 HOURS, THE Rx/ENROLLMENT FORM IS FAXED BACK TO THE MD WITH A REJECTION EXPLANATION LETTER
218
A NOTE IS ENTERED IN CHIPS THAT THE APPLICATION WAS REJECTED
YES
220
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS MD TO VERIFY RECEIPT & ACCURACY OF THE PATIENT'S Rx & THIS CONTACT IS RECORDED IN CHIPS
222
THE INTAKE/REIMBURSEMENT SPECIALIST SENDS CONSENT FORM AND A COVER LETTER TO THE PATIENT
224
THE INTAKE/REIMBURSEMENT SPECIALIST FAXES A STATEMENT OF MEDICAL NECESSITY TO THE MD TO COMPLETE
226
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE & BENEFITS
228
IS COVERAGE FOR XYREM APPROVED?
NO
232
SEE NORD PROCESS FOR PATIENTS WHO ARE UNINSURED OR UNDERINSURED
NO
230
IS THE PATIENT WILLING/ABLE TO PAY?
YES
234
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
236
ONCE PAYMENT IS RECEIVED, INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx/ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
YES
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
A

FIG. 2A

EXHIBIT B

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January 30, 2012

BY EMAIL

F. Dominic Cerrito
JONES DAY
222 East 41st Street
New York, New York 10017-6702

Re: *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*,
Civil Action No. 10-6108 (ES)(CLW)

Dear Mr. Cerrito:

We write regarding ROXANE LABORATORIES, INC.'S INITIAL INVALIDITY AND NONINFRINGEMENT CONTENTIONS PURSUANT TO LOCAL PATENT RULE 3.6, served on April 14, 2011 and ROXANE LABORATORIES, INC.'S INITIAL INVALIDITY AND NONINFRINGEMENT CONTENTIONS RE: '059 PATENT PURSUANT TO LOCAL PATENT RULE 3.6, served on August 24, 2011.

Roxane intends to amend its initial invalidity and noninfringement contentions in the following manner:

(1) amend our invalidity contentions to add new bases for invalidity based on prior art FDA materials and publicly available presentations; and

(2) amend our noninfringement contentions to add citations to additional documents to be relied upon. We will not be amending the noninfringement contentions themselves.

We affirm that our amendments to the invalidity contentions will not be subject to Roxane's interrogatories seeking Jazz's contentions regarding Roxane's invalidity contentions.

Please let us know whether Jazz objects to Roxane's amendments as described above. If Jazz objects, we request a meet and confer at 3 pm EST on February 3, 2012. Please suggest an alternate time if Jazz is not available at that time.

Sincerely,

LOCKE LORD LLP

Miki Goodin

cc: All counsel of record

EXHIBIT C

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Attorneys & Counselors

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February 3, 2012

BY FEDEX AND E-MAIL

Gabriel P. Brier
Jones Day
222 East 41st Street
New York, NY 10017-6702

Re: ***Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.,***
Civil Action No. 10-6108 (SDW)(MCA) (D.N.J.)

Dear Gabe:

This responds to your February 2, 2012 correspondence regarding Roxane's amendment of its initial contentions.

Roxane will amend its invalidity contentions to add new bases for invalidity based on the following prior art materials contained in Jazz's document production to date, produced after Roxane served its initial contentions in April 2011:

JPI-00004208-JPI-00004263;
JPI-00243340-JPI-00243692;
JPI-00243951-JPI-00244117; and
JPI-00330493-JPI-00330592.

Enclosed are additional publicly available prior art materials that Roxane intends to rely upon for its contentions, bearing production numbers ROXGHB034607 to ROXGHB035120. Roxane discovered these additional materials, which are missing from Jazz's production, following a review of the materials Jazz produced *after* Roxane served its initial contentions and upon conducting its own further investigation.

Regarding the noninfringement contentions, Roxane will amend to add citations to the following documents that were produced after Roxane served its contentions in April 2011:

ROXGHB018777-ROXGHB018783;
ROXGHB018793-ROXGHB018799; and
ROXGHB031196-ROXGHB031695.

Please let us know whether Jazz objects to Roxane's amendments. If Jazz objects, please let us know whether you are available on Monday, February 6 at 3 pm EST or suggest an alternative time for a meet and confer.

Sincerely,

LOCKE LORD LLP

Miki Goodin

Miki Goodin

MG:db
Enclosure

cc: All Counsel of Record (E-mail only)

EXHIBIT D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC.,	)	
	)	
Plaintiff,	)	CIVIL ACTION NO.:
	)	2:10-cv-06108 (SDW) (MCA)
vs.	)	
	)	
ROXANE LABORATORIES, INC.,	)	
	)	
Defendant,	)	
	)	

ROXANE LABORATORIES, INC.'S INITIAL INVALIDITY AND NONINFRINGEMENT CONTENTIONS PURSUANT TO LOCAL PATENT RULE 3.6

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Attorneys for Defendant
Roxane Laboratories, Inc.

ROXANE'S NONINFRINGEMENT CONTENTIONS BEGINNING AT TAB 9 ARE HIGHLY CONFIDENTIAL AND ARE BEING PRODUCED AS OUTSIDE COUNSELS' ATTORNEYS' EYES ONLY UNTIL THE ENTRY OF A DISCOVERY CONFIDENTIALITY ORDER, PURSUANT TO L. PAT. R. 2.2

INDEX

Pursuant to the Court's order at the March 22, 2011 telephonic status conference and Local Patent Rule 3.6, Defendant Roxane Laboratories, Inc. ("Roxane") hereby provides Plaintiff Jazz Pharmaceuticals Inc. ("Plaintiff") with Roxane's initial invalidity contentions regarding U.S. Patent Nos. 6,472,431, 6,780,889, 7,262,219, 7,8,51,506, 7,668,730, 7,765,106, and 7,765,107 ("the patents in suit") pursuant to Local Patent Rule 3.6(b), copies of documents Roxane relies on in support of its invalidity contentions pursuant to Local Patent Rule 3.6(c), Roxane's initial noninfringement contentions regarding the patents in suit pursuant to Local Patent Rule 3.6(d) and copies of documents Roxane relies on in support of its noninfringement contentions pursuant to Local Patent Rule 3.6(e).

GENERAL CONSIDERATIONS

1. Roxane reserves the right to amend, supplement and/or modify these contentions as discovery proceeds in this case and new facts are developed and/or expert discovery proceeds.

2. Roxane reserves the right to amend, supplement and/or modify these contentions upon entry of a claim construction order in this case.

3. Roxane reserves the right to amend, supplement and/or modify these contentions based on Plaintiff's allegations of infringement and validity.

4. These contentions are provided to Plaintiff without any waiver of any privilege or other doctrine of protection, including but not limited to attorney client privilege or work product doctrine.

5. Provision of these contention statements does not prejudice or limit Roxane's rights to pursue discovery of any other defenses, including, but not limited to, other invalidity or noninfringement defenses.

6. Roxane does not take any particular position on any claim construction issues in these contention statements and nothing in these contentions shall be construed to limit Roxane's

rights to assert the same or a different claim construction during that portion of these proceedings.

7. These invalidity and noninfringement contentions are not set forth in any particular order and the order of presentation shall not be construed to limit Roxane's right to present all, more or none of these contentions at any hearing or trial in this matter.

8. Roxane's noninfringement contentions are HIGHLY CONFIDENTIAL and are being produced on an OUTSIDE COUNSEL'S ATTORNEYS' EYES ONLY until the entry of a Discovery Confidentiality Order pursuant to L. Pat. R. 2.2.

Tab 1-2

E. The claims of United States Patent No. 7,668,730 are invalid:

1. The method claims of the '730 patent are invalid on the ground that the claimed subject matter is not encompassed by 35 U.S.C. § 101. The patent claims are invalid because the patentee admittedly seeks to patent an algorithm or an abstract idea, *see Bilski v. Kappos*, 130 S.Ct. 3218, 3229-30 (2010), and the claims do not satisfy the machine-or-transformation test, *see In re Bilski*, 545 F.3d 943, 962-63 (Fed. Cir. 2008).

2. First, the claims of the distribution patents are directed to functions or algorithms that are implemented in computer software or a combination of software and human implemented procedures. (*See*, *e.g.*, '730 patent at col. 2, line 66-col. 3, line 13.) The Supreme Court has repeatedly rejected patents that claim a formula or an algorithm. *See*, *e.g.*, *Gottschalk v. Benson*, 409 U.S. 63, 71 (1972); *Parker v. Flook*, 437 U.S. 584, 594 (1978); *In re Grams*, 888 F.2d 835, 837, n.1 (Fed. Cir. 1989) ("It is of no moment that the algorithm is not expressed in terms of a mathematical formula. Words used in a claim operating on data to solve a problem can serve the same purpose as a formula."); *Bilski v. Kappos*, 130 S.Ct. at 3231. The claims are also directed to a patent ineligible, abstract idea, *i.e.*, the concept of checking for potential abuse of a prescription drug by a patient or the prescribing doctor and applying that concept to a specific drug, GHB.

3. Second, the method claims of the distribution patents are not patent-eligible because the claimed methods do not transform an article into a different state or thing. The patents merely claim a method of distributing sensitive drugs that does not transform or make the drugs any less sensitive. And while the methods arguably include a "data-gathering step," wherein the pharmacy technician, specialist or pharmacist must "confirm[] with a patient that educational material has been read" or "confirm[] receipt by the patient of the prescription drug,"

the Federal Circuit has noted that "gathering data would not constitute a transformation of any article." *Bilski*, 545 F.3d at 963. And while the claimed methods refer to periodic reports that are generated "to evaluate potential diversion patterns" or "potential for abuse, misuse, or diversion," this is merely an addition of "non-essential post-solution activity" that will not save the claims from invalidity. *See Bilski*, 545 F.3d at 962-63. Generating a report containing data to be analyzed later is not the main purpose of the claimed process—distributing sensitive drugs in a manner to minimize risk and protect against abuse. (*See*, *e.g.*, '730 patent at col. 1, lines 6-7.)

4. Third, the claims of the distribution patents are not tied to a particular machine. While many of the steps require uses of so-called "exclusive computer system under the control of an exclusive central pharmacy," "exclusive central computer system," "computer processor" or "exclusive central pharmacy that maintains a central database," the specification does not require any specific type of computer system—the software can be executed "on a digital signal processor, ASIC, microprocessor, or other type of possessor operating on a computer system, such as a personal computer, server or other computer system." (*See*, *e.g.*, '730 patent at col. 3, lines 10-14.) The Supreme Court in *Gottschalk* rejected a claimed process that utilized any general-purpose digital computer of any type. *See Gottschalk*, 409 U.S. at 71-72. The Board of Patent Appeals and Interferences has followed the Gottschalk approach and has rejected applications that are not tied to a specific computer system. *See*, *e.g.*, *Ex Parte Kuno, et al.*, Appeal No. 2009-006896 (B.P.A.I. Dec. 13, 2010); *Ex Parte Monk, et al.*, Appeal No. 2009-013250 (B.P.A.I. Dec. 30, 2010).

5. Finally, no patent can be obtained for a method an essential component of which consists of human mental participation. If a method necessarily involves human judgment and

choice, then the method will not meet the standard of definiteness required for patent protection. *See, e.g., Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1356 (Fed. Cir. 2005) ("The scope of claim language cannot depend solely on the unrestrained, subjective opinion of a particular individual purportedly practicing the invention. *See Application of Musgrave*, 57 C.C.P.A. 1352, 431 F.2d 882, 893 (1970)."). The claims of the distribution patents are invalid for indefiniteness because they require someone, for example, a pharmacy specialist, technician or pharmacist, to make certain subjective judgment calls as to whether the patient indeed received and read the program materials or whether there is potential for abuse of the prescription drug by the patient. The applicants repeatedly argued to the PTO that the claimed methods of distribution or distribution models "analyse[] (sic) for and determine[] potential abuse situations and current and anticipated patterns of potential adverse reactions." (*See*, *e.g.*, '730 PH, 9/30/04 Petition to Make Special at ROXGHB004395.) Neither the claims nor the specifications of the distribution patents, however, provide objective steps or criteria for evaluating the potential for abuse or on how to verify whether the patient has indeed truthfully reviewed the program materials—the technician could accept what the patient says or could exercise his or her own judgment to determine whether the patient is being truthful or not. Because the claimed methods seek to address the problems associated with the abuse and illegal distribution of sensitive prescription drugs like GHB, pharmacy specialists, technicians and pharmacists must be given authority to act on their "gut" feeling as to whether a certain patient is being deceitful or untrustworthy. Patent claims that require such human mental participation are indefinite and not proper patent-eligible subject matter.

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	Borsand (U.S. Patent Application Publication No. 2003/0074225), ROXGHB004109-36, ("Borsand"), **Califano (U.S. Patent Application Publication No. 2003/0033168), ROXGHB004137-70, ("Califano"),** **"An Interview with Orphan Medical about Xyrem" ("An Interview with Orphan Medical about Xyrem," Feb. 12, 2001, http://www.talkaboutsleep.com/sleepdisorders/archives/Narcolepsy_xyrem_interview.htm), ROXGHB004250-52 ("An Interview with Orphan Medical about Xyrem"),** **Lilly (U.S. Patent Application Publication No. 2004/0176985), ROXGHB004253-64 ("Lilly"),** **Melker (U.S. Patent Application Publication No. 2002/0177232), ROXGHB004265-81 ("Melker"),** **Moradi (U.S. Patent Application Publication No. 2004/0019794), ROXGHB004282-312 ("Moradi"),** **Ukens ("Specialty Pharmacy," Jun. 5, 2000, Drug Topics, v. 144, p. 40), ROXGHB004313-20 ("Ukens"), and** **Williams (U.S. Patent No. 6,315,720), ROXGHB004321-31 ("Williams")**
(preamble) 1. A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising: a "method of distributing" a drug "under exclusive control of an exclusive central pharmacy, the method comprising"	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a claim limitation, then it is disclosed in the prior art as follows: The preamble limitations are disclosed in at least Moradi and Ukens. The June 19, 2006 Office Action, ROXGHB004525-ROXGHB004545 ("the 6/19/06 OA") and the October 3, 2007 Examiner's Answer, ROXGHB004708-ROXGHB004725 ("the Examiner's Answer") each found "a method of distributing a drug under exclusive control of an exclusive central pharmacy, the method comprising" disclosed among paragraphs 3 (ROXGHB004295) and 24 (ROXGHB004296) of Moradi. Also, the October 18, 2006 Office Action, ROXGHB004586-ROXGHB004600 ("the 10/18/06 OA") and the Examiner's Answer each found an exclusive central pharmacy disclosed among page 3,

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	paragraphs 3-5 of Ukens (ROXGHB004315). The August 31, 2009 Decision on Appeal, ROXGHB004750-ROXGHB004763 ("BPAI Decision") decided August 31, 2009, stated: "But for the Examiner's finding, that Moradi and Lilly disclose 'exclusive' computer databases, the Examiner's remaining findings characterizing the scope and content of the cited references as well as the differences between the claimed subject matter and the prior art have not been rebutted. Accordingly, as to these findings, they are accepted as being undisputed" (BPAI Decision, p. 6, ROXGHB004756).
distributing a "prescription" drug	Disclosed in at least paragraph [0003] of Moradi: "This invention generally relates to the field of ***prescription delivery systems***, and more particularly to the field of automated prescription handling." (*See* Moradi paragraph [0003]; emphasis added, ROXGHB004295).
a "computerized" method	Disclosed in at least paragraph [0022] of Moradi: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022]; emphasis added, ROXGHB004296). One skilled in the art would have been motivated to modify Moradi to include the exclusive central pharmacy of Ukens. *See* 10/18/06 OA and Examiner's Answer ("limit access to dangerous drugs (page 3, paragraph 5 of Ukens)".)
(clause a) receiving in a computer processor all prescription requests, for any and all patients being prescribed the prescription drug, only at the	In the Examiner's Answer, the Examiner found that "receiving all prescription requests at the exclusive central pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
exclusive central pharmacy from any and all medical doctors allowed to prescribe the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the any and all medical doctors;	doctor" is disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi, paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly, and page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision, held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"receiving in a computer processor all prescription requests . . ."	As noted above in connection with the preamble, *supra*, at least paragraph [0022] of Moradi states that: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022]; emphasis added, ROXGHB004296).
"for any and all patients being prescribed" the drug, "only at the exclusive central pharmacy from any and all medical doctors allowed to prescribe" the drug, and "various credentials of the any and all medical doctors "	Ukens discloses this feature at least by describing, *inter alia*, "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed." (*See* Ukens p. 3, para. 1, ROXGHB004315). Thus, Ukens teaches that all prescription requests, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all medical doctors allowed to prescribe it. Moreover, such discussion by Ukens teaches that the various doctor credentials recognized by the Examiner disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi would, in the context of the one pharmacy of Ukens, correspond to the any and all medical doctors allowed to prescribe the specialty medication.

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
(clause b) requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;	
requiring " entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations"	In the 6/19/06 OA, the 10/18/06 OA, and the Examiner's Answer, the Examiner found that "requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations" is disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly, and page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly stating: "To one of ordinary skill in the art reading Lilly, Lilly's data storage is 'exclusive' in that it is the sole data storage that 'contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information.'" (Decision, p. 10, ROXGHB004760). The BPAI Decision holds all other findings of the Examiner to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"such that all prescriptions for" the drug are "processed only by the exclusive central pharmacy "	Ukens teaches "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)), which also indicates that such specialty medications are "prescribed." (*See* Ukens p. 3, para. 1, ROXGHB004315).

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
processing all prescriptions "using only the exclusive computer database"	This feature is shown by Borsand. Borsand describes storing ***all*** pharmaceutical-related information ***only once*** and in a ***single*** database 62 and, thus, discloses an exclusive computer database and processing prescriptions using only the exclusive computer database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). Moreover, at least Fig. 3 of Borsand indicates the pharmaceutical-related information stored in single database 62 to include pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, ***patient*** information, and ***provider*** information. Borsand further indicates that such a provider can be a ***physician***: "A ***health care provider 30*** includes any person capable of issuing a pharmaceutical 32 prescription 28 such as a ***physician***, physician's assistant, or veterinarian."

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	(*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). One skilled in the art at the time would have been motivated to modify Moradi and Ukens to include the exclusive computer database of Lilly at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "ensure that prescribers have an accurate view of their patients' use of prescription drugs and to help protect professionals from lawsuits and other potential liabilities (para. 58 of Lilly)." One would have been further motivated to modify Moradi, Ukens and Lilly to process prescriptions using ***only*** an exclusive computer database as taught by Borsand at least to allow all pharmaceutical-related information to be stored on a single database that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines. (*See* Borsand paragraph [0043], ROXGHB004127.)
(clause c) checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the prescription drug; checking doctor "credentials" checking the doctor "credentials" with a computer processor	In the 6/19/06 OA and the Examiner's Answer, the Examiner found "checking the credentials of the doctor" disclosed by paragraph 118 of Moradi (ROXGHB004304). The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Also disclosed in Moradi. *See*, for example, paragraph [0022] of Moradi which states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)).

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
checking the doctor "credentials" to determine doctor "eligibility" to "prescribe" the drug	At least Moradi paragraph [0118] (ROXGHB004304) discloses checking the doctor's credentials ("DEA number" and "license number") to determine the eligibility of the doctor to prescribe the prescription drug.
checking the "credentials" of the "any and all doctors"	As noted, *supra*, in connection with clause "a," at least by discussing "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3 para. 3, ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed" (*see* Ukens p. 3 para. 1, ROXGHB004315), Ukens teaches that all prescription requests, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all medical doctors allowed to prescribe the specialty medication. Checking the credentials of the doctor, as the Examiner recognized was disclosed in paragraph 118 of Moradi (ROXGHB004304), would, in the context of Ukens' single pharmacy, correspond to the any and all doctors allowed to prescribe the specialty medication.
(clause d) confirming with a patient that educational material has been read prior to shipping the prescription drug;	
confirming "with a patient that educational material has been read prior to shipping" the drug	In the 6/19/06 OA and the Examiner's Answer, the Examiner found that "confirming with the patient that educational material has been read prior to shipping the drug" is disclosed by paragraph [0084] of Califano (ROXGHB004163). The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). One skilled in the art at the time would have been motivated to modify one or more of Moradi, Ukens, Lilly, and Borsand to implement Califano's teaching of confirming, prior to shipping a drug, that a patient has read educational material at least to, as found by the Examiner in the 6/19/06 OA and the Examiner's Answer, "ensure that the patient knows about the risks and dangers associated with the drug (para. 43 of Califano)."

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	See also, Williams, col. 8, line 57 to col. 9, line 2 and col. 10, lines 23-46, ROXGHB004325-26. One skilled in the art at the time would have been further motivated to modify one or more of Moradi, Ukens, Lilly, Borsand, and Califano to implement Williams' teaching regarding educational material at least to ensure patient compliance with taking a drug. (*See* Williams col. 3 ln. 56-59, ROXGHB004323.)
(clause e) checking the exclusive computer database for potential abuse of the prescription drug; checking the "computer database for potential abuse of" the drug	In the Examiner's Answer, the Examiner found the feature of clause "e" of "checking the … computer database for potential abuse of the … drug" among paragraphs 6 (ROXGHB004295), 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi. The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
an "exclusive computer database"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found this feature among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the findings of the Examiner. (BPAI Decision, p. 6, ROXGHB004756).
(clause f) mailing the prescription drug to the patient only if no potential abuse is found by the patient to whom the prescription drug is prescribed and the doctor prescribing the prescription drug; mailing the drug to the patient "only if no	In the 10/18/06 OA and the Examiner's Answer, the Examiner found the feature of "only mailing the drug to the patient if no potential abuse is found …" to be

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
potential abuse is found"	disclosed among paragraphs 6 (ROXGHB004295), 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi. The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." *See also* Borsand paragraph [0120], ROXGHB004134.
mailing the drug to the patient "only if no potential abuse is found by the patient … and the doctor"	Borsand discloses checking, both before and after prescription 28 is filled, for evidence of fraud or misuse by ***provider 30*** and evidence of fraud or misuse by ***patient 22***. Borsand further explains that prescription 28 is canceled where such fraud or misuse is detected: "The system 20 facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 ***even*** after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the ***cancellation*** or modification of a ***prescription 28***. The modification of a prescription at 132 is an event triggered process. There must be an event that triggers the modification or cancellation of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a ***provider 30***, pharmacist 40, or ***patient 22***." (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)). "A ***health care provider 30*** includes . . . a ***physician***, physician's assistant, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). It would have been obvious to modify the prior art teachings to only mail the drug to the patient if no potential abuse is found by both the patient and the doctor in view of Borsand's teaching to check for fraud and abuse before and after filling the prescription and to cancel a prescription if evidence is found of fraud or misuse by either the patient or the doctor.
(clause g) confirming receipt by the patient of the	

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
prescription drug; and "confirming receipt by the patient of" the drug	In the 6/19/06 OA and the Examiner's Answer, the Examiner found that "confirming receipt by the patient of the drug" is disclosed by the abstract of Moradi. The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause h) generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns. generating the periodic reports "with the computer processor"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found that "generating periodic reports via the exclusive computer database to evaluate potential diversion patterns" is disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the Examiner's finding of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Taught at least in paragraph [0051] of Lilly: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)).

E. Roxane will not infringe the claims of United States Patent No. 7,668,730:

The '730 patent contains seven independent claims, claims 1, 2, 7, 8, 9, 10 and 11. Roxane will not directly infringe the '730 patent claims because Roxane will not perform the steps of the claimed methods—among others, Roxane will not utilize the same exclusive central pharmacy, employing the same computer database system as Jazz, to distribute its proposed ANDA product. Thus, under the Roxane distribution system, all prescriptions for all patients from all doctors will not be received only by an exclusive central pharmacy and will not be processed only by the exclusive central pharmacy using only its exclusive computer database. *See BMC Resources, Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378-79 (Fed. Cir. 2007).

There is also no indirect infringement of the '730 patent claims by Roxane because no single party will directly infringe or perform every step of the method claims. *See Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1272 (Fed. Cir. 2004). The claimed methods require more than one actor to perform each and every claim step and more than one party to exercise "control or direction" over the entire claimed methods. *See Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1329 (Fed. Cir. 2008). And even if there were to exist a contractual relationship between certain of the parties, there is no agency relationship between the different parties who perform the method steps and no party is contractually obligated to the other to perform all of the steps. *See Akamai Techs., Inc. v. Limelight Networks, Inc.*, -- F.3d --, 2010 WL 5151337, at *6 (Fed. Cir. 2010).

In addition, Roxane will not infringe any of the '730 patent claims under the doctrine of equivalents because the claim language clearly requires that "all prescription requests" for "any and all patients" from "any and all doctors" be processed only by a single, exclusive central

pharmacy using only its single, exclusive computer database. As this is not the case with the Roxane method of distribution, infringement under the doctrine of equivalents is precluded by the vitiation doctrine. Moreover, the patentees amended the claims for purposes of patentability to require these elements. (*See* '730 PH, 11/2/09 Amendment at 2 (ROXGHB004772).) Based on this amendment and the representations made by the patentees for patentability, the patentees are estopped from arguing that Roxane's distribution system for its proposed ANDA product that is separate and distinct from Jazz's distribution system would infringe under the doctrine of equivalents. Also, because Roxane's distribution method is not insubstantially different from the claimed distribution, Roxane will not infringe the '730 patent claims under the doctrine of equivalents.

The documents that support Roxane's allegations of noninfringement of the '730 patent include but are not limited to, ROXGHB000056; ROXGHB004771-ROXGHB004786; ROXGHB005421-ROXGHB5428.

Claims of Pat. No. 7,668,730	Claim Terms	Literally Present/Absent
1. A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising: receiving in a computer processor all prescription requests, for any and all patients being prescribed the prescription drug, only at the exclusive central pharmacy from any and all medical doctors allowed to prescribe the prescription drug, the prescription requests	A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:	The preamble is not a limitation. However, if the Court should hold otherwise, this is **literally absent**. In the Roxane distribution system, there is no exclusive central pharmacy that will exclusively control computerized distribution of sodium oxybate.
	receiving in a computer processor all prescription requests, for any and all patients being prescribed the	**Literally absent.** In the Roxane distribution system, there is no computer processor that will receive all

Claims of Pat. No. 7,668,730	Claim Terms	Literally Present/Absent
containing information identifying patients, the prescription drug, and various credentials of the any and all medical doctors; requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database; checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the prescription drug; confirming with a patient that educational material has been read prior to shipping the prescription drug; checking the exclusive computer database for potential abuse of the prescription drug; mailing the prescription drug to the patient only if no potential abuse is found by the patient to whom the prescription drug is prescribed and the doctor prescribing the prescription drug; confirming receipt by the patient of the prescription drug; and generating with the computer processor periodic reports via the exclusive computer database to evaluate	prescription drug, only at the exclusive central pharmacy from any and all medical doctors allowed to prescribe the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the any and all medical doctors	prescription requests for sodium oxybate for any and all patients only at the exclusive central pharmacy from any and all medical doctors.
	requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations,	**Literally absent.** In the Roxane distribution system, the information will not be entered into an exclusive computer database associated with the exclusive central pharmacy.
	such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database	**Literally absent.** In the Roxane distribution system, all prescriptions for sodium oxybate will not be processed only by the exclusive central pharmacy using only the exclusive computer database.
	checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the prescription drug	**Literally absent.** The Roxane distribution system does not include the computer processor at the exclusive central pharmacy checking the credentials of any and all doctors prescribing sodium oxybate.
	confirming with a patient that educational material has been read prior to shipping the prescription drug;	**Literally absent.** In the Roxane distribution system, there is no exclusive central pharmacy that will confirm with a patient that educational

Claims of Pat. No. 7,668,730	Claim Terms	Literally Present/Absent
potential diversion patterns.		material has been read prior to shipping the sodium oxybate. The patient is a separate actor who is required to participate in this confirming step.
	checking the exclusive computer database for potential abuse of the prescription drug;	**Literally absent.** The Roxane distribution system does not include checking the exclusive computer database associated with the exclusive central pharmacy for potential abuse of the sodium oxybate.
	mailing the prescription drug to the patient only if no potential abuse is found by the patient to whom the prescription drug is prescribed and the doctor prescribing the prescription drug;	**Literally absent**. In the Roxane distribution system, there is no exclusive central pharmacy that will mail the sodium oxybate to the patient. Furthermore, Roxane will not mail the sodium oxybate to the patient.
	confirming receipt by the patient of the prescription drug; and	**Literally absent**. In the Roxane distribution system, there is no exclusive central pharmacy that will confirm receipt by the patient. Roxane will not have direct contact with the patient. The patient is a separate actor who is required to participate in this confirming step.
	generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	**Literally absent**. The Roxane distribution system does not include the computer processor at the exclusive central pharmacy using the exclusive computer database to generate periodic reports.

Dated: April 14, 2011

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CERTIFICATE OF SERVICE

I hereby certify that on this 14th day of April, 2011, I caused a true and correct copy of the foregoing ROXANE LABORATORIES, INC.'S INITIAL INVALIDITY AND NONINFRINGEMENT CONTENTIONS PURSUANT TO LOCAL PATENT RULE 3.6 to be delivered by overnight delivery to:

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February 3, 2012

BY EMAIL

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Re: *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.,*
Civil Action No. 10-6108 (SDW)(MCA) (D.N.J.)

Dear Gabe:

We write regarding Jazz's document production.

Correspondence from Dayton T. Reardan to the FDA dated May 30, 2001 produced as JPI-00243698 references a CD-ROM "that contains both the video in MPG format as well as the script of video in MSWord format." While it appears that Jazz attempted to produce the CD-ROM as JPI-00243699 through JPI-00243765, those production pages bear a message which states, "UNSUPPORTED OR EXCLUDED FILE TYPE."

Please produce a copy of the CD-ROM referenced in Mr. Reardan's May 30, 2001 correspondence to FDA immediately.

Sincerely,

LOCKE LORD LLP

Miki Goodin

cc: All Counsel of Record

EXHIBIT F

Locke Lord LLP
Attorneys & Counselors

111 South Wacker Drive
Chicago, IL 60606
Telephone: 312-443-0700
Fax: 312-443-0336
www.lockelord.com

Myoka Kim Goodin
Direct Telephone: 312-443-0271
Direct Fax: 312-896-6271
mkgoodin@lockelord.com

January 30, 2012

BY EMAIL

F. Dominic Cerrito
Jones Day
222 East 41st Street
New York, NY 10017-6702

Re: *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*,
Civil Action No. 10-6108 (ES)(CLW)

Dear Mr. Cerrito:

We write to follow-up regarding the subpoenas Roxane previously provided you, commanding the seven inventors of the eight patents-in-suit to appear for deposition during the months of February and March.

Thank you for agreeing to accept service of those deposition subpoenas. As you offered during the meet and confer teleconference on January 9, 2012, please let us know the city and the date on which each of the inventors are available to sit for their deposition so that we can make the appropriate arrangements.

Sincerely,

LOCKE LORD LLP

Miki Goodin

cc: All Counsel of Record

EXHIBIT G

Archived: Sunday, February 26, 2012 5:19:28 PM
From: Goodin, Miki
Sent: Wednesday, February 15, 2012 4:33:42 PM
To: 'F. Dominic Cerrito'
Cc: Clement, Alan B.; 'Andrew S Chalson'; Wayda, Andrea L.; 'Lizza, Charles M.'; Abramowitz, David; 'eshih@jonesday.com'; 'estops@jonesday.com'; 'Gabriel Brier'; 'Mark Olinsky'; Fill, Peter N.; 'rgreco@RGGLiberty.com'; Feder, Scott; 'Hensler, Sarah A.'; 'Theodora McCormick'; 'Baton, William C.'
Subject: RE: Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.
Importance: Normal
Attachments: 01-30-12 Ltr to Cerrito (inventor deps).pdf ;

Dear Mr. Cerrito,

Pursuant to the parties' prior discussions, we will postpone the subpoenaed deposition of Douglas Danielson that was scheduled for tomorrow, February 16 at 9 a.m. in Grand Rapids, MI as well as the subpoenaed depositions of Colette Goderstad, Martha Hamilton, Harry Cook, Patrice Engel, Robert Gagne, and Dayton Reardon scheduled in Edina, MN.

We look forward to your response to the attached letter, proposing dates and locations for the depositions of the inventors of the patents in suit.

Sincerely,

Miki

From: Goodin, Miki
Sent: Monday, January 30, 2012 4:16 PM
To: 'F. Dominic Cerrito'
Cc: Clement, Alan B.; 'Andrew S Chalson'; Wayda, Andrea L.; 'Lizza, Charles M.'; Abramowitz, David; 'eshih@jonesday.com'; 'estops@jonesday.com'; 'Gabriel Brier'; 'Mark Olinsky'; Fill, Peter N.; 'rgreco@RGGLiberty.com'; Feder, Scott; 'Hensler, Sarah A.'; 'Theodora McCormick'; 'Baton, William C.'

Subject: Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.

Dear Mr. Cerrito,

Please see the attached correspondence.

Sincerely,

Miki

Myoka Kim Goodin

Locke Lord LLP

111 South Wacker Drive

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Myoka Kim Goodin
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mkgoodin@lockelord.com

January 30, 2012

BY EMAIL

F. Dominic Cerrito
Jones Day
222 East 41st Street
New York, NY 10017-6702

Re: *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*,
Civil Action No. 10-6108 (ES)(CLW)

Dear Mr. Cerrito:

We write to follow-up regarding the subpoenas Roxane previously provided you, commanding the seven inventors of the eight patents-in-suit to appear for deposition during the months of February and March.

Thank you for agreeing to accept service of those deposition subpoenas. As you offered during the meet and confer teleconference on January 9, 2012, please let us know the city and the date on which each of the inventors are available to sit for their deposition so that we can make the appropriate arrangements.

Sincerely,

LOCKE LORD LLP

Miki Goodin

cc: All Counsel of Record

EXHIBIT H

Locke Lord LLP
Attorneys & Counselors

111 South Wacker Drive
Chicago, IL 60606
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Fax: 312-443-0336
www.lockelord.com

David B. Abramowitz
Direct Telephone: 312-443-0591
Direct Fax: 312-896-6591
dabramowitz@lockelord.com

February 21, 2012

BY EMAIL

Gabriel P. Brier
Jones Day
222 East 41st Street
New York, NY 10017-6702

Re: *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*,
Civil Action No. 10-6108 (ES)(CLW) (D.N.J.)

Dear Gabe:

Roxane has issued over ten deposition notices and subpoenas to Jazz and third-parties represented by Jones Day, many of which have been pending for well over thirty days. We, however, have yet to receive a single proposed date or confirmation for any of these depositions.

Given that fact discovery in this case is set to close on March 30, 2012, approximately forty days from now, please provide proposed dates and locations for all of these depositions by close of business on Thursday, February 23, 2012.

If we do not receive proposed dates or locations by that time, we request a meet-and-confer on the issue on Friday, February 24, 2012 at 2:30 p.m. EST, to discuss the timing and locations of these depositions.

Sincerely,

LOCKE LORD LLP

David B. Abramowitz

cc: All counsel of record

EXHIBIT I

JONES DAY

222 EAST 41ST STREET • NEW YORK, NEW YORK 10017.6702
TELEPHONE: +1.212.326.3939 • FACSIMILE: +1.212.755.7306

Direct Number: (212) 326-7827
gbrier@JonesDay.com

February 22, 2012

VIA E-MAIL

Myoka Kim Goodin
Locke Lord LLP
111 South Wacker Drive
Chicago, Illinois 60606

Re: *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*
Civil Action No. 10-6108 (ES)(CLW)

Dear Miki:

Following are dates when the inventors of the patents-in-suit and other third parties subpoenaed by Roxane are available for depositions:

- Harry Cook – April 27 and May 1;
- Douglas Danielson – April 16, 17, 23 and 24;
- Patti Engel – April 3 and 10;
- Bob Gagne – March 29;
- Colette Goderstad – May 3, 4, 17 and 18;
- Martha Hamilton – April 18, 19 and 20;
- Judy Kelloway – March 22;
- Dayton Reardon – April 17 and 24; and
- Pamela Stahl – March 20.

Please confirm the dates Roxane would like to schedule each deposition as soon as possible so that the deponents can reserve those dates in their respective calendars.

Sincerely,

Gabriel P. Brier

cc: counsel of record (via e-mail)

SILLS CUMMIS & GROSS
A PROFESSIONAL CORPORATION

The Legal Center
One Riverfront Plaza
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Tel: 973-643-7000
Fax: 973-643-6500

One Rockefeller Plaza
New York, NY 10020
Tel: 212-643-7000
Fax: 212-643-6500

Theodora McCormick
Member of the Firm
Direct Dial: (973) 643-5390
E-mail: tmccormick@sillscummis.com

650 College Road East
Princeton, NJ 08540
Tel: 609-227-4600
Fax: 609-227-4646

March 19, 2012

Via ECF and Overnight Delivery
The Honorable Cathy L. Waldor
United States Magistrate Judge
M.L. King, Jr. Federal Bldg. & Courthouse, Room 4C
50 Walnut Street
Newark, New Jersey 07102
Fax: (973) 776-7865

Re: *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*
Civil Action No. 2:10-cv-06108 (ES)(CLW)

Dear Judge Waldor:

We along with Locke Lord LLP represent defendant Roxane Laboratories, Inc. ("Roxane") in this action. We submit this reply in support of Roxane's February 27, 2012 request for leave to supplement its Initial Invalidity and Noninfringement Contentions (D.E. 101) and in response to Jazz Pharmaceuticals, Inc.'s ("Jazz") March 14, 2012 letter opposing Roxane's request (D.E. 107, 108). Because Jazz does not oppose Roxane's request to amend its Initial Noninfringement Contentions, this reply will only address Roxane's request relating to its Initial Invalidity Contentions. With regard to the supplementation of noninfringement contentions, based on Jazz's agreement, Roxane respectfully requests that this Court grant Roxane leave to supplement its Initial Noninfringement Contentions. With respect to the supplementation of its invalidity contentions, for the following reasons and the reasons set forth in Roxane's February 27, 2012 letter, Roxane respectfully requests that the Court grant Roxane leave to supplement its Initial Invalidity Contentions.

Roxane requests leave to supplement its Initial Invalidity Contentions with material prior art it has recently discovered, despite earlier diligent searching. Jazz is incorrect to argue that (1) Roxane's request to supplement is untimely; (2) Roxane was not diligent in its search for additional prior art; (3) the art with which Roxane seeks to supplement its Initial Contentions is

duplicative and not material; and (4) Jazz would be unfairly prejudiced by Roxane's proposed supplementation. Accordingly, Roxane respectfully requests that the Court grant Roxane's request.

Should the Court agree with Jazz that Roxane's request is untimely or that good cause does not exist here, Roxane nonetheless respectfully requests that the Court allow Roxane to supplement its Initial Invalidity Contentions under the *Pennypack*factors.

ARGUMENT

A. Roxane's request to supplement its Initial Contentions is timely.

As Magistrate Judge Shwartz recently opined in *Prometheus Laboratories Inc. v. Roxane Laboratories, Inc.*, Civil Action Nos. 11-1241, 11-230, a request to amend initial contentions under those specific factual circumstances was untimely where the movant waited *five* months to request an amendment that allegedly could have been raised in the original contentions. (D.E. 109 at 15 (Mar. 12, 2012 Tr. of Recorded Op. at 12-13).) Importantly and unlike here, the requested amendment in *Prometheus* was to assert a Section 112 written description invalidity argument that was based on the patent specification. Contrary to the facts in *Prometheus,* this is not the case here. Roxane did not "wait" five months to bring the new invalidity contention to Jazz's attention—Roxane spent about three months conducting its due diligence before submitting its motion for leave to supplement its contentions. Further, Roxane's newly discovered prior art materials were not of record during the prosecution of the distribution patents and Roxane did not possess them when it prepared its Initial Invalidity Contentions in April 2011.

1. Extensive investigation and analysis was required to satisfy Roxane's Rule 11 obligations.

Jazz complains that Roxane's request is untimely because Roxane delayed until February 27 to submit its motion for leave to supplement its Initial Contentions. First, Jazz's citation to "February 27" is a red-herring. Almost a month before February 27, on January 30, Roxane notified Jazz of its intention to request leave to supplement its Initial Contentions and requested a meet and confer to discuss obtaining Jazz's consent to the amendment. (D.E. 101, Ex. B.) Jazz then obfuscated Roxane's attempts to meet and confer, until Roxane finally made its motion on February 27.

But even before Roxane could make its January 30 meet and confer request, Roxane had to satisfy its Rule 11 obligations and investigate to be sure that its "defenses and other legal contentions are warranted by existing law" and its "factual contentions have evidentiary support" as required by Rule 11(b) of the Federal Rules of Civil Procedure. Roxane conducted its due diligence and investigation as expeditiously as possible given the number and length of the

distribution patent claims to determine whether Roxane had a reasonable basis to assert supplemental, previously undisclosed bases for the contention that the claims of the distribution patents[1] are invalid. Roxane approached Jazz as soon as Roxane felt its contentions had sufficient evidentiary support (as explained below) and were warranted by existing law.

Contrary to what Jazz argues, Roxane diligently investigated (and will continue to do so, through depositions) to confirm that both the additional prior art materials it relies upon that are not in the prosecution histories of the distribution patents, and the two prior art materials that were before the Patent Office were indeed publicly available. As part of its Rule 11 investigation, Roxane also painstakingly analyzed each of the claims in the distribution patents, some of which span more than a column in length (*see* D.E. 108-2, Ex. D at JPI-163-66 (claims 1, 3, 5, and 7)) to confirm that these newly-discovered, material prior art are not cumulative of the art that was before the Patent Office, before making its motion to the Court.

2. Roxane's newly discovered prior art materials were not of record during prosecution of the distribution patents.

In its supplemental invalidity contentions, Roxane intends to rely on several 35 U.S.C. §102(b) prior art references, which describe each and every claim element and limitation of the distribution patents. These materials that will be discussed in Roxane's supplemental Invalidity Contentions are:

(a) the Preliminary Clinical Safety Review of NDA No. 21196, dated May 3, 2001 (never produced by Jazz, excerpts attached hereto as Exhibit J) ("Preliminary Clinical Safety Review"),

(b) the video and script of the video submitted to FDA on May 30, 2001 for the Peripheral and Central Nervous System Drugs Advisory Committee (*See* Xyrem Prescription and Distribution Process Video Script 2/2/01 ("Video and Script") attached hereto as Exhibit K; *see also* Mar. 15, 2012 Brier ltr. attached hereto as Exhibit L at 2, producing video and script on March 15, 2012 as JPI-243699.000001 through JPI-243699.000012), and

(c) the Peripheral and Central Nervous System Drugs Advisory Committee Briefing Booklet for the June 6, 2001 meeting (excerpts attached hereto as Exhibit M, JPI-243340 through JPI-243692) ("Briefing Booklet").

None of the above three items were before the patent examiner during the prosecution of the distribution patents and none are listed on the face of the distribution patents. (*See* D.E. 108-1,

[1] The "distribution patents" as used herein means U.S. Patent Nos. 7,668,730 ("the '730 patent"), 7,765,106 ("the '106 patent"), 7,765,107 ("the '107 patent"), and 7,895,059 ("the '059 patent").

Ex. B at JPI-119; D.E. 108-2, Ex. D at JPI-143; D.E. 108-2, Ex. E at JPI-168; D.E. 108-2, Ex. F at JPI-253.) Roxane discovered these documents through its own diligent, independent search, review and analysis of publicly available information obtained from the FDA web site.

Jazz's opposition argues as if all of the references Roxane now seeks to rely on were before the Patent Office since the new references are merely cumulative. Jazz is mistaken. While Roxane does plan to rely on two prior art references that were listed on the face of the distribution patents (but unapplied by the Examiner) (D.E. 108-1, Ex. C, (1) NADDI November 2001 National Conference presentation at JPI-4242 through JPI-4255 ("NADDI Presentation") and (2) Excerpt of Transcript of June 6, 2001 Peripheral and Central Nervous System Drugs Advisory Committee meeting at JPI-4257 through JPI-4263 ("June 6, 2001 Transcript"), these references alone were insufficient to render the claimed inventions invalid. It is only when the three new references are combined with the prior two references, does invalidity arise, as explained in more detail below in section B.1.

3. Roxane has not been in possession of the prior art materials for eight months.

Jazz is flat-out wrong, when it states that "all of Jazz documents that Roxane seeks to add were produced to Roxane in this case in July, 2011." (D.E. 108, March 14, 2012 Lizza Opposition at 3 (emphasis in original).) As Jazz is well-aware, item (b) above, which is one subject of Roxane's February 27, 2012 letter to Your Honor raising deficiencies in Jazz's document production, was just produced to Roxane on Thursday, March 15. (Ex. K at 2.) And as Jazz admits on page 4 of its March 14, 2012 submission (D.E. 108), Roxane was in possession of other necessary material in late November 2011. Moreover, while item (a) above may not be a document prepared by Jazz, it relates to Jazz's NDA No. 21196[2] and is publicly available. This document was also *never* produced to Roxane, let alone in July 2011. It is curious why Jazz failed to produce this document to Roxane as it is unquestionably relevant to this litigation and responsive to Roxane's production requests.

As for item (c) above that was included in Jazz's July 5, 2011 production, Roxane had to conduct its own investigation, as described above, before it could determine that the material in question was indeed publicly available and therefore is material prior art. Furthermore, item (c) was buried in Jazz's July 5, 2011 "document dump" of over 10,000 documents totaling 347,463 pages. Roxane reviewed and analyzed almost 250,000 pages of Jazz's production before it discovered item (c) and began its investigation as to whether the material was publicly disclosed.

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[2] As Your Honor may be aware, Jazz acquired Orphan Medical and its NDA No. 21196 for XYREM®.

Roxane cannot be faulted for conducting its diligent investigation and review before moving this Court for permission to supplement its Initial Contentions, which affect four patents containing 41 prolix claims.

B. Good cause exists for Roxane's request for leave to supplement its Initial Contentions

As discussed above, Roxane only recently discovered the materials it will rely upon in its supplemental Invalidity Contentions. These prior art materials are not only material but were indeed publicly available.

1. The references Roxane will rely upon are not cumulative of the documents listed on the face of the distribution patents.

Contrary to what Jazz argues, the additional documents that Roxane independently found are not duplicative of the two documents that are listed on the face of and were of record during the prosecution of the distribution patents. For example, neither the June 6, 2001 Transcript nor the NADDI Presentation (which were before the PTO) disclose the important claim feature of the singular exclusive nature of the central pharmacy being computerized with a computer database storing all prescriptions for XYREM® from any and all patients and any and all doctors. The lack of the these features in the prior art was the main reason that the Patent Office allowed the distribution patents to issue (*see* 12/16/2009 Notice of Allowability of the '730 patent[3] attached hereto as Exhibit N at ROXGHB004805- ROXGHB004807). In contrast, the Preliminary Clinical Safety Review, Video and Script and the Briefing Booklet describe these important claimed features that were missing from the prior art before the Patent Office at the time the Patent Office decided to allow the claims to issue.

Additionally, the references before the Patent Office did not describe all of the "controls" claimed in the '106 and '107 patents. In contrast, the Preliminary Clinical Safety Review, Video and Script and the Briefing Booklet describe all of the claimed "controls." For example, the Preliminary Clinical Safety Review describes the following "controls" claimed in the '106 and '107 patents that neither the NADDI Presentation nor the June 6, 2001 Transcript describe:

- "verifying the patient has reviewed the educational materials" (Ex. J at ROXGHB035107.)
- "shipping to another pharmacy for delivery" (Ex. J at ROXGHB035108.)
- "questioning early refills" (Ex. J at ROXGHB035108.)

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[3] U.S. Patent Application No. 10/322,348 issued as the '730 patent. (See D.E. 108-1, Ex. B at JPI-118.)

- "flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions" (Ex. J at ROXGHB035108.)
- "limiting the prescription to a one month supply" (Ex. J at ROXGHB035108) and
- "making the database available to the DEA for checking for abuse patterns in the data, for cash payments, and for inappropriate questions." (Ex. J at ROXGHB035106- ROXGHB035108.)

By way of further example, neither the NADDI Presentation nor the June 6, 2001 Transcript disclose the control of "receiving the name of an at least 18 year old designee to receive the drug," which the Briefing Booklet discloses. (Ex. M at 310-11.)

Because the additional documents that Roxane independently located contain disclosures necessary for making an invalidity assertion that are not contained in the two documents which were already part of the prosecution histories of the distribution patents, Jazz's assertion that these references are cumulative and not material is incorrect.

2. Roxane's search and investigation has been diligent.

Jazz blindly focuses on just the two documents listed on the face of the distribution patents to argue that Roxane's search for these additional documents and materials was not diligent, ignoring the necessary and newly found materials that are essential to Roxane's proposed new invalidity contentions. Thus, the fact that Roxane cited extensively to the prosecution history of the distribution patents in its Paragraph IV Certification notice letter is inapposite. Roxane is not relying solely on the documents listed on the face of the patents, as Jazz intimates; and Roxane's investigation to satisfy its Rule 11 obligations before submitting its motion for leave to supplement was extensive.

As discussed above, Roxane independently discovered after months of search and review, the main documents and materials (items (a) through (c) above) it will rely upon, and concluded after additional months of extensive investigation that those materials were indeed non-cumulative to those listed on the face of the distribution patents.

3. Roxane's newly discovered prior art materials were publicly available more than one year before the filing date of the application which later issued as the '730 patent.

Following its investigation, Roxane was able to determine that the materials it will rely on for its supplemental Invalidity Contentions were publicly available on the FDA website as of one year prior to the filing date of the application which later issued as the '730 patent and, therefore, constitute printed publications pursuant to 35 U.S.C. §102(b). Roxane continues its

investigation and to that end, has subpoenaed for deposition, former Orphan Medical employees who were involved in making at least some of these presentations.

By way of example, with respect to the June 6, 2001 Transcript and items (a)-(c) identified above, Roxane conducted extensive investigation and analysis to determine that those materials were indeed publicly available and therefore a printed publication under 35 U.S.C. §102(b). Without this investigation and determination, Roxane could not meet its Rule 11 obligations to move the Court for leave to supplement its Initial Invalidity Contentions.

Through its investigations, Roxane has found that the June 6, 2001 FDA meeting of the Peripheral and Central Nervous System Drugs Advisory Committee was not only open to the public, but was publicized on the Center for Drug Evaluation and Research ("CDER") website as late as May 23, 2001. (*See* Web Archive printout of "Calendar of CDER Advisory Committee Meetings" as of June 7, 2001 *accessible at* http://web.archive.org/web/20010607183937/http://www.fda.gov/cder/coe.htm, attached hereto as Exhibit O; 66 F.R. 24391 (May 14, 2001) attached hereto as Exhibit P.) Roxane was also able to find that the information presented at that June 6 meeting, including the entirety of the June 6, 2001 Transcript, the Preliminary Clinical Safety Review, the Video and Transcript, and the Briefing Booklet were publicly available on the FDA website at least as of October 4, 2001, possibly earlier. (*See* Web Archive printout of "CDER 2001 Meeting Documents" as of Oct. 4, 2001 *accessible at* http://web.archive.org/web/20011004081740/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm, attached hereto as Exhibit Q at 7-8; *see also* Web Archive printout of "Briefing Information" for June 6, 2001 Peripheral and Central Nervous System Drugs Advisory Committee meeting *accessible at* http://web.archive.org/web/20010811143424/http://www.fda.gov/ohrms/dockets/ac/01/briefing/3754b1.htm, attached hereto as Exhibit R (Preliminary Clinical Safety Review accessible through link labeled "Safety Review").) While it was not evident from the prosecution history of the distribution patents whether the information from and discussed at the June 6, 2001 FDA meeting was publicly disseminated, such that the information could constitute "printed publications" under 35 U.S.C. §102(b), the findings of Roxane's investigation confirm that they indeed were.

4. There will be no prejudice to Jazz should the Court grant Roxane's motion.

Jazz has not given any concrete reason why it would be prejudiced by Roxane's supplementation of its Invalidity Contentions. Jazz complains, without explanation, that it would be prejudiced because claim construction briefs have been completed and a claim construction hearing is scheduled for next month. Claim construction, however, is determined as of the filing date of the patents based on the context of the claim term in the patent claim, information and definitions provided in the patent specification and statements or representations made to the

Patent Office during prosecution of the patent. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313-17 (Fed. Cir. 2005). The prior art not a part of the prosecution history is extrinsic evidence that at best has minor implication to the claim construction analysis. *Id.* at 1317-19. Moreover, during the *Markman* briefing, for almost every single claim term in the distribution patents, Jazz took the position that the term did not need to be construed. Jazz can hardly claim prejudice that terms need a different construction now based on their own statements to the FDA of which they must have had knowledge.

And there is no explanation as to why Roxane's supplementation would lengthen the case—Jazz has yet to take a single deposition of Roxane's witnesses and the Court has not yet set any deadlines for expert discovery. Jazz, therefore, has ample opportunity to take discovery on Roxane's supplemental contentions, pursuant to the current schedule. Jazz will see the contentions again in the form of expert report(s) and Jazz can submit its own expert reports in rebuttal and take the depositions of Roxane's invalidity expert(s).

C. Analysis of the *Pennypack* factors support Roxane's motion for leave to supplement.

Should the Court find, however, that Roxane's request was untimely, or that there is no good cause for Roxane's supplementation of its Invalidity Contention, Roxane nonetheless respectfully requests that the Court permit supplementation under *Pennypack.*

Even if a party did not comply with its discovery obligations, the district court has the discretion to allow evidence following an analysis of the following factors: (1) the prejudice or surprise to the opposing party; (2) the ability of the opposing party to cure the prejudice; (3) the extent of disruption of the proceedings; and (4) bad faith or willfulness in failing to comply. *SeeMeyers v. Pennypack Woods Home Ownership Assn.*, 559 F.2d 894, 904-05 (3d Cir. 1977), *overruled on other grounds by Goodman v. Lukens Steel Co.*, 777 F.2d 113 (3d Cir. 1985).

Here, the *Pennypack*factors compel the allowance of Roxane's supplementation of the Initial Contentions: (1) There is no prejudice or surprise to Jazz because the prior art materials that Roxane will rely on are Jazz's own documents (based on developments by the inventors or other Orphan employees); (2) Jazz has the ability to cure the prejudice because it has not yet taken any depositions or expert discovery in this case; (3) because there currently exists no pretrial case schedule on expert discovery, there would be no disruption of the proceedings; and (4) there was no bad faith or willfulness in Roxane's inability to have included these invalidity bases when it submitted its April 2011 Initial Invalidity Contentions.

Because all four *Pennypack* factors favor permitting Roxane to supplement its Invalidity Contentions to include discussions of the proposed 102(b) prior art, Roxane respectfully requests the Court to grant its motion for leave to supplement its Initial Invalidity Contentions.

* * *

For the foregoing reasons and for the reasons stated in its February 27, 2012 submission to the Court, Roxane respectfully requests this Court's leave to amend its Initial Invalidity and Noninfringement Contentions pursuant to Local Patent Rule 3.7.

In addition, should the Court entertain oral argument on this issue, Roxane respectfully requests that the Court hold an in-person hearing. We thank Your Honor for your time and consideration of this matter.

Respectfully submitted,

Theodora McCormick

cc: USDJ Hon. Esther Salas
All Counsel of Record (via ECF)

Exhibit J

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

PRELIMINARY CLINICAL SAFETY REVIEW OF NDA

Brand Name:	**Xyrem**
Generic Name:	**Sodium Oxybate**
Sponsor:	**Orphan Medical, Inc.**
Indication:	**Narcolepsy**
NDA Number:	**21196**
Original Receipt Date:	**10/3/00**
Clinical Reviewer:	**Ranjit B. Mani, M.D.**
Review Author:	**Ranjit B. Mani, M.D.**
Review Completed:	**5/3/01**

Table of Contents

1. Review Sources

This submission contains an original New Drug Application for Xyrem® (sodium oxybate; γ-hydroxybutyrate) oral solution. The application is dated 9/30/2000 and was received by the Center for Drug Evaluation and Research of this Agency on 10/3/00.

In this review the words/phrases "γ-hydroxybutyrate (GHB)", "sodium oxybate", and "Xyrem®" have been used interchangeably.

Xyrem® has been developed by Orphan Medical, Inc. for the treatment of narcolepsy under IND # 49641 and Treatment IND # 57271. Data obtained from individual sponsor-investigator INDs #s 21654 (M. Scharf) and 19911 (L. Scrima) have also been used in support of this application.

Note that this is a preliminary, and not final review. Further editing of this review is possible.

1.1 Materials from NDA

In reviewing this application I have read the following volumes of the NDA submission of 9/30/00. These volumes have been read almost entirely in electronic format.

Volumes 1, 5, 25-34, 36-63, 100-104 and 114-122

I have also reviewed the following:

- A separate submission dated 12/16/00 containing the final reports for several clinical trials: OMC-SXB-16, OMC-SXB-20 and OMC-SXB-21
- The sponsor's responses to a number of requests for information from this reviewer
- A 120-Day Safety Update
- Risk management materials, comprising physician and patient information materials, supplied by the sponsor

1.2 Related Reviews, Consults

I have utilized the many reviews that I have done, since 1997, of submissions under IND # 49641 and Treatment IND # 57271 for details about this drug.

Consults that were obtained from other Divisions within the Agency and have been reviewed by me include reports from

- The Controlled Substances Staff
- The Office of Post-Marketing Drug Risk Assessment

1.3 Other Reviews

I have reviewed publications submitted by the sponsor as part of the NDA and the following recently published article:

Zvosec DL et al. Adverse Events, Including Death, Associated With The Use Of 1,4-Butanediol. N Engl J Med 2001;344:87-94

"movement disorder" was considered to be the same as the periodic leg movements). She discontinued the study medication but her subsequent course is unclear.

13.12 Reviewer's Comments

- The spectrum of adverse events seen in this Safety Update is broadly similar to that in the Integrated Summary of Safety
- A causal relationship between GHB use and depression/suicide cannot be established from the deaths, serious adverse events and adverse event dropout reports reviewed above; the patients listed had a preceding history of depression or a psychiatric disorder.

14. Risk Management Program

14.1 Structure

In response to a concern that medically prescribed Xyrem® may be diverted for illegal use, or may be consumed accidentally (e.g., by small children), the sponsor has proposed a risk management program. The components of this program are as follows:

14.1.1 Closed-Loop Distribution System

14.1.1.1 Manufacture

The bulk drug will be manufactured at a single site:(b)(4)----------
(b)

The drug product will be manufactured by(b)(4)----------
(b)(4)---------- A secondary manufacturer will be (b)(4)----------
(b)(4)---------- Both these companies as ----------
(b)(4)---------- will perform drug substance release
----------ported to be FDA- and DEA-compliant, "fill-finish" facilities

Following manufacture the drug product will be stored at a facility compliant with Schedule III regulations, where a consignment inventory will be maintained. The inventory will be owned by Orphan Medical, Inc., and the facility will be managed by(b)(4)----------(see below) which will maintain the consignment inventory.

14.1.1.2 Distribution

The primary and exclusive distributor of Xyrem® to patients will be(b)(4)----------
(b)(4)---------- A back-up distributor, currently used for the sponsor's treatment IND # 57271, is(b)(4)---------- Xyrem® will NOT be placed in retail pharmacy outlets.

The functions of(b)(4)----------will be to

- Distribute Xyr----------
- Maintain inventory and distribution records
- Maintain a patient registry

(b)(4)----------will purchase its inventory at wholesale pricing from (b)(4)-----
(b)(4)----------that inventory will be maintained at a pre-set level.
Pharmacy purchases from the manufacturer will be "recognized" by Orphan Medical.

(b)(4)----------will operate in the following manner
- ----------hysician to(b)(4)----------
- Upon receipt of a prescription this company will contact the prescribing physician and
  - Identify his/her name, license and DEA registration
  - Verify the prescription
  - (Obtain patient insurance information
- Nb)(4)--------will then verify that the physician is eligible to prescribe Xyrem® ---------- the National Practitioner Databank which contains current information about the authority of individual physicians to prescribe controlled substances. This stage of verification will include confirming that the physician has an active DEA number and will check on whether any actions are pending against the physician
- If the physician is a first-time prescriber of Xyrem® that pharmacy will then ship comprehensive printed and video materials to that physician: these materials (see Xyrem® Physician Success Program below) also contain information regarding the proper handling of the drug with an outline of precautions to be taken against diversion
- N(b)(4)-------will then contact the patient's insurance company to obtain ----------is will include obtaining a certificate of medical necessity from the physician and assignment of benefits from the insurance company. Subsequent reimbursement for prescription costs will be taken care of by a (b)(4)---------reimbursement specialist
- N----------will notify the patient of his/her approval status
- Once approval has been established, (b)(4)---------will verify the patient's home address and availability for ship----------ange shipment through (b)(4)----------or a similar carrier. The shipment will be accompanied by comprehensive printed and video materials (see Xyrem® Patient Success Program below) that also contain information regarding the proper handling of the drug with an outline of precautions to be taken against diversion
- Receipt of the drug by the patient will be ensured through the following
  - The courier service's own tracking system for shipments
  - A phone call by the pharmacy to the patient, no more than 24 hours after the shipment is delivered, to verify that the medication and educational materials have been received
- If the patient is unavailable to accept a shipment of Xyrem® and execute the required receipt, the package will be returned to the pharmacy.
- If a shipment is lost, an investigation will be launched to find it.
- All patient assignment of benefit forms and registry information will need to be signed and sent back to the pharmacy before the next scheduled refill can occur

- Every patient and prescribing physician will be registered with (b)(4)---------n a secure database. The database will contain the physician's name, address, telephone and facsimile numbers, DEA and state license numbers and prescribing frequency. The database will be made available for review by the DEA as well as other federal and state agencies upon request. From this database it will be possible to obtain the following information
  Prescriptions by physician specialty
  Prescriptions by patient name
  Prescriptions by volume (frequency)
  Prescriptions by dose
- If required by the patient's insurance company the product may be shipped by (b)(4)---------to another pharmacy for patient pick-up. The sponsor anticipates ----------be an unusual occurrence, and has a mechanism for verifying the second pharmacy's ability to protect against diversion of GHB before shipping the drug there.
- Prescription refills will be permitted in the number specified in the original prescription. In addition
  - If a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned by the pharmacist
  - A lost, stolen, destroyed, or spilled prescription/supply will be documented and the prescription replaced to the extent necessary to honor the original prescription (e.g., a destroyed or spilled bottle will reduce the prescription refill amount). The pharmacist has the discretion to grant or not grant refill requests under those circumstances and at a minimum will contact the prescribing physician to determine if the physician has any special concerns in regard to that refill request. New supplies of Xyrem® will be sent to the patient only if the pharmacist and physician are in agreement.
  - Repeat instances of lost, stolen, destroyed, or spilled prescriptions/supplies will be flagged for monitoring and future instances thoroughly questioned
- The quantity of medication to provided with each refill will be guided by the following
  - With the first prescription it is planned to provide the patient with only one month's supply of Xyrem®.
  - Following further contact between the pharmacy and patient, and verification that the patient understands the material in the Xyrem® Patient Success Program, supplies of Xyrem® that are intended to last longer than a month may be shipped
  - The quantity of drug shipped to the patient with each refill may also be regulated based on the requirements of the patient's health insurance plan and the terms of the prescription itself
  - It is anticipated that the majority of patients will receive only one month's shipment at a time and never more than 3 months' supply per shipment.

14.1.2 Drug Product Kit

The drug product kit will consist of

- The drug product, a clear solution, in a 240 mL amber bottle with a closure mechanism that is child-resistant
- The Press-In-Bottle-Adapter (PIBA Well) which will be inserted into the bottle by the pharmacist

- An Exacta-Med Dispenser which allows the patient to withdraw the appropriate dose of drug
- Two child-resistant dosing cups, one for each of 2 nightly doses. The first dose will be consumed just prior to lying down at bedtime and the second dose will be placed at the bedside, and sealed with a childproof lid until consumed by the patient 2.5 to 4 hours later.
- A package insert which includes a patient information sheet*

Every box of Xyrem® shipped to the patient will contain all the above items

*The patient information sheet includes the following information
- Dosing instructions
- Preparation of dose
  The steps involved in dose preparation and use are as follows
  - Remove bottle cap
  - Insert measuring device into bottle containing PIBA Well
  - Draw up prescribed dose
  - Remove measuring device from bottle
  - Empty dose into first dosing cup
  - Dilute with 60 mL of water
  - Repeat procedures with second dosing cup
  - Place second dosing cup at bedside after securing lid
  - Set alarm for no later than 4 hours after first dose
  - Drink first dose sitting up and immediately lay down
  - Awake for second dose.
  - Drink second dose sitting up
- Side-effects
- Special concerns: memory problems, dependence, withdrawal, changes in behavior and thinking, pregnancy
- Safe use of Xyrem®:
  - scheduling
  - self-observation for behavioral changes
  - cautions regarding concurrent use of medications and alcohol, driving, operating machinery, piloting an aircraft and pregnancy
  - caution against sharing Xyrem® with others
  - safe storage and disposal

14.1.3 Xyrem® Physician Success Program

This program consists of a videotape and printed material.

14.1.3.1 Distribution

This program will be distributed as follows
- "Customer targets." This phrase refers to a database of physicians who have prescribed modafinil more than 4 times (about 4000 physicians have done so at present but the data will be refreshed when Xyrem® is launched). When Xyrem® is launched the program will be mailed to the target physicians as well as handed to them by sales representatives. The mailing as well as the receipt from sales representatives will be documented. No physician samples will be provided by the sales representatives
- When a physician prescribes the drug for the first time, he/she will receive also be mailed the program: the mailing will be documented as will a follow-up phone call to the physician confirming receipt

Exhibit K

Xyrem Prescription and Distribution Process

Video Script 2/2/01)

Audio	Video	Titles
1. [Fade in music]	Graphic texture of oranges and yellows	
[Up music.]	logo of Xyrem emerges	Fade in first title/logo graphic.
		Xyrem® (Sodium Oxybate) Oral Solution
[Fade out music.]		Fade out first title/logo graphic. Fade in video title.
		Prescription and Distribution Process
2. Narcolepsy, it is a serious debilitating condition that diminishes the quality of life for approximately 125,000 Americans.	Fade to head-to chest shot of narrator.	
3. Xyrem is a promising new medication that, for some patients with narcolepsy, can significantly reduce the incidence of cataplexy, as well as improve symptoms of daytime sleepiness.	Fade to table-top shot of Xyrem box and a display of its contents.	
4. But, because Xyrem is a controlled substance, Orphan Medical wants to make certain that "only" patients for whom it is prescribed have ongoing access to this important treatment.	Fade back to shot of narrator sitting on desk.	

5. Orphan Medical is committed to a distribution plan that is both safe and effective for patients and also protects the general public by minimizing opportunities for the diversion of Xyrem to unauthorized individuals.	Fade to shot of Orphan representative making a presentation about success plans—perhaps pointing to a bullet point on an overhead screen.	
6. To achieve that goal, Orphan Medical--after extensive consultation with law enforcement, prosecutors, field law enforcement personnel, pharmaceutical distribution experts, forensic experts, DEA consultants, and drug diversion experts-- has developed a comprehensive, restrictive distribution program.	Fade to build graphic that begins with shot of Xyrem box in center of screen.	Fade in titles as mentioned. • **law enforcement** • **prosecutors** • **field law enforcement personnel** • **pharmaceutical distribution experts** • **forensic experts** • **DEA consultants** • **drug diversion experts**
7. In addition to thorough patient and physician education about Xyrem,	Fade to shot of narrator holding up a variety of patient/physician education material and, then, setting it down on the desk.	
8. As well as multiple security checks before, during and after prescription fulfillment.	Cut to split-screen shot showing a) pharmacist assistant verifying doctor's license b) pharmacist unlocking cabinet, c) patient signing for delivery by Federal Express.	

9. The purpose of this video is to outline, step-by-step, all of the security measures that will occur whenever a prescription of Xyrem is written and filled.	Cut back to narrator.	
10.	Fade to freeze-frame shot of a physician consulting with a patient.	Fade in title with freeze frame.
When Xyrem first becomes available, a select group of physicians with a documented history of prescribing medications for patients with narcolepsy will receive an educational module, in the mail, called the Physician Success Program.	Begin action	**Notify A Select Group of Physicians about Xyrem®** Fade out title
11. This program will introduce these selected physicians to Xyrem and includes a videotape, Physician Success Program contact information, a patient education presentation, templates for medical records and patient contracts, and information about third-party payor reimbursement. This mailing will be documented and no medication samples will ever be provided.	Fade to table-top display of Physician Success Program materials.	Fade in titles when mentioned in narration. • **Documented mailing** • **No physician samples**

12. Complementing this effort, a representative from Orphan Medical will visit each targeted physician and reinforce the information provided in the Physician Success Program. The representative will ask the physician to sign a receipt if any additional Physician Success Program materials are left for the physician's office.	Fade to shot of rep and physician meeting and discussing Physician Success Program materials.	
13. A crucial component of the secure distribution of Xyrem is the use of a specialty pharmacy. The specialty pharmacy is a single, centrally-located facility that will have a variety of distribution, documentation, and security responsibilities.	Fade in narrator	Fade in title **Specialty Pharmacy** Fade out title.
14. A staff of dedicated pharmacists, reimbursement specialists, and customer service representatives will provide a closed-loop distribution system that will not only serve patients and prescribers, but will also be able to generate data, recording prescribers, patients and dosing that could provide information for any possible investigations and prosecutions for state and federal authorities.	Fade to shot of pharmasist	

15. This distribution system begins with a secure holding warehouse area where an inventory of Xyrem is kept, according to scheduling requirements by federal and state laws and checked several times a day.	Fade to shot of pharmacy employee unlocking holding warehouse to reveal Xyrem supply.	Fade in benefit title. **Secure inventory storage**
16. On a regular basis, a small supply of Xyrem is moved from the gated and locked warehouse to a gated and locked area within the same pharmacy. Only qualified pharmacists and pharmacy technicians, dedicated to the Xyrem Program will be allowed access or will handle Xyrem.	Cut to shot of pharmacy employees transferring inventory.	
17. Both Orphan and the pharmacy acknowledge and document every time any inventory is moved.	Slow fades shot of a) pharmacy personnel signing some transaction documentation b) Orphan personnel at computer screen documenting the same.	
18. Now, let's take a step-by-step look at how the specialty pharmacy provides verification and documentation of both the prescription and the prescribing physician before preceding to fill any requests for Xyrem.	Fade to shot of narrator.	
19. When a physician determines that Xyrem is an appropriate medication for a patient,	Fade to shot of physician in the office using Orphan Medical's materials to educate a patient about Xyrem.	
20. The prescription is faxed or mailed, depending on each states pharmacy board regulations, directly to the specialty pharmacy.	Fade to shot of physician faxing prescription.	

21. Upon receipt of the prescription, the specialty pharmacy first verifies if the prescribing physician is on Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data from the physician's home State Board of Health to determine if there are any pending or previous actions against the physician.	Cut to shot of pharmacy employee picking up prescription fax and sitting down at a computer to verify physician's eligibility. Freeze frame.	Fade in title with freeze frame. **Physician verification**
22. Next, the pharmacy calls the physician's office to verify the origin of the prescription.	Fade to split-screen shot of pharmacist and physician on the phone. Freeze frames.	Fade in title with freeze frames. **Prescription verification**
23. If it is the physician's first time prescribing Xyrem, the specialty pharmacy will ship a Xyrem Physician Success Program to the Physician's office to ensure that the physician is given every opportunity to become thoroughly familiar with a prescriber's responsibilities regarding Xyrem.	Fade to table-top display of the Physician Success Program components.	
24. Another important benefit of using a single, specialty pharmacy for the distribution of Xyrem is that it's possible to keep all the data about inventory, physicians, reimbursement, patients, and delivery in one efficient and quickly-accessible location.	Fade to shot of narrator.	Fade in benefit title. **All data in one location**

25. Some of the data available include prescriptions by physician specialty, prescriptions by patient name, prescriptions by volume or frequency, and prescriptions by dose.	Fade to build title graphic.	Fade in title. **Data Available** Fade in bullet points when mentioned. • **Prescriptions by physician specialty** • **Prescriptions by patient name** • **Prescriptions by volume (frequency)** • **Prescriptions by dose**
26. The specialty pharmacy will also be responsible for contacting the patient's third-party payor to research benefits, file claims, appeal denials, and collect reimbursement.	Cut to shot of pharmacy employee on phone with insurance company.	
27. The specialty pharmacy will also follow specific procedures for communicating with the patient both before and after the Xyrem is shipped.	Fade to shot of narrator.	
28. First, the specialty pharmacy will contact the patient directly to make specific arrangements for the patient or the patient's authorized designee to personally receive the package containing the Xyrem and to discuss or verify third-party payor reimbursement.	Slow fades of patient and pharmacist discussing arrangements over the phone.	Fade in title. **Patient communication**

29. Throughout this entire process of verification and documentation, if any of the data or behavior suggests the possibility that Xyrem may be used inappropriately, the specialty pharmacy is empowered to contact the appropriate authorities.	Pharmacy finds a doctors that does not verify.	
30. The patient's medication will be shipped overnight by Federal Express utilizing a tracking system designed specifically for the specialty pharmacy.	Fade to shot of pharmacy employee putting Xyrem in Fed Ex packaging.	Fade in title. **Overnight delivery**
31. And, if it is the patient's first time receiving Xyrem, the specialty pharmacy will also include the Patient Success Program in the package.	Cut to close-up shot of pharmacy employee adding the Patient Success Program to the Fed Ex packaging.	
32. This program will introduce the patient to their responsibilities pertaining to Xyrem and includes a videotape, Patient Success Program contact information, advice for safe in-home storage and disposal, advice for traveling with Xyrem, and information about third-party payor reimbursement.	Fade to table-top display of Patient Success Program materials.	
33. Shipments of Xyrem can only be left with the patient or the patient's authorized designee. Therefore, if the patient or the patient's designee is not available to receive or sign for the Xyrem, the package will be returned to the specialty pharmacy. Also, if the package is somehow lost, the specialty pharmacy will initiate an immediate investigation.	Fade to shot of Fed Ex employee with package knocking on a patient's door. Patient—answers the door and they have a brief conversation. The Fed Ex employee shakes his head and gets signature. At the same time, the person closes the front door.	

34. Because the specialty pharmacy provides next-day, follow up through their in-house FedEx computer stations, they will telephone the patient within 24 hours after receiving the shipment of Xyrem.	Fade to shot of specialty pharmacy employee working at an in-house FedEx computer station.	Fade in title. **Real-time tracking**
35. During this call, the specialty pharmacy will confirm receipt of the Xyrem prescription and the Patient Success program,	Cut to split-screen shot of pharmacy employee and patient on the phone. Patient has all the Xyrem materials spread out on a table.	
36. counsel the patient about Xyrem dosing and compliance,	Cut to close-up shot of patient removing contents of the Xyrem box.	
37. and ensure the patient's understanding of the Patient Success Program as well as the patient's legal responsibilities and liabilities relating to the bifercated scheduling of Xyrem.	Cut to slow fades of pharmacy employee and patient on the phone. Patient is holding and reading a patient education brochure.	
38. The specialty pharmacy also keeps track of expected prescription refill dates and will contact the patient ahead of time. Patients who request a refill before their refill date will be flagged and their physician contacted. The physician verification process is repeated before every refill is sent.	Pharmacy finds a patient that does not verify on getting a refill	
39. As you can see, the Xyrem prescription and distribution process is a comprehensive program that ensures the responsible distribution of this important medication.	Fade to shot of narrator.	

40. Both physicians and patients will receive a thorough education about the use and safe handling of Xyrem.	Fade to shot of physician and patient in the office reviewing patient education materials.	Fade in title. **Thorough physician and patient education**
41. Strict adherence to security and verification protocols will minimize diversion of the medication to unauthorized individuals.	Fade to shot of Fed Ex employee at patient's door. Patient is signing the Fed Ex receipt and receiving the package of Xyrem.	Fade in title. **Helps prevent diversion**
42. A staff of dedicated specialists provide a closed-loop distribution system that will not only serve patients and prescribers, but will also have information to support any possible investigations and prosecutions.	Fade to shot of pharmacy employee entering data on a PC.	Fade in title. **Prosecution assistance**
43. And, most importantly, the Xyrem prescription and distribution process will ensure that this life-changing medication will be available to the thousands of patients who so desperately need it. [Fade in music.]	Fade to shot of happy patient after talking on phone at home with the success program.	
44. [Up music.]	Fade to black.	Roll credits, disclaimers, contact information, copyright, etc.

Exhibit L

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March 15, 2012

VIA E-MAIL & OVERNIGHT COURIER

Myoka Kim Goodin
Locke Lord LLP
111 South Wacker Drive
Chicago, Illinois 60606

Re: *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*
Civil Action No. 10-6108 (ES)(CLW)

Dear Miki:

We write regarding Roxane's February 29, 2012 letter to the Court concerning alleged deficiencies in Jazz's document production. As an initial matter, we are confused by Roxane's failure to raise any of these issues with Jazz before going to the Court. We are also confused concerning Roxane's inability to locate responsive documents in Jazz's production. As for Roxane's other complaints, Jazz either has produced or is amenable to producing responsive documents to the extent they exist. Accordingly, Roxane's February 29th letter to the Court has no merit and should be withdrawn.

In its letter, Roxane complains that it has not received marketing documents and forecasts from Jazz. This is incorrect. Jazz produced its marketing materials relating to XYREM® nearly six months ago. (*See* enclosed Aug. 15, 2011 letter to David Abramowitz regarding production of JPI-00358173-792.) Also, forecasts for XYREM® sales were produced at JPI-00463234. Roxane's request for a Court order compelling Jazz to produce final marketing documents and forecasts is therefore moot. Roxane should withdraw that request.

Roxane also accuses Jazz of failing to produce profit-and-loss statements. This is also incorrect. Such documents were produced at JPI-00463226 through JPI-00463233. Roxane's request for a Court order concerning production of profit-and-loss statements is therefore moot, and should be withdrawn.

Roxane further complains that Jazz's document production concerning conception and reduction "seems to be lacking." As Roxane is aware, Jazz did not own XYREM® when the research and development underlying the patents-in-suit was conducted. Jazz has produced all such non-privileged documents in its possession, custody or control. Roxane therefore should withdraw its request for a Court ordering relating to conception and reduction to practice documents.

With respect to Jazz's acquisition of Orphan Medical, Jazz has produced any communications and agreements in its possession between Jazz and Orphan regarding sodium oxybate. We have searched for but have been unable to find the group of documents referred to in the "Due Diligence Index" identified in your letter. To the extent there are any individual documents on that index that Roxane believes would be relevant but has not otherwise been produced, Jazz would be agreeable to searching for such individual documents. We note, however, that the list refers to several documents concerning subject matter that would be unlikely to contain responsive information concerning XYREM® or sodium oxybate, e.g., documents concerning human resources, corporate information, tax information, financing information, and other products. Roxane should therefore withdraw its request for a Court order relating to due diligence documents.

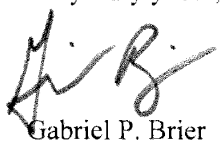
With respect to alleged off-label prescribing, Jazz produced responsive documents at JPI-00476740-745. The enclosed disc contains replacement copies of these documents that are being produced because the initial production contained processing errors.[1] This moots Roxane's request for an order compelling the production of documents concerning alleged off-label use, and that request should be withdrawn.

With respect to Roxane's request for a video and script submitted to the FDA on May 30, 2001 by Orphan Medical, the enclosed production disc contains a copy of the video at JPI-00243699.000001 and the transcript at JPI-00243699.000002-012. This moots Roxane's request for an order compelling production of the CD-ROM, and that request should be withdrawn.

With respect to Roxane's complaints regarding email attachments, Jazz is willing to consider specific examples of emails with allegedly missing attachments identified by Roxane. In that regard, the attachment for the email identified in your February 29th letter is included on the enclosed disc at JPI-00458946.000001-015. Jazz does not agree, however, to reproduce thousands of emails without any attempt by Roxane to identify specific emails with missing attachments. If Roxane has more specific examples of emails with allegedly missing attachments, please provide them. Otherwise, Roxane should withdraw its request for an order concerning email production.

In light of the above, we request that Roxane withdraw its February 29, 2012 letter to the Court regarding alleged deficiencies in Jazz's production. Please let us know by close of business on Friday, March 16 whether Roxane agrees to do so.

Very truly yours,



Gabriel P. Brier

Enclosures

cc: counsel of record (via e-mail w/o enclosures)

[1] The enclosed disc also contains more legible copies of the documents numbered JPI-00463218-234.

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August 15, 2011

VIA E-MAIL & OVERNIGHT COURIER

David B. Abramowitz
Locke Lord Bissell & Liddell LLP
111 South Wacker Drive
Chicago, Illinois 60606

Re: *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*
Civil Action No. 10-6108 (ES)(CLW)

Dear David:

Subject to the stipulated Discovery Confidentiality Order in this matter, enclosed are documents and things bearing Bates numbers JPI-00358173 through JPI-00358792.

Sincerely,

Gabriel P. Brier

Enclosure

cc: counsel of record (via e-mail w/o enclosure)

Exhibit M

ORPHAN MEDICAL

May 3, 2001

Advisors and Consultants Staff
Center for Drug Evaluation and Research, ORM
Food and Drug Administration
HFD-21, Room 1093
5630 Fishers Lane
Rockville, MD 20852
Peripheral and Central Nervous System Drugs Advisory Committee,
c/o Dr. Sandra Titus; 301-827-7001

Subject: **Xyrem® (sodium oxybate) oral solution, NDA #21-196**
USER FEE NUMBER 3,814, ORPHAN DESIGNATION NUMBER 94-858

Peripheral and Central Nervous System Drugs Advisory Committee
Briefing Booklet for June 6, 2001 Presentation

Dear Advisory Committee Member:

This briefing booklet presents data for the use of Xyrem for treatment in narcolepsy, a seriously debilitating disease. The disease is lifelong after onset, which usually occurs in the second and third decade of life. Historically, diagnosis takes an average of ten years due to low physician awareness. These factors and disease symptomatology negatively affect patients' education, employment potential and interpersonal relationships for the rest of their lives. Current treatments are unsatisfactory, and although approved therapies for daytime sleepiness exist, no therapies are approved for the auxiliary REM-related symptoms of cataplexy, hypnagogic hallucinations, and sleep paralysis. For these reasons Xyrem represents an important new therapeutic advance to meet an unmet medical need.

Narcolepsy affects an estimated 125,000 individuals in the United States, an incidence that qualifies for orphan drug designation. Excessive daytime sleepiness is diagnostic of this disease, while the REM-related symptoms affect 60-90% of patients. About 25,000 individuals have cataplexy of severity requiring pharmacologic intervention.

Limited patient availability has influenced the size of the database. Xyrem safety, efficacy, pharmacokinetics, abuse pharmacology, scheduling and risk management are summarized in this booklet from over 250 volumes of electronic and paper information which has been submitted to FDA for review.

This NDA was designated a priority by the FDA shortly after submission in recognition of the fact that narcolepsy is serious and debilitating with inadequate therapeutic options, particularly for cataplexy. The compelling medical need of narcoleptic patients for additional therapeutic options is summarized in section 2.

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The premise for approval for efficacy is based upon four double-blind controlled clinical trials, two of which were sponsored by the company and two of which were conducted by academics, one in the US and one in the Netherlands. Efficacy is summarized in section 3 of this booklet.

The company has collected data from over 400 patients during the course of its two INDs, including a treatment IND approved by FDA in 1998 (section 4). In addition, an investigator in this country has been treating a small group of patients (N=143) for up to 18 years under his IND. The company has collected information from his database that reflects over 900 patient years of clinical safety data. Information from such a database is not usually available for a new chemical entity. Questions related to this database led to the cancellation of the initial advisory committee review scheduled for March 15th. The company has now addressed these questions and our response is under review by FDA. Overall the safety data set, while not large (604 patients and subjects), supports the safe use of Xyrem for the proposed indication.

The pharmacokinetics and abuse pharmacology are included for completeness in sections 5 and 6 respectively. Also included are sections dealing with scheduling and risk management.

Public health issues related to GHB have been well recognized for over 10 years. FDA took action to remove GHB from the market in 1990 due to public health risks of abuse and its illegal promotion as a 'dietary supplement'. FDA subsequently approached Orphan Medical to develop this compound in narcolepsy in 1994. FDA again took additional action when analogues began to surface over the last 5 years. The scheduling of Xyrem was completed in 2000 following extensive public debate in Congress with advice from FDA, DEA and other stakeholders. A federal law was enacted in 2000 to create a bifurcated schedule for GHB with all illicit use falling under schedule 1 and medical use placed into schedule 3. This law, along with the 2000 World Health Organization expert working committee recommendation for schedule 4, and the HHS recommendation to Congress is included in section 7. Regrettably, these laws do not adequately address promotion of precursor chemicals as abuse alternatives to GHB.

The advisory committee has also been asked to review and discuss the risk management of Xyrem. Risk management refers to minimization of public health issues associated with a pharmaceutical product. There is no evidence that Xyrem has been diverted or used for any purpose but to evaluate its safety and efficacy in treating narcolepsy. We believe that the precautions included in the Company's post-marketing program will constrain in every way possible the risks associated with this medicine while allowing its use by patients to meet their medical needs. These precautions include mechanisms to educate physicians and patients about the proper use of Xyrem, the unique implications of the bifurcated schedule, as well as closed-loop prescription and distribution systems to restrict the opportunity for diversion or misuse. Included with this package of information from Orphan Medical is a short 8-minute video on the prescription process, along with patient and physician education materials (the two binders). The risk of diversion and abuse of Xyrem is further reduced when these post-

marketing processes to which the Company has committed are combined with the scheduling restrictions recommended by FDA and imposed by Public Law 106-172. It should be noted that narcolepsy patients and their physicians are already very familiar with the responsible use of controlled substances since they typically manage symptoms with schedule 2 amphetamine related medications and other medications in schedule 4.

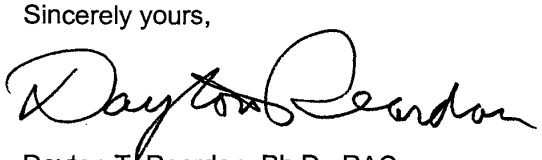
It is an unfortunate fact that illicit GHB substances, not Xyrem, represent a risk to the public health. This risk will neither be increased by approval of Xyrem, nor decreased by denial of approval due to the easy availability of analogues of GHB. While Orphan Medical has no legal responsibility for the illicit use of GHB or its precursor chemicals, we have made a moral and practical commitment to assist the FDA, DEA and other law enforcement and abuse specialists in their efforts to minimize the public health risk of illicit GHB substances.

Sodium oxybate, or gamma hydroxybutyrate, is defined as a new chemical entity since it has never been approved for human use in the United States. Products containing oxybate have been approved in Europe, as an anesthetic since the 1960s, and in Italy for use in treatment of alcoholism since 1994. We believe the data presented herein establish the medical need, efficacy and safety of Xyrem, and provide the basis for our request for approval of the following proposed indication:

> *Xyrem® (sodium oxybate) oral solution is indicated to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy.*

Should you have any questions not addressed in this briefing booklet, please let us know through Dr. Sandra Titus, the Committee's Executive Secretary.

Sincerely yours,



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cc: Russell Katz MD for NDA #21-196

Xyrem® (sodium oxybate) oral solution

NDA #21-196

Briefing Booklet for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting

June 6, 2001

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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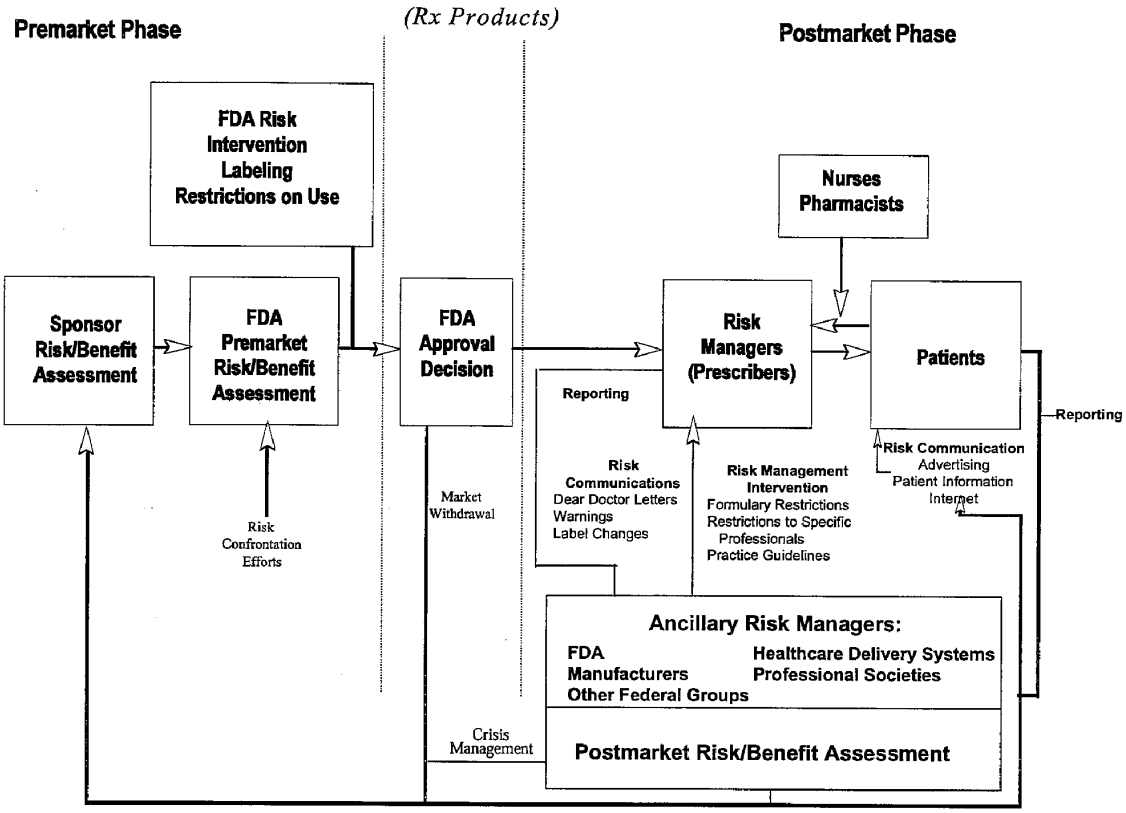
SECTION 8
RISK MANAGEMENT

8.0 RISK MANAGEMENT

8.1 Introduction to Risk Management

The system used to manage the risks presented by medical products during their pre-market and post-market phases involves many different parties with various, and sometimes different, interests. Each party's goal, however, is limitation of the risk a medical product presents to the patient and the public. It is a complex system, presented graphically in Figure 8.1.

Figure 8.1. Complex System for Managing the Risks of Medical Products



Wishing to simplify and update this risk management system, the FDA established a Task Force in 1999 to reconsider the existing system, identify issues, and recommend solutions (Task Force on Risk Management 1999).

One of the major issues highlighted by the Task Force was that each of the partners within this system lacked clearly defined roles and responsibilities. The Task Force further determined that actions of the participants are not well integrated and coordinated.

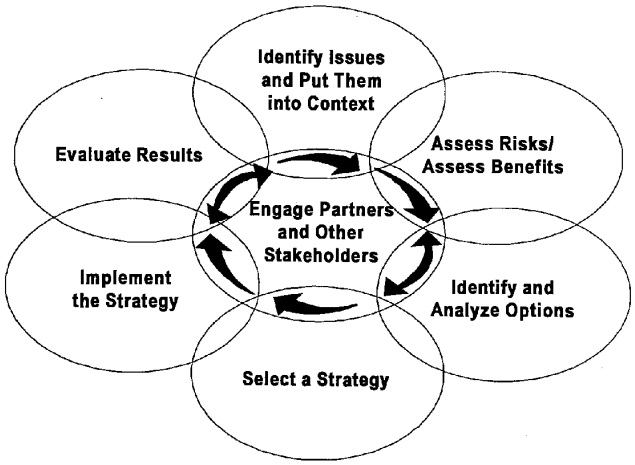
An example is the reporting of adverse events. All pharmacists are trained to identify adverse events, and to report them to the manufacturer, which, in turn, reports them to the FDA. This process is not always effective within the current healthcare environment, in which patients can make several visits to many different physicians, use multiple pharmacies, and take over-the-counter or nutritional products without medical supervision.

Rarely is a thorough medication audit performed on a patient, and consequently, patients may not receive informed counseling regarding potential medication interactions. Resultant adverse events often are not correlated to concomitant medications. While regulations do exist to support counseling of patients by trained pharmacists, many retail pharmacies have addressed this obligation by simply providing written instructions for a given medication, and the opportunity for integration of care is again lost.

Integration of a patient's total care is impossible without all of the care providers working in concert.

The Task Force concluded that "risk confrontation" is key to the effective management of risk associated with medical products. It recommended a simplified model that takes into account the current health care delivery environment (see Figure 8.2).

Figure 8.2. Proposed Risk Management Model



Risk confrontation is the identification of salient risks and the design of methods to address these risks. This model revolves around the participation of relevant partners and stakeholders, that is, interested parties that can contribute to effective risk management. These parties, referred to as the "Interested Community," have to be involved in the risk identification and management processes.

Orphan Medical has embraced and incorporated the conclusions of the FDA Task Force in the design of its risk management system. These are presented in the next sections.

8.1.1 RISK MANAGEMENT OF XYREM USING THE RISK CONFRONTATION MODEL

8.1.1.1 Identify Issues and Put Them Into Context

The first step in the risk confrontation model is to identify issues and understand their real-world implications. Orphan Medical invited stakeholders to participate in a series of meetings, between 1998 and 2001, in order to discuss Xyrem and its potential risks. Stakeholders included in these meetings were:

- Narcolepsy patient organizations
- Narcolepsy patients
- Physicians expert in treating narcolepsy
- Drug abuse experts
- Criminal prosecutors
- Forensics experts
- Sexual assault investigators

- Drug abuse trend experts
- Legislative personnel
- Field law enforcement
- Various law enforcement officers who train other officers in drug recognition issues
- Emergency room physicians
- Toxicologists and Poison Control Center directors
- The National Association of State Controlled Substance Authorities (NASCSA)
- The National Association of Drug Diversion Investigators (NADDI)
- Rape crisis centers and advocates

The objectives of the meetings were to:

1. Identify all of the key risks relating to the use of Xyrem as well as illicit GHB and related chemicals; and to
2. Propose methods to contain the risks identified.

The stakeholders first agreed on the following list of facts and issues.

- Narcolepsy is a disabling disease estimated to affect fewer than 140,000 people in the United States. Since it is a difficult disease to diagnose, only an estimated 75,000 individuals with narcolepsy have received an accurate diagnosis and are receiving treatment.
- Cataplexy, a disabling symptom of narcolepsy, is distinguished by a loss of muscle tone when the patient is confronted by emotional stimulus. It is estimated that the number of diagnosed/treated narcolepsy-with-cataplexy patients in the U.S. is approximately 25,000. Current treatments for cataplexy are limited in their effectiveness and can have troubling adverse effect profiles, leading to their discontinuation by some patients.
- Physicians and narcolepsy patients are familiar with the restrictions and risks associated with controlled substances. Schedule II and IV medicines are typically used in the attempt to control the symptoms of narcolepsy.
- The results of clinical trials in which Xyrem was evaluated indicate that it is safe and efficacious when used to treat narcolepsy.
- Illicit use of GHB and related chemicals is growing, with serious physical consequences to users being identified (Zvosec 2001).
- The sources of illicit GHB and related chemicals range from home made products and “reagent kits” sold on the Internet to two industrial chemicals, of which 100 million gallons were produced in the US last year (Caruso 1997). Illicit GHB and related chemicals can also be obtained as nutritional supplements from health food stores. All illicit products vary in purity, content, and dose.
- Xyrem has never been reported as a source of abused GHB by toxicologists, ER personnel, or law enforcement personnel.

- Poly-drug use is common in the abuser population (Galloway 2000), with little known about drug interactions among various illicit drugs. Use of alcohol in combination with GHB is common, leading to dangerous, potentially synergistic, effects (McCabe 1971).
- In general, toxicologists, emergency medicine personnel, and other medical personnel lack knowledge of GHB and related chemicals and training in how to treat their misuse, especially when ingested with alcohol or other illicit drugs.
- Law enforcement personnel also usually lack knowledge and training in how to identify illicit GHB and related chemicals.
- State laws addressing illicit GHB and related chemicals are not uniform. Differences also exist between federal and state laws.
- Within the Interested Community, very little scientific information regarding abuse of GHB, drug diversion investigations, law enforcement training, identification, activities, and state efforts dealing with controlled substances exists, and even less is shared.
- Currently, diversionary activities are difficult to identify and investigate due to the lack of integration in pharmacy reporting systems.
- Often investigations are initiated many months after a crime occurs, owing to the need to collect extensive data. Thus, illicit use is simply "caught" versus prevented.
- Widespread distribution of controlled substances through community pharmacy increases the potential for diversion.
- Sexual assault investigation protocols do not include screening or testing for illicit GHB and related chemicals.
- Most hospital diagnoses are presumptive. Very few laboratories identify or quantify GHB, GBL and 1,4-Butanediol in blood or urine. These drugs are not part of routine drug screening methodologies in hospitals.
- Urine screening for illicit GHB and related chemicals is not specific enough to distinguish between the ingested agents: all are identified as GHB.
- Available on-line and other information resources that report sanctions of physicians accused of diversion are not used by appropriate parties.
- Legislation has reduced the illicit use of GHB-containing products, however, readily obtained chemicals such as GBL and 1,4BD are increasingly being used as substitutes.
- Further state legislation is needed to apply penalties to the misuse of these substitute sources of GHB.

After identifying these facts and issues, the groups reached these conclusions:

- Xyrem should be made available for patients who need it, but must be handled responsibly by all involved parties.
- A comprehensive approach, involving key stakeholders and partners, is needed to manage the risk that Xyrem could become a source of abused product while allowing access to it by patients whose conditions can be improved by its medicinal properties.
- To reduce the threat to public health posed by illicit GHB, information about GHB must be shared within and among the scientific, medical, and law enforcement communities.

8.1.1.2 Assess Risks/Assess Benefits

The second step in addressing risk management, as described by the FDA Task Force, is to assess the overall benefits and risks of a given medical product. Elsewhere in this document, the medical need for Xyrem is presented, as are data regarding the safety and efficacy of Xyrem.

It should noted that after review of controlled trials assessing Xyrem in narcolepsy patients, the FDA asked Orphan Medical to initiate a Treatment IND. By definition, Treatment IND protocols are granted only when medicines under clinical evaluation treat patient populations whose medical condition is "life threatening or debilitating" and where no acceptable therapeutic alternative exists.

The medical need, efficacy, safety, and Treatment IND information was also shared with the stakeholders and partners that Orphan Medical involved in the development of its risk management approach.

The law enforcement stakeholders involved were initially skeptical about the need for this medication, but, upon learning about narcolepsy and the clinical results of Xyrem, these parties agreed that the therapeutic need for Xyrem was compelling. They continue to be very concerned, of course, about the use of illicit GHB and related chemicals and asked that Orphan Medical address both the potential for inappropriate prescribing of Xyrem and the potential for diversion, two factors which could contribute to the complexity of the illicit GHB drug environment.

Other stakeholders voiced concern about the addictive potential of illicit GHB and related chemicals and whether there is a risk of addiction among narcolepsy patients from their use of Xyrem. Orphan Medical has, and will continue to share, information it has about the abuse or addiction potential of Xyrem. The Abuse Liability and Overdosage section in this document addresses these issues. Orphan Medical has also pledged to assist, where it can, efforts to evaluate the abuse and addictive properties of other GHB related compounds. All of the stakeholders understand that these compounds do not fall under the responsibility of the Company, but that the Company's current and future data may be helpful in efforts to contain the risk presented by these illicit compounds.

All stakeholders agreed that it was important for Orphan Medical to consider risk management solutions that will allow Xyrem to reach the intended population of narcolepsy patients while minimizing the risk that Xyrem may be obtained by those seeking to misuse it.

8.1.1.3 Identify and Analyze Options

Orphan Medical presented to the stakeholders options it could have followed to date, but were dismissed since the options did not combine the goals of providing Xyrem to those who need it, managing risk associated with Xyrem in a responsible manner, and

assisting the stakeholders where possible to reduce the risk of illicit GHB and related chemicals.

Clearly, Orphan Medical could have chosen to ignore risk issues around illicit GHB and related chemicals, and instead focus solely on the medical use of Xyrem. It could have attempted to shift the focus of attention to problems with alcohol, Ecstasy, amphetamines, Rohypnol and other club drugs with greater frequency of use and levels of abuse than GHB. It could have designed its risk management system in a manner that assumes physicians, patients and pharmacists will work together to minimize risks once Xyrem is approved.

Instead, Orphan Medical has invested substantial resources to address issues around Xyrem, and around illicit GHB and related chemicals that are not, strictly speaking, the Company's responsibility. Along with stakeholders and partners, Orphan Medical has pro-actively developed approaches and solutions to these issues. These were arrived at through consideration of possible alternatives available to Orphan Medical, listed below.

8.1.1.3.1 Distribution Options

- Use a traditional pharmaceutical distribution model that relies on current controls to prevent, minimize, and prosecute diversion.
- Establish a specialty distribution model that includes customized controls to meet the needs of the stakeholders.

8.1.1.3.2 Scheduling Timing Options

- Wait for Xyrem approval and scheduling designation at the time of NDA approval, the customary administrative approach.
- Prior to the Xyrem NDA submission, support and move for the legislative scheduling of Xyrem, illicit GHB and related chemicals, which allows greater control over these compounds and allows prosecution of illicit use sooner.

8.1.1.3.3 Scheduling Designation Options

- Support Schedule II designation that allows prescription monitoring and strong penalties for illicit use, but entails a much broader distribution system, thereby creating many more points of potential diversion.
- Support Schedule IV designation that permits use of a centralized mail order-based distribution system serving small patient populations, but offers minimal penalties for illicit use.
- Support Schedule III designation that allows for centralized mail order-based distribution to small patient populations, and offers greater penalties for illicit use.
- Support the HHS recommended "bifurcated schedule" of Schedule I/Schedule III, that allows central, mail order-based distribution to small patient populations, and offers the strongest possible penalties for illicit use.

8.1.1.3.4 Prescribing Options

- A system that allows investigation of inappropriate use/action based on verification and/or identification of:
    - A patient's diagnosis
    - A physician's appropriateness
    - Prescription and dispensing of an appropriate dose
    - Appropriate frequency of prescription
    - Inappropriate use

- A system that relies on state or federal authorities to investigate based on their verification and/or identification of:
    - A patient's diagnosis
    - A physician's appropriateness
    - Prescription and dispensing of an appropriate dose
    - Appropriate frequency of prescription
    - Inappropriate use

- A prescription system that relies on the physician, patient, and pharmacist to oversee verification and/or identification of:
    - A patient's diagnosis
    - A physician's appropriateness
    - Prescription and dispensing of an appropriate dose
    - Appropriate frequency of prescription
    - Inappropriate use

8.1.1.4 Select a Strategy

The fourth step identified by the Task Force in the risk confrontation model is to select a strategy. After much discussion with stakeholders and partners, and consideration of alternatives, Orphan Medical has developed the following risk management strategy. (The key elements of this strategy are in italics.)

8.1.1.4.1 Strategy Selected

Confront issues of risk regarding Xyrem and co-develop risk management solutions with other stakeholders.

Pharmaceutical companies often seek to minimize the perception of risk associated with their products by highlighting problems with other products or allowing risk management of products to be addressed by other stakeholders, such as physicians or pharmacists once the product is commercially available. Orphan Medical concluded this approach was not appropriate for Xyrem.

A closed distribution system has been designed to address risk management of Xyrem. In addition to assigning responsibility for some risk management to the traditional

stakeholders, the system also places more than usual responsibility on the patient, state authorities, and federal authorities.

Assist stakeholders in confronting the risks associated with illicit GHB, and related chemicals.

The risks associated with illicit GHB and related chemicals originate from the distribution of raw chemicals, home-made formulations, and the sales of nutritional supplements and of "reagent kits" over the Internet. Most pharmaceutical companies would refuse help to efforts to curb these risks since there is little that the pharmaceutical company, physicians, and pharmacists can do in regard to illicit GHB. Orphan Medical, however, has pledged its help to efforts to contain the public risk associated with illicit GHB and related chemicals. The Company has shared its data with NIDA, forensic science groups, toxicologists and emergency medicine physicians. Orphan Medical is involved in collaboration and sponsorship of studies relating to abuse pharmacology.

Orphan Medical has tried to set an example of how a company can help advance the science and understanding of an abuse substance and work with physicians, drug abuse specialists, law enforcement and other stake holders to better address risks posed by illicit substances.

8.1.1.4.2 Development Option Selected

Develop Xyrem for a small patient population where adequate therapy does not exist, understanding its importance in that population.

While conventional wisdom in the pharmaceutical industry is to develop a medication for the largest possible indication, Orphan Medical's mission is to develop and market pharmaceuticals of high medical value for patients with rare diseases for which few, or inadequate, therapeutic alternatives exist. Larger pharmaceutical companies typically ignore such diseases and conditions because the potential revenue is inadequate to generate acceptable returns.

Orphan Medical, on the other hand, has conducted trials and collected data that it believes demonstrate Xyrem's safety and efficacy in this small patient population. Xyrem will be marketed only for the approved label claim, with DDMAC (FDA's Division of Drug Marketing, Advertising and Communications) having "jurisdiction" over promotional activities.

8.1.1.4.3 Scheduling Timing Option Selected

Pro-actively support, prior to any approval of Xyrem, the legislative scheduling of GHB compounds, including Xyrem, illicit GHB and related chemicals, to allow greater control and prosecution of misuse.

Traditionally, consideration of a medication's schedule status occurs during the NDA review and its definitive schedule is designated at the time of approval. Due to the

widespread availability of illicit GHB and its growing chemical abuse in the late 1990's, many states began to legislatively schedule GHB. In those states which enacted GHB scheduling initiatives, the "street use" quickly shifted from GHB to GBL, 1,4BD or other related chemicals. Due to the metabolism of these agents in the body to GHB, these agents were used not only to make illicit GHB, but eventually they were simply ingested in order to obtain a "GHB-like" effect. Thus, well-intentioned legislation was ultimately ineffective since it was too narrow and did not also include GHB precursor chemicals.

Orphan Medical, along with stakeholders, concluded it would be in the best interest of the overall risk management of Xyrem to support Federal legislation to schedule GHB and related chemicals. Orphan Medical worked with other interested parties and stakeholders to help obtain legislation as quickly as possible. In early 2000 President Clinton signed into effect PL 106-172, The Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 (Public Law 106-172).

8.1.1.4.4 Scheduling Designation Option Selected

Support congressional scheduling based on the HHS recommended "bifurcated schedule" of schedule I/schedule III that allows for central, mail order-based distribution of Xyrem to a small patient population, and also provides for the strongest possible penalties for illicit use.

One of the main issues raised by stakeholders was the application of the schedule that would apply the harshest penalties possible for the illicit use of GHB and related chemicals, yet allow access to Xyrem for narcolepsy patients who need it. PL 106-172 followed the recommendations of FDA and as presented to the DEA by the Department of Health and Human Services on May 19, 1999 (Satcher, written communication).

This bifurcated schedule made illicitly used GHB a Schedule I substance and provided Schedule III designation for medicines containing GHB that might be approved by the FDA in the future. It is important to note that the Schedule I provisions apply to approved products if they are used illicitly.

The HSS report, submitted to the DEA by David Satcher, M.D., Ph.D., Assistant Secretary for Health and Surgeon General, is based on a document prepared by FDA's Drug Abuse Evaluation Staff. That document includes an eight-factor analysis regarding the recommended scheduling of Xyrem. The following information is excerpted from that documen (US Department of Justice 1997).

> "GHB products are currently being studied under FDA authorized investigational new drug applications. None of the reports of actual abuse of GHB that support the scheduling recommendation in part I has involved GHB that was diverted from an authorized study. Moreover, given the ease with which GHB can be synthesized from readily available materials, it is considerably less likely that these authorized studies will become a source for unlawful use or abuse of GHB. In essence, the widespread availability of clandestinely produced GHB decreases the

> abuse liability and potential for abuse of the products being studied in authorized research programs and well-supervised clinics. For this reason, a GHB product or substance that is the subject of an authorized protocol and is being studied under a carefully designed research protocol has "low potential for abuse relative to drugs or other substances in schedule III." (Emphasis added.) (see U.S.C. 12 (b)(4)(A)".

8.1.1.4.4.1 Medical Use

Dr. Satcher's report goes on to address the medical use of GHB:

> "A GHB product, however, has recently been granted a protocol under 21 CFR 312.34 to allow for expanded, treatment use of the product in patients who suffer from cataplexy associated with narcolepsy. In this instance the study and development of a GHB product is sufficiently far along to suggest that authorized formulations of GHB may be considered as having a "currently accepted medical use with severe restrictions" under the CSA (see 21 U.S.C. 812 (b)(2)(B); see also 47 FDA 281241, June 29, 1982)".

8.1.1.4.4.2 Physical or Psychological Dependence

Dr. Satcher also states,

> "There is no well-developed evidence from clinical studies to suggest that GHB leads to psychological dependence. The few available anecdotal case reports suggest only mild withdrawal symptoms that may be indicative of 'low risk of physical dependence.' Similarly, from these few anecdotal reports, instances of escalation of GHB dose, increased frequency of use, and continued use despite adverse consequences, are only suggestive of dependence production. There is no evidence to suggest that abuse of GHB leads to 'severe' dependence (see 21 U.S.C. 812 (b)(2)(C)). When compared to substances in Schedules II and III, GHB's physical and psychological dependence producing effects appear to be 'limited' (see 21 U.S.C. 812 (b)(4)(C))."

The Assistant Secretary for Health and Surgeon General concludes:

> "Formulations of GHB currently are being studied under FDA-authorized INDs. At least one sponsor's formulation has been granted Orphan Drug status under section 526 of the Food, Drug, and Cosmetic Act, and is available under a treatment use protocol under 21 CFR 212.34. None of the reports of actual abuse of GHB that support the Schedule I recommendation has involved GHB diverted from an authorized study. Given the ease with which GHB can be synthesized from readily available materials, it is unlikely that authorized studies will become a source of GHB for abuse. Rather, the abuse potential of GHB, when used under an

> authorized research protocol, is consistent with substances typically controlled under Schedule IV. Information on the dependence producing effects of GHB is limited, but can suggest that its potential for physical and psychological dependence is also consistent with control under Schedule IV". (Emphasis added.)
>
> "Authorized formulations of GHB, however, do not meet the 'accepted medical use' criteria set forth in Schedule IV. At best, an authorized formulation of GHB is far enough along in the development process to meet the standard under Schedule II of a drug or substance having a 'currently accepted medical use with severe restrictions.' Under these circumstances, FDA recommends placing authorized formulations of GHB in schedule III, a level of control higher than Schedule IV to take into account the lack of an accepted medical use and a level of control lower than schedule II to take into account the abuse and dependence liability findings for authorized formulations of GHB." (Emphasis added)

Stakeholders, potential specialty medications distribution partners, drug diversion investigators, State Boards of Pharmacy, legal experts and others were consulted on the issue of scheduling. They strongly supported a schedule III designation because it allows for a "closed loop" distribution system. A "closed loop" system provides for the confirmation of the shipment and receipt of medicine. Prescribing information, including frequency and dosing data, can be accessed from a single source. With this system, Xyrem's distribution can be monitored and controlled relatively easily and accurately since product is distributed from a single location, unlike a typical pharmaceutical distribution system that allows for widespread distribution through multiple retail pharmacies.

Such a centralized, mail order-based system is very well suited to minimize diversion and related risk issues. Narcolepsy is limited in its incidence so the number of patients is easily managed. Moreover, since the disease is chronic, prescriptions are repetitive and usage can be monitored for unusual patterns.

In practice, some state pharmacy laws do not allow for mail order distribution of Xyrem. (Mail order is legal, but prescriptions for Schedule II agents have to be submitted in person.) The Schedule III designation was necessary to implement this system of direct-to-patient delivery. The closed distribution system for Xyrem, along with the physician and patient education components of the program, will be addressed at length later in this document.

Another issue addressed in PL 106-172 was the "listing" of the industrial chemical GBL, requiring special reporting by chemical manufacturers. Unfortunately, this legislation did not address other related chemicals. Orphan Medical is actively supporting efforts on a state-by-state basis to include GHB precursor chemicals in various analog and sexual assault statutes[1].

[1]various state analog laws

8.1.1.4.5 Prescribing Options Selected

Confront risk by targeting promotional and selling efforts to those physicians (and physician specialties) identified as most likely to treat narcolepsy patients, and develop a system of responsible distribution that includes physician and patient education programs to help minimize physician off-label prescribing and patient misuse of Xyrem.

Certain stakeholders asked if Orphan Medical could somehow control who prescribes Xyrem, and control how Xyrem is prescribed. Orphan Medical cannot dictate or directly limit who prescribes Xyrem as it does not have accrediting jurisdiction over physicians. Further, it cannot limit the indications for which Xyrem might be prescribed, as this would constitute an imposition on the practice of medicine, for which Orphan Medical is not licensed.

Orphan Medical can, however, attempt to address this issue by prospectively identifying and targeting those physicians and physician specialties most likely to treat narcolepsy. This will be accomplished by utilizing a number of research sources and analyzing selected data. (Note that, because narcolepsy is a rare disease with a small patient population, most research sources provide limited information and/or data. Furthermore, these sources of information and data are highly unreliable because survey sample sizes are small. However, certain assumptions can be made.)

The first source consulted was the American Board of Sleep Medicine (ABSM). This organization issues certificates of special knowledge in sleep medicine to physicians and PhDs in related fields. The knowledge base of sleep medicine is derived from many disciplines, including neuroanatomy, neurophysiology, respiratory physiology, pharmacology, psychology, psychiatry, neurology, general internal medicine, pulmonary medicine, pediatrics, and others. As of February 2001, there were 1,517 professionals identified by ABSM as certified sleep specialists.

According to the American Medical Association (AMA), many clinicians practice sleep medicine under their primary specialty, such as neurology, pulmonology, psychiatry. Sleep medicine, however, is not listed as one of the 24 major board specialties recognized by the AMA, and only 48 physicians within the United States have identified themselves to the AMA as practicing sleep medicine. While this group of physicians is certainly qualified to prescribe Xyrem, it clearly does not treat the entire narcoleptic population.

The National Disease and Therapeutic Index (NDTI), identifies physician specialties that prescribe medications for a given disease. The NDTI data, like the ABSM information, report the involvement of numerous medical specialties in treating narcolepsy. NDTI data for 1999 and 2000 (January-June) identified the following specialties that prescribe medication for patients with a diagnosis of narcolepsy: neurology, pulmonary diseases, psychiatry, family practice, osteopathic medicine, internal medicine, and general practice.

IMS HEALTH Information Services, through its National Prescription Audit information, tracks prescribers of Provigil (modafinil). Since Provigil is indicated for the treatment of daytime sleepiness associated with narcolepsy, it could be presumed that Provigil prescribers are physicians treating narcolepsy patients. Again, it was noted that the number of medical specialties is large; Provigil prescribers are classified as follows: neurology, pulmonary diseases, psychiatry, internal medicine, sleep medicine, and 24 other specialties.

All of these data sources corroborate; that is, physicians who practice sleep medicine, diagnose and treat sleep disorders (narcolepsy, in particular), and prescribe medicines for these disorders fall within a defined range of medical specialties. As part of its marketing strategy, and consistent with its risk management goals, Orphan Medical has identified, within this group of specialties, key physicians on whom to focus initial marketing and sales efforts.

Prior to the launch of Xyrem, these physicians will be checked with the AMA and with the National Prescribers Databank (NPD) to determine if they are medical license holders and further licensed to prescribe controlled substances. Because the NPD is updated quarterly, State Medical Boards will be searched on-line to determine if disciplinary actions have been taken against any of these physicians which have not yet been reported to the NPD database. If any of the physicians has had privileges revoked, the central database will be flagged and the physician will be removed from Orphan Medical's list, with no mailings or detail calls made to them. In addition, the central pharmacy will be instructed not to fill prescriptions received from such physicians. These database checks (AMA, NPD and State Medical Boards available on-line) will periodically occur to ensure that physician eligibility has not changed.

At the launch of Xyrem, each of the key physicians identified by Orphan Medical will receive a traditional "detail call" from an Orphan Medical sales representative. During this call, a Xyrem Physician Success Program℠ will be reviewed with the physician and left behind. This educational program outlines the prescription and distribution process for Xyrem. DDMAC-approved information, regarding the benefits and risks of Xyrem in the intended patient population, will also be provided to these physicians.

Because a single, central pharmacy will handle distribution of Xyrem, as well as its educational materials, it will be possible to keep consolidated records of which physicians and patients have received educational materials on Xyrem. In addition, pharmacy data on prescribing physicians will be collected. It will be the pharmacy's role, not Orphan Medical's, to share with appropriate state and federal authorities the data regarding the prescribing of Xyrem. Available data, including physician name, physician specialty, and frequency of prescribing will assist appropriate authorities in an investigation, should one become necessary. The centralized, real-time nature of these data will allow for rapid identification in the rare case of diversion.

The second issue raised around the risk management of Xyrem is that of "off label" prescribing. It is important to note that an NDA holder has the responsibility to

manufacture and promote a medication consistent with its label claim. All promotions are subject to FDA review, and U.S. laws permit no off-label promotion.

Orphan Medical is a manufacturer and marketer, not a pharmacy or distributor. Orphan Medical will sell Xyrem to the specialty pharmacy, which is then responsible for filling prescriptions according to the laws governing the practice of pharmacy in each state.

According to stakeholders in the areas of pharmacy practice and law, there is no state or federal territory in which confidentiality laws allow for a manufacturer to know the name of a given patient or the dose of a given prescription. Orphan Medical has no legal means to ascertain if a given physician has accurately diagnosed a patient's disease. Nor is the pharmacist in a position to approve or disapprove of the use of Xyrem in a given patient. The practicalities of how prescriptions are filled in the U.S. do not allow for a specialty pharmacy to "police" the practice of medicine by a given physician. The role of the central pharmacist will be to fill the prescription; perform a medication audit to determine what other ethical medications, over the counter products, and nutritional supplements the patient may be taking; and given the doctor-patient-pharmacist relationship, enter into a dialog with the physician about the treatment of a given patient if appropriate.

Fortunately, the current system used in the U.S. for managing the risks associated with controlled substances allows for appropriate stakeholders to police individual physician and patient behavior. The Xyrem system preserves this important feature.

In every state in the U.S., a pharmacy is required by law to cooperate with state and federal authorities, including State Medical Boards, DEA and FDA, in any investigation dealing with physician or patient behavior. The controlled substance tracking system has been designed to provide data on both patient use and physician prescribing of controlled substances.

According to the stakeholders familiar with drug diversion, however, the current systems do not work prospectively; they identify inappropriate use long after it happens. Consider the "patient" who is an abuser, seeking various narcotics. This patient may visit an emergency room one day and be prescribed a narcotic, which is filled at a local pharmacy. This same patient may travel to a neighboring town the next day and be prescribed a second narcotic, which is filled at that local pharmacy. This cycle could be repeated in town after town for a long period of time before triplicate prescription forms identify the situation. If the patient is able to obtain different identification for each visit this activity may never be caught.

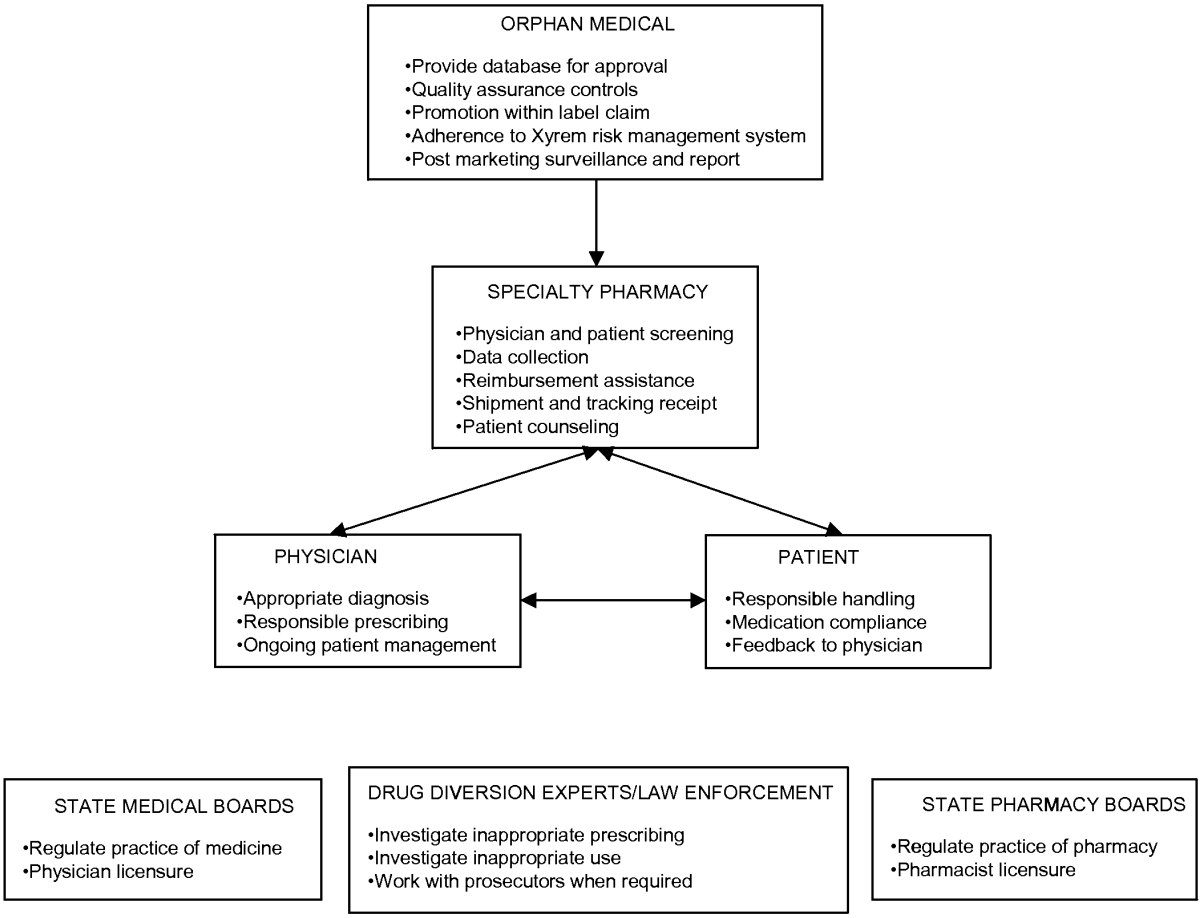
The Xyrem risk management system ensures that the centralized pharmacy will identify patients who are attempting to duplicate prescriptions. All data collected will be available to state and federal authorities, on whatever timeframe they determine to be appropriate. This allows law enforcement agencies to more easily fulfill their responsibility for which they have the training and authority to perform. Incidentally, individuals caught trying to manipulate health care systems for illicit purposes as described above will be subject to Schedule I penalties as outlined in PL 106-172.

This briefing book contains an 8 minute video demonstrating the specific prescription process for Xyrem. Viewing it will aid in understanding the systems Orphan Medical will use to fulfill its stated risk management goals:

- **Make Xyrem available in a responsible manner to patients who need it;**
- **Keep Xyrem out of the hands of those who would use it illicitly; and**
- **Provide responsible assistance to law enforcement investigation and prosecution efforts if illicit use occurs.**

Figure 8.3 describes the roles and responsibilities of each of the involved parties in the Xyrem risk management system.

Figure 8.3. Xyrem: Risk Management Roles and Responsibilities



Stakeholders involved in developing this system strongly support that a risk management system similar to Orphan Medical's be required of any manufacturer who submits an ANDA (generic application) or NDA for any GHB-containing product.

The Xyrem risk management system has been designed to confront risk through responsible distribution as well as through patient and physician education programs. Details of this program follow.

The Xyrem risk management system has been designed with the input of stakeholders to confront and minimize the potential risk of both unintended and intended misuse of Xyrem.

Starting from the Risk Confrontation model outlined by the FDA Task Force, Orphan Medical developed the Xyrem risk management system. It reflects the input and involvement of stakeholders and partners in the identification of risk issues, of potential solutions, and of the final selection of strategies. FDA and DEA input on the program has been sought and has not yet been received.

Bulk drug for Xyrem is manufactured at a single site and it is formulated into finished product at a separate, single site. From there, finished Xyrem is shipped to a central pharmacy.

Each of these facilities meets FDA and DEA requirements for controlled substances: the bulk drug manufacturer meets Schedule I requirements; the drug product manufacturer meets Schedule I and Schedule III requirements; and the central pharmacy is compliant with Schedule III requirements. Each facility is designed to provide secure storage of controlled substances.

Using a central pharmacy is more costly than using conventional distribution channels and systems. Using a single pharmacy also eliminates the opportunity to "fill the retail distribution pipeline." (Generally, pipeline sales of pharmaceuticals are significant, and generate initial sales.) Orphan Medical is foregoing this pipeline opportunity because it feels Xyrem can be better managed through a single pharmacy, rather than on the shelves and loading docks of, perhaps, thousands of pharmacies and distribution centers around the country.

Receiving, storage, and shipping controls are in place to ensure that the amount of Xyrem shipped from the manufacturer is equal to that received at the pharmacy. Discrepancies are investigated and reported appropriately. Xyrem, once received at the specialty pharmacy, goes into a secure holding area dedicated solely to storage of Xyrem and accessible only to authorized employees. Measures such as cages, security alarms, cameras and key cards are used to ensure security. On a weekly basis, the specialty pharmacy determines the amount of Xyrem it is likely to need for fulfillment of prescriptions, and the appropriate amount of product is transferred to "owned inventory".

This is the point at which Xyrem is "sold" by Orphan Medical to the specialty pharmacy. This transfer of ownership allows the specialty pharmacy to collect confidential data such as patient names and medication doses. This is information that Orphan Medical will not have, but the specialty pharmacy can collect because of the doctor/pharmacist/patient relationship.

As was discussed previously, physicians most likely to prescribe Xyrem will be identified and "pre-screened" prior to the launch of Xyrem. When the FDA approves Xyrem, the Xyrem Physician Success Program will be shared with those physicians who have met the screening criteria.

The Xyrem Physician Success Program contains details about Xyrem's unique prescription process, its distribution, the reimbursement program, and physician responsibilities regarding Xyrem. Approximately 25 Orphan Medical sales representatives nationwide will begin making "detail calls" on these physicians. These representatives will have been trained to present efficacy and safety information within the approved label claim as directed by DDMAC. At the first detail call, the sales representative will leave behind the Xyrem Physician Success Program, giving the physician a lasting source of information regarding Xyrem's unique distribution system and special handling process. At no time will samples of Xyrem be carried by sales representatives or left with physicians.

Once a physician decides that Xyrem is appropriate for a given patient, he or she will write a prescription for Xyrem and fax it to the specialty pharmacy. Upon receipt, the specialty pharmacy will verify the physician's eligibility by checking the AMA, DEA, or State Medical Board on-line databases, as previously described. This step will ensure that the prescription was written by a "real" physician with current privileges to prescribe controlled medications.

After physician verification is complete, the specialty pharmacy will contact the physician's office to confirm patient information. By adding this step, the process is likely to "catch" any prescriptions written on stolen or counterfeit prescription pads. During the call, the patient's name, social security number, telephone number and insurance information will also be obtained. The specialty pharmacy will also ask for an assignment of benefits form, so it can work on the patient's behalf to obtain insurance coverage, and for a letter of medical necessity, if it is needed from the insurance company.

While the patient's specific information is needed for insurance purposes, the collection of it by the specialty pharmacy assists in the building of a patient registry which also aids in diversion prevention. The prescribing physician will also be contacted if a prescription appears to be a duplicate or if the dosing frequency appears unusual.

Once the insurance reimbursement is obtained, the Xyrem shipping process begins. The specialty pharmacy will contact the patient to notify him/her of coverage, and arrange a time for a next-day delivery when the patient or his/her designee is to be

present. Xyrem will not be left with anyone other than the patient or the designee (who cannot be a minor), and it will not be left unattended.

Once the shipment designee and time of delivery is determined, the Xyrem prescription and the Patient Success Program℠ is shipped via Federal Express. Federal Express offers real-time tracking so packages can be tracked from point of shipping to point of receipt, and points in-between.

If a shipment becomes lost, the appropriate state/federal authorities will be contacted, and the investigation can begin at the point of loss. If the patient or designee is not available at the location and time designated, the package will not be left on the doorstep, or with a neighbor. Finally, the package will not be returned to the local Federal Express station, but after a same-day redelivery attempt will be returned to the specialty pharmacy.

When the proprietary tracking system shows that the patient has received the shipment, the pharmacist at the specialty pharmacy will contact the patient to:

- confirm receipt of the Xyrem prescription;
- confirm receipt of the Patient Success Program;
- counsel the patient regarding Xyrem administration, dosing and compliance; and
- confirm the patient's understanding of the contents of the Xyrem Patient Success Program and the patient's responsibilities.

This system allows documentation of a patient's receipt of educational materials and communication with the patient about responsibilities and any other matters brought up in the conversation with the pharmacist.

The centrally located, real-time data collected by the specialty pharmacy will be invaluable to the identification of suspicious prescribing or use, and will aid appropriate state and federal investigation and prosecution.

Orphan Medical is grateful for the contributions and efforts of the many stakeholders who have diligently helped identify issues, proposed options, and assisted the company in selecting means to confront and manage the potential risks associated with Xyrem. With their assistance, Orphan Medical has designed a comprehensive system to effectively and responsibly manage risk, while giving narcolepsy patients and their physicians an important medicine to treat this debilitating disease.

Exhibit N

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/322,348	12/17/2002	Dayton T. Reardan	101.031US1	5446

21186 7590 12/31/2009

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

DATE MAILED: 12/31/2009

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 446 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 446 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

Notice of Allowability	Application No.	Applicant(s)	
	10/322,348	REARDAN ET AL.	
	Examiner	Art Unit	
	LENA NAJARIAN	3686	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *11/2/09*.

2. ☒ The allowed claim(s) is/are *32-42*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 20091102
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

DETAILED ACTION

Examiner's Amendment

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with David D'Zurilla (Reg. No. 36,776) on 12/10/09.

The application has been amended as follows:

32. (Currently Amended) A computerized method of distributing a ~~sensitive~~ prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor all prescription requests, for any and all patients being prescribed the ~~sensitive~~ prescription drug, only at the exclusive central pharmacy from any and all medical doctors allowed to prescribe the ~~sensitive~~ prescription drug, the prescription requests containing information identifying patients, the ~~sensitive~~ prescription drug, and various credentials of the any and all medical doctors;

requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, such that all prescriptions for the ~~sensitive~~ prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the prescription drug;

confirming with a patient that educational material has been read prior to shipping the ~~sensitive~~ prescription drug;

checking the exclusive computer database for potential abuse of the ~~sensitive~~ prescription drug;

mailing the ~~sensitive~~ prescription drug to the patient only if no potential abuse is found by the patient to whom the ~~sensitive~~ prescription drug is prescribed and the doctor prescribing the ~~sensitive~~ prescription drug;

confirming receipt by the patient of the ~~sensitive~~ prescription drug; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

33. (Currently Amended) A computerized method of distributing a ~~sensitive~~ prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor all prescription requests, for any and all patients being prescribed the ~~sensitive~~ prescription drug, only at the exclusive central pharmacy from any and all medical doctors allowed to prescribe the ~~sensitive~~ prescription drug, the prescription requests containing information identifying patients, the ~~sensitive~~ prescription drug, and various credentials of the any and all medical doctors;

entering the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, such that all prescriptions for the ~~sensitive~~ prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the prescription drug;

checking the exclusive computer database for potential abuse of the ~~sensitive~~ prescription drug;

mailing the ~~sensitive~~ prescription drug to a patient only if no potential abuse is found by the patient to whom the ~~sensitive~~ prescription drug is prescribed and the doctor prescribing the ~~sensitive~~ prescription drug;

confirming receipt by the patient of the ~~sensitive~~ prescription drug; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

35. (Currently Amended) The method of claim 33 and further comprising selectively blocking shipment of the ~~sensitive~~ prescription drug to a patient.

37. (Currently Amended) The method of claim 33 wherein the ~~sensitive~~ prescription drug comprises gamma hydroxy butyrate (GHB).

38. (Currently Amended) A computerized method of distributing a ~~sensitive~~ prescription drug under control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor prescription requests, for any and all patients being prescribed the ~~sensitive~~ prescription drug, only at the central pharmacy from any and all authorized prescribers allowed to prescribed the ~~sensitive~~ prescription drug, the prescription requests containing information identifying patients, the ~~sensitive~~ prescription drug, and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of the ~~sensitive~~

prescription drug, such that all prescriptions for the ~~sensitive~~ prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe the prescription drug;

confirming with a patient that educational material has been read prior to providing the ~~sensitive~~ prescription drug to the patient;

requiring checking of the exclusive computer database for potential abuse associated with the patient and the authorized prescriber;

providing the ~~sensitive~~ prescription drug to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom the ~~sensitive~~ prescription drug is prescribed and the authorized prescriber of the ~~sensitive~~ prescription drug;

confirming receipt by the patient of the ~~sensitive~~ prescription drug; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

39. (Currently Amended) A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor prescription requests for GHB, for any and all patients being prescribed GHB, only at the central pharmacy from any and all authorized prescribers allowed to prescribe GHB, the prescription requests for GHB containing information identifying patients and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB, such that all

prescriptions for GHB are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe GHB;

confirming with the patient that GHB educational material has been read prior to providing GHB to the patient a first time;

requiring checking of the exclusive computer database for potential GHB abuse associated with the patient;

providing GHB to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom GHB is prescribed and the authorized prescriber of the GHB;

confirming receipt by the patient of the GHB; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns.

40. (Currently Amended) A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor prescription requests for GHB, for any and all patients being prescribed GHB, only at the central pharmacy from any and all authorized prescribers allowed to prescribe GHB, the prescription requests containing information identifying patients and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB, such that all prescriptions for ~~the sensitive drug~~ GHB are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe GHB;

confirming with the patient that GHB educational material has been read prior to providing GHB to the patient a first time;

requiring checking of the exclusive computer database for potential GHB abuse associated with the patient;

mailing GHB to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom GHB is prescribed and the authorized prescriber of the GHB;

confirming receipt by the patient of the GHB; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns.

41. (Currently Amended) A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:

manufacturing GHB;

providing manufactured GHB only to the exclusive central pharmacy;

receiving in a computer processor all prescription requests for GHB, for any and all patients being prescribed GHB, only at the central pharmacy from any and all authorized prescribers allowed to prescribe GHB, the prescription requests containing information identifying patients and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB, such that all prescriptions for GHB are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe GHB;

confirming with the patient that GHB educational material has been read prior to providing GHB to the patient a first time;

requiring checking of the exclusive computer database for potential GHB abuse associated with the patient;

mailing GHB to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom GHB is prescribed and the doctor prescribing the GHB;

confirming receipt by the patient of the GHB; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns.

42. (Currently Amended) A computerized method of distributing a ~~sensitive~~ prescription drug under control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor all prescription requests, for any and all patients being prescribed the ~~sensitive~~ prescription drug, only at the central pharmacy from any and all authorized prescribers allowed to prescribed the ~~sensitive~~ prescription drug, the prescription requests containing information identifying patients, the ~~sensitive~~ prescription drug, and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of the ~~sensitive~~ prescription drug, such that all prescriptions for the ~~sensitive~~ prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe the prescription drug;

confirming with the patient that educational material has been read prior to providing the ~~sensitive~~ prescription drug to the patient;

requiring checking of the exclusive computer database for potential abuse by the patient to whom the ~~sensitive~~ prescription drug is prescribed and the authorized prescriber allowed to prescribe the ~~sensitive~~ prescription drug;

providing the ~~sensitive~~ prescription drug to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom the ~~sensitive~~ prescription drug is prescribed and the authorized prescriber allowed to prescribe the ~~sensitive~~ prescription drug; and

confirming receipt by the patient of the ~~sensitive~~ prescription drug.

Allowable Subject Matter

2. Claims 32-42 are allowed.

3. The following is an examiner's statement of reasons for allowance: Claims 32, 33, 38, and 42, now renumbered as claims 1, 2, 7, and 11, are directed to a computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy.

The closest prior art of record, Moradi (US 2004/0019794 A1), Lilly et al. (US 2004/0176985 A1), Califano et al. (US 20030033168 A1), and Ukens ("Specialty Pharmacy") teach receiving prescription requests, checking the credentials of the doctors, checking a database for potential abuse of the drug, confirming receipt by the patient of the drug, confirming with the patient that educational material has been read prior to shipping the drug, generating reports to evaluate potential diversion patterns, and restricting distribution of a medication to one pharmacy.

However, the closest prior art of record does not teach or fairly suggest that *all* prescriptions for the prescription drug are processed only by the exclusive central pharmacy *using only the exclusive computer database.* The exclusive computer database is checked for potential abuse of the prescription drug and the prescription drug is mailed/provided only if no potential abuse is found by the patient to whom the prescription drug is prescribed *and* the doctor/authorized presciber prescribing the prescription drug.

Dependent claims 34-37 (now renumbered as claims 3-6) incorporate the allowable subject matter of claim 33, through dependency, and are also allowable for the same reasons.

Claims 39, 40, and 41 are directed to a computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy.

The closest prior art of record, Moradi (US 2004/0019794 A1), Lilly et al. (US 2004/0176985 A1), Califano et al. (US 20030033168 A1), and Talk About Sleep ("An Interview with Orphan Medical about Xyrem") teach receiving prescription requests, checking the credentials of the doctors, checking a database for potential abuse of the drug, confirming receipt by the patient of the drug, confirming with the patient that educational material has been read prior to shipping the drug, generating reports to evaluate potential diversion patterns, and providing GHB through a specialty distribution system that utilizes a central pharmacy.

However, the closest prior art of record does not teach or fairly suggest that *all* prescriptions for GHB are processed only by the exclusive central pharmacy *using only the exclusive computer database.* The exclusive computer database is checked for potential GHB abuse and GHB is provided/mailed only if no potential abuse is found by the patient to whom GHB is prescribed *and* the doctor/authorized prescriber of the GHB.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably

accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

4. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LENA NAJARIAN whose telephone number is (571) 272-7072. The examiner can normally be reached on Monday - Friday, 9:30 am - 6:00 pm.

6. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jerry O'Connor can be reached on (571) 272-6787. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or (571) 272-1000.

/L. N./
Examiner, Art Unit 3686
In
12/16/09

/Gerald J. O'Connor/
Supervisory Patent Examiner
Group Art Unit 3686

Exhibit O

Calendar of CDER Advisory Committee Meetings

Page Updated May 23, 2001 03:17 PM

This area includes meetings and events that are related to CDER's mission. It is advised that participants verify the time and location of meetings and events. There are other meetings and events listed on the FDA Meetings Page.

Tentative Advisory Committee Meetings (updated 5/8/2001)

- Advisory Committee Agendas
- Advisory Committee Information
- Advisory Committee Transcripts

CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION
ADVISORS AND CONSULTANTS STAFF

May 2001 Meetings

Cardiovascular and Renal Drugs Advisory Committee

May 24, 2001, from at 8:30 a.m. to 5 p.m. and on May 25, 2001, from at 9 a.m. to 3:30 p.m., National Institutes of Health, 9000 Rockville Pike, Building 10, Clinical Center, Jack Masur Auditorium, Bethesda, MD. **ADDITIONAL INFORMATION**: Joan C. Standaert, Center for Drug Evaluation and Research (HFD-110), 419-259-6211 or John M. Treacy (HFD-21), 301-827-7001. Oral presentations from the public will be scheduled between approximately 8:30 a.m. and 9:00 a.m. on May 24, 2001. **Agenda**: On May 24, 2001, the committee will discuss: (1) published interim analyses of ALLHAT (antihypertensive and lipid lowering treatment to prevent heart attack trial) sponsored by the National Heart, Lung, and Blood Institute, National Institutes of Health; and (2) Response to the Citizen's Petition of Lawrence D. Bernhardt and Arnold Liebman, regarding new drug application (NDA) 19-668, Cardura (doxazosin), Pfizer Inc. On May 25, 2001, the committee will discuss NDA 20-920 Natrecor (nesiritide), Scios Inc., for treatment of acute heart failure.

June 2001 Meetings

Peripheral and Central Nervous System Drugs Advisory Committee

June 6, 2001, 8 a.m. to 5 p.m., Holiday Inn, 8120 Wisconsin Avenue, Bethesda Maryland. The hotel phone number is 301-652-2000.
ADDITIONAL INFORMATION: Sandy Titus, Center for Drug Evaluation and Research (HFD-21), 301/827-7001 or e-mail: Tituss@cder.fda.gov.
Oral presentations from the public will be scheduled between approximately 1 p.m. to 2 p.m.
Agenda: On June 6, 2001, the committee will consider the safety and efficacy of new drug application (NDA) 21-196, Xyrem®, (sodium oxybate, Orphan Medical, Inc.) proposed to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness for persons with narcolepsy. A main focus of the deliberations will be on risk management issues.

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March 29, 2012

Via ECF and Overnight Delivery
The Honorable Cathy L. Waldor
United States Magistrate Judge
M.L. King, Jr. Federal Bldg. & Courthouse, Room 4C
50 Walnut Street
Newark, New Jersey 07102
Fax: (973) 776-7865

Re: *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*
Civil Action No. 2:10-cv-06108 (ES)(CLW)

Dear Judge Waldor:

We along with Locke Lord LLP represent defendant Roxane Laboratories, Inc. ("Roxane") in this action. Pursuant to a request from Your Honor's Law Clerk, we submit the following materials relating to Roxane's February 27, 2012 request for leave to supplement its Initial Invalidity and Noninfringement Contentions (D.E. 101) and March 19, 2012 reply in support of Roxane's request for leave to supplement its Initial Invalidity Contentions (D.E. 110).

Attached and enclosed hereto as Exhibits A-1 through A-4 are the newly discovered prior art references that Roxane relies upon to supplement to its Initial Invalidity Contentions:

Exhibit A-1: the FDA's Preliminary Clinical Safety Review of NDA No. 21196, dated May 3, 2001 ("Preliminary Clinical Safety Review"). Roxane's supplemental Invalidity Contentions will rely on and cite to the "Risk Management Program" section (section 14) pages 108 through 111. An excerpted copy of this exhibit was attached as Exhibit J to Roxane's March 19, 2012 submission (D.E. 110).

Exhibit A-2: the video of the Xyrem Prescription and Distribution Process submitted to FDA on May 30, 2001 for the FDA's Peripheral and Central Nervous System Drugs Advisory Committee meeting on June 6, 2001.

Exhibit A-3: script of the video (Exhibit A-2) of the Xyrem Prescription and Distribution Process submitted to FDA by Orphan Medical on May 30, 2001 for the FDA's Peripheral and Central Nervous System Drugs Advisory Committee meeting on June 6, 2001. A copy of this exhibit was attached as Exhibit K to Roxane's March 19, 2012 submission (D.E. 110).

Exhibit A-4: the Peripheral and Central Nervous System Drugs Advisory Committee Briefing Booklet for the June 6, 2001 meeting ("Briefing Booklet"). Roxane's supplemental Invalidity Contentions will rely on and cite to the "Risk Management" section (section 8) pages 293 through 311. An excerpted copy of this exhibit was attached as Exhibit M to Roxane's March 19, 2012 submission (D.E. 110).

Attached and enclosed hereto as Exhibits B-1 and B-2 are the secondary prior art references that Roxane also relies upon to supplement its Initial Invalidity Contentions, that were cited in the Patent Office records during the prosecution of U.S. Patent Nos. 7,668,730 ("the '730 patent"), 7,765,106, 7,765,107 and 7,895,059:

Exhibit B-1: "Diversion Prevention Through Responsible Distribution," a presentation given at NADDI (National Association of Drug Diversion Investigators) National Conference (Nov. 2001) ("NADDI Presentation"), bearing production numbers JPI-00004242 – JPI-00004255.

Exhibit B-2: Transcript of proceedings for the Peripheral and Central Nervous System Drugs Advisory Committee meeting, Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, held at Holiday Inn, Bethesda, Maryland (June 6, 2001), bearing production numbers ROXGHB034618 – ROXGHB034998. **Please note**: we have attached the entire transcript for the Court's convenience, however, only the pages bearing production numbers ROXGHB034618 and ROXGHB034795 – ROXGHB034802 were cited to the Patent Office and Roxane's supplemental Invalidity Contentions will rely on and cite to those pages.

Attached and enclosed hereto as Exhibits C-1 through C-3 are publicly available documents and images from the FDA and web.archive.org websites that establish that Exhibits A-1 through A-4 were publicly available more than one year before December 17, 2002, the filing date of the application which later issue as the '730 patent:

Exhibit C-1: Print out from the FDA website listing the 2001 FDA Advisory Committee Meeting Documents by Center, *accessible at* http://www.fda.gov/ohrms/dockets/ac/01docsbc.htm, showing that the materials for the Peripheral and Central Nervous System Drugs Advisory Committee materials were last updated on July 13, 2001.

Exhibit C-2: Print out from web.archive.org of "CDER 2001 Meeting Documents" *accessible at*http://web.archive.org/web/20011004081740/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm, showing that briefing information materials:

- Exhibit A-1, Preliminary Clinical Safety Review;
- Exhibit A-2, the video of the Xyrem Prescription and Distribution Process;
- Exhibit A-3, script of the video of the Xyrem Prescription and Distribution Process; and
- Exhibit A-4, Briefing Booklet

were publicly available as of October 4, 2001, if not earlier, through the "Briefing Information 3754b1.htm" link on this page found on pages 7-8 of this exhibit. The information on this page can also be accessed by clicking on the hyperlink labeled "Peripheral and Central Nervous System Drugs Advisory Committee," from Exhibit C-1 above.

Exhibit C-3: Print out from web.archive.org of "Briefing Information" for June 6, 2001 Peripheral and Central Nervous System Drugs Advisory Committee meeting *accessible at*http://web.archive.org/web/20010811143424/http://www.fda.gov/ohrms/dockets/ac/01/briefing/3754b1.htm, showing that:

- the "Preliminary Clinical Safety Review" (Exhibit A-1), was publicly available as of August 11, 2001 through the hyperlink on this page labeled "Safety Review"
- the video of the Xyrem Prescription and Distribution Process (Exhibit A-2) was publicly available as of August 11, 2001 through the hyperlink on this page labeled "Video"
- the script for the video of the Xyrem Prescription and Distribution Process (Exhibit A-3) was publicly available as of August 11, 2001 through the hyperlink on this page labeled "Xyrem Prescription and Distribution Process, Video Script 2/2/01)" and
- the "Briefing Information" (Exhibit A-4) was publicly available as of August 11, 2001 through the hyperlink on this page labeled "Briefing Information."

* * *

We thank Your Honor for accepting Roxane's request for an in-person oral argument on this issue. Should Your Honor find it helpful, Roxane will be happy to submit Roxane's proposed supplement to its Invalidity Contentions, as well as Roxane's Initial Invalidity Contentions and any additional briefing the Court would like in advance of the oral argument. We again thank you for your time and consideration of this matter.

Respectfully submitted,

Theodora McCormick

cc: All Counsel of Record (via ECF and email)

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **v.** **ROXANE LABORATORIES, INC.,** **Defendant.**	**Civil Action No. 10-6108 (SDW)(MCA)** **REPLY TO COUNTERCLAIMS** **(Filed Electronically)**

Plaintiff Jazz Pharmaceuticals, Inc. ("Jazz Pharmaceuticals"), by its undersigned attorneys, for its Reply to the Counterclaims of Defendant Roxane Laboratories, Inc. ("Roxane"), responds as follows:

1. Jazz Pharmaceuticals admits on information and belief the allegations of paragraph 1 of the Counterclaims.

2. Jazz Pharmaceuticals admits the allegations of paragraph 2 of the Counterclaims.

3. Jazz Pharmaceuticals admits that there is a justiciable controversy between the parties hereto concerning the '889, '219, '730, '106 and '107 patents, and denies all other allegations of paragraph 3 of the Counterclaims.

4. Paragraph 4 states a legal conclusion for which no answer is required. To the extent an answer is required, Jazz Pharmaceuticals admits that this Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), and denies all other allegations of paragraph 4 of the Counterclaims.

5. Paragraph 5 states a legal conclusion for which no answer is required. To the extent an answer is required, Jazz Pharmaceuticals admits that this Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 2201 and 2202, and denies all other allegations of paragraph 5 of the Counterclaims.

6. Jazz Pharmaceuticals admits the allegations of paragraph 6 of the Counterclaims.

7. Jazz Pharmaceuticals denies the allegations of paragraph 7 of the Counterclaims.

8. Jazz Pharmaceuticals denies the allegations of paragraph 8 of the Counterclaims.

9. Jazz Pharmaceuticals denies the allegations of paragraph 9 of the Counterclaims.

10. Jazz Pharmaceuticals admits that it holds approved NDA No. 21-196 for sodium oxybate oral solution which it sells under the trade name XYREM® pursuant to an FDA approved Risk Evaluation and Mitigation Strategy ("REMS"), and denies all other allegations of paragraph 10 of the Counterclaims.

11. Paragraph 11 states a legal conclusion for which no answer is required. To the extent an answer is required, Jazz Pharmaceuticals admits that it owns the '730, '106 and '107

patents, the claims of which speak for themselves, and denies all other allegations of paragraph 11 of the Counterclaims.

12. Jazz Pharmaceuticals admits that the '730, '106 and '107 patents are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to XYREM®, and denies all other allegations of paragraph 12 of the Counterclaims.

COUNTERCLAIM COUNT 1

13. Jazz Pharmaceuticals denies the allegations of paragraph 13 of the Counterclaims.

COUNTERCLAIM COUNT 2

14. Jazz Pharmaceuticals denies the allegations of paragraph 14 of the Counterclaims.

COUNTERCLAIM COUNT 3

15. Jazz Pharmaceuticals denies the allegations of paragraph 15 of the Counterclaims.

COUNTERCLAIM COUNT 4

16. Jazz Pharmaceuticals denies the allegations of paragraph 16 of the Counterclaims.

COUNTERCLAIM COUNT 5

17. Jazz Pharmaceuticals denies the allegations of paragraph 17 of the Counterclaims.

COUNTERCLAIM COUNT 6

18. Jazz Pharmaceuticals denies the allegations of paragraph 18 of the Counterclaims.

COUNTERCLAIM COUNT 7

19. Jazz Pharmaceuticals denies the allegations of paragraph 19 of the Counterclaims.

COUNTERCLAIM COUNT 8

20. Jazz Pharmaceuticals denies the allegations of paragraph 20 of the Counterclaims.

COUNTERCLAIM COUNT 9

21. Jazz Pharmaceuticals denies the allegations of paragraph 21 of the Counterclaims.

COUNTERCLAIM COUNT 10

22. Jazz Pharmaceuticals denies the allegations of paragraph 22 of the Counterclaims.

COUNTERCLAIM COUNT 11

23. Jazz Pharmaceuticals incorporates by reference its replies to paragraphs 1-22 of the Counterclaims as if fully set forth herein.

24. Jazz Pharmaceuticals admits that Roxane purports to seek an order requiring Jazz Pharmaceuticals to remove the '730 patent from the Orange Book listing with respect to XYREM®, and denies all other allegations of paragraph 24 of the Counterclaims.

25. Jazz Pharmaceuticals denies the allegations of paragraph 25 of the Counterclaims.

COUNTERCLAIM COUNT 12

26. Jazz Pharmaceuticals incorporates by reference its replies to paragraphs 1-25 of the Counterclaims as if fully set forth herein.

27. Jazz Pharmaceuticals admits that Roxane purports to seek an order requiring Jazz Pharmaceuticals to remove the '106 patent from the Orange Book listing with respect to XYREM®, and denies all other allegations of paragraph 27 of the Counterclaims.

28. Jazz Pharmaceuticals denies the allegations of paragraph 28 of the Counterclaims.

COUNTERCLAIM COUNT 13

29. Jazz Pharmaceuticals incorporates by reference its replies to paragraphs 1-28 of the Counterclaims as if fully set forth herein.

30. Jazz Pharmaceuticals admits that Roxane purports to seek an order requiring Jazz Pharmaceuticals to remove the '107 patent from the Orange Book listing with respect to XYREM®, and denies all other allegations of paragraph 30 of the Counterclaims.

31. Jazz Pharmaceuticals denies the allegations of paragraph 31 of the Counterclaims.

COUNTERCLAIM COUNT 14

32. Jazz Pharmaceuticals incorporates by reference its replies to paragraphs 1-31 of the Counterclaims as if fully set forth herein.

33. Jazz Pharmaceuticals denies the allegations of paragraph 33 of the Counterclaims.

ROXANE'S PRAYER FOR RELIEF

Jazz Pharmaceuticals denies that Roxane is entitled to judgment in its favor and denies that Roxane is entitled to any relief as set forth in its Counterclaims, Affirmative Defenses and/or Prayer for Relief.

DEFENSES

First Defense: Failure to State a Claim

Roxane's Counterclaims fail to state a claim upon which relief may be granted.

Second Defense: Lack of Standing

Roxane's Counterclaim 14 fails for lack of standing.

Third Defense: Exhaustion

Roxane's Counterclaim 14 fails for failure to exhaust administrative remedies.

Fourth Defense: Necessary Party

Roxane's Counterclaim 14 fails for failure to name a necessary party.

Fifth Defense: Subject Matter Jurisdiction

Roxane's Counterclaim 14 fails for lack of subject matter jurisdiction.

WHEREFORE, Jazz Pharmaceuticals prays for judgment in its favor on Roxane's Counterclaims and for the relief requested in Jazz Pharmaceuticals' Complaint for Patent Infringement.

Dated: February 7, 2011

By: s/ Charles M. Lizza

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **v.** **ROXANE LABORATORIES, INC.,** **Defendant.**	Lead Action cv-10-6108 **Civil Action No. 11-660 (SDW)(MCA)** **REPLY TO COUNTERCLAIMS** **(Filed Electronically)**

Plaintiff Jazz Pharmaceuticals, Inc. ("Jazz Pharmaceuticals"), by its undersigned attorneys, for its Reply to the Counterclaims of Defendant Roxane Laboratories, Inc. ("Roxane"), responds as follows:

1. Jazz Pharmaceuticals admits on information and belief the allegations of paragraph 1 of the Counterclaims.

2. Jazz Pharmaceuticals admits the allegations of paragraph 2 of the Counterclaims.

3. Jazz Pharmaceuticals admits that there is a justiciable controversy between the parties hereto concerning the '431 and '506 patents, and denies all other allegations of paragraph 3 of the Counterclaims.

4. Paragraph 4 states a legal conclusion for which no answer is required. To the extent an answer is required, Jazz Pharmaceuticals admits that this Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), and denies all other allegations of paragraph 4 of the Counterclaims.

5. Paragraph 5 states a legal conclusion for which no answer is required. To the extent an answer is required, Jazz Pharmaceuticals admits that this Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 2201 and 2202, and denies all other allegations of paragraph 5 of the Counterclaims.

6. Jazz Pharmaceuticals admits the allegations of paragraph 6 of the Counterclaims.

7. Jazz Pharmaceuticals denies the allegations of paragraph 7 of the Counterclaims.

8. Jazz Pharmaceuticals denies the allegations of paragraph 8 of the Counterclaims.

9. Jazz Pharmaceuticals denies the allegations of paragraph 9 of the Counterclaims.

COUNTERCLAIM COUNT 1

10. Jazz Pharmaceuticals denies the allegations of paragraph 10 of the Counterclaims.

COUNTERCLAIM COUNT 2

11. Jazz Pharmaceuticals denies the allegations of paragraph 11 of the Counterclaims.

COUNTERCLAIM COUNT 3

12. Jazz Pharmaceuticals denies the allegations of paragraph 12 of the Counterclaims.

COUNTERCLAIM COUNT 4

13. Jazz Pharmaceuticals denies the allegations of paragraph 13 of the Counterclaims.

COUNTERCLAIM COUNT 5

14. Jazz Pharmaceuticals incorporates by reference its replies to paragraphs 1-13 of the Counterclaims as if fully set forth herein.

15. Jazz Pharmaceuticals admits that Roxane purports to seek an order requiring Jazz Pharmaceuticals to remove the '506 patent from the Orange Book listing with respect to XYREM®, and denies all other allegations of paragraph 15 of the Counterclaims.

16. Jazz Pharmaceuticals denies the allegations of paragraph 16 of the Counterclaims.

ROXANE'S PRAYER FOR RELIEF

Jazz Pharmaceuticals denies that Roxane is entitled to judgment in its favor and denies that Roxane is entitled to any relief as set forth in its Counterclaims, Affirmative Defenses and/or Prayer for Relief.

DEFENSE

Failure to State a Claim

Roxane's Counterclaims fail to state a claim upon which relief may be granted.

WHEREFORE, Jazz Pharmaceuticals prays for Judgment in its favor on Roxane's Counterclaims and for the relief requested in Jazz Pharmaceuticals' Complaint for Patent Infringement.

Dated: April 18, 2011

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Jazz Pharmaceuticals, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **v.** **ROXANE LABORATORIES, INC.,** **Defendant.**	**Civil Action No. 11-660 (SDW)(MCA)** **CERTIFICATE OF SERVICE** **(Filed Electronically)**

SARAH A. HENSLER, of full age, certifies as follows:

1. I am an attorney-at-law of the State of New Jersey and an associate at the law firm of Saul Ewing LLP, counsel for Plaintiff Jazz Pharmaceuticals, Inc. ("Jazz") in the above-captioned matter.

2. On April 18, 2011, true and correct copies of Jazz's (1) Reply to Counterclaims and (2) Certificate of Service were filed electronically with the Court, and copies of same were sent via e-mail to the following counsel:

Mark S. Olinsky
Sills Cummis & Gross P.C.
The Legal Center
One Riverfront Plaza
Newark, New Jersey 07102
molinsky@sillscummis.com

Attorneys for Defendant
Roxane Laboratories, Inc.

I certify that the foregoing statements made by me are true. I understand that if any of the foregoing statements made by me are willfully false, I am subject to punishment.

Dated: April 18, 2011

By: Sarah A Hensler
Sarah A. Hensler

Mark S. Olinsky
Theodora McCormick
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Roxane Laboratories, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **vs.** **ROXANE LABORATORIES, INC.,** **Defendant.**	**C.A. No. 2:10-cv-06108 (SDW) (MCA)**

ROXANE LABORATORIES, INC.'S ANSWER, AFFIRMATIVE DEFENSES AND COUNTERCLAIMS TO PLAINTIFF'S COMPLAINT

Defendant, Roxane Laboratories, Inc. ("Roxane"), for its Answer, Affirmative Defenses and Counterclaims to Plaintiff Jazz Pharmaceuticals, Inc.'s Complaint for Patent Infringement ("the Complaint"), states as follows:

Nature of the Action

1. Roxane admits that the Complaint purports to be a civil action for patent infringement. Roxane also admits that it filed an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA"), seeking approval to commercially market a generic version of Jazz Pharmaceuticals' XYREM® drug product prior to the expiration of United States Patent Nos. 6,780,889 (the "'889 patent"), 7,262,219 (the "'219

patent"), 7,668,730 (the "'730 patent"), 7,765,106 (the "'106 patent"), and 7,765,107 (the "'107 patent") (collectively, "the patents-in-suit"). Roxane denies all other allegations contained in paragraph 1 of the Complaint.

The Parties

2. Roxane admits on information and belief that Jazz Pharmaceuticals is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304. Roxane denies all other allegations contained in paragraph 2 of the Complaint.

3. Roxane admits the allegations contained in paragraph 3 of the Complaint.

4. Roxane admits that it is registered to do business in the State of New Jersey and maintains a registered agent for service of process in New Jersey. Roxane further admits that it sells generic drug products throughout the United States, including this judicial district. Roxane further admits that it has litigated patent cases in this district and that, in at least some of those actions, Roxane has asserted counterclaims. Roxane denies all other allegations contained in paragraph 4 of the Complaint.

Jurisdiction and Venue

5. Roxane admits the allegations contained in paragraph 5 of the Complaint.

6. For purposes of this action, Roxane consents to this Court's jurisdiction. Roxane denies all other allegations contained in paragraph 6 of the Complaint.

7. For purposes of this action, Roxane consents that venue is proper in this district. Roxane denies all other allegations contained in paragraph 7 of the Complaint.

The Patents in Suit

8. Roxane admits that what purports to be a copy of the '889 patent is attached to the Complaint as Exhibit A. Roxane further admits that Exhibit A (a) is entitled "Microbiologically

Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," and (b) lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan as "Inventors." Roxane denies all other allegations contained in paragraph 8 of the Complaint.

9. Roxane admits that what purports to be a copy of the '219 patent is attached to the Complaint as Exhibit B. Roxane further admits that Exhibit B (a) is entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," and (b) lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan as "Inventors." Roxane denies all other allegations contained in paragraph 9 of the Complaint.

10. Roxane admits that what purports to be a copy of the '730 patent is attached to the Complaint as Exhibit C. Roxane further admits that Exhibit C (a) is entitled "Sensitive Drug Distribution System and Method," and (b) lists Dayton T. Reardan, Patti Engle and Bob Gagne as "Inventors." Roxane denies all other allegations contained in paragraph 10 of the Complaint.

11. Roxane admits that what purports to be a copy of the '106 patent is attached to the Complaint as Exhibit D. Roxane further admits that Exhibit D (a) is entitled "Sensitive Drug Distribution System and Method," and (b) lists Dayton T. Reardan, Patti A. Engle and Bob Gagne as "Inventors." Roxane denies all other allegations contained in paragraph 11 of the Complaint.

12. Roxane admits that what purports to be a copy of the '107 patent is attached to the Complaint as Exhibit E. Roxane further admits that Exhibit E (a) is entitled "Sensitive Drug Distribution System and Method," and (b) lists Dayton T. Reardan, Patti A. Engle and Bob

Gagne as "Inventors." Roxane denies all other allegations contained in paragraph 12 of the Complaint.

The XYREM® Drug Product

13. Roxane admits that New Drug Application ("NDA") No. 21-196 was approved by the FDA and that Jazz Pharmaceuticals is listed as the applicant for that NDA. Roxane denies all other allegations contained in paragraph 13 of the Complaint.

14. Roxane admits that the '889, '219, '730, '106 and '107 patents are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to XYREM®. Roxane denies all other allegations contained in paragraph 14 of the Complaint.

Acts Giving Rise to this Suit

15. Roxane admits that it filed ANDA No. 202090. Roxane's ANDA speaks for itself as to its contents. Roxane denies all other allegations contained in paragraph 15 of the Complaint.

16. Roxane admits that it provided a written certification to the FDA pursuant to Section 505 of the FFDCA. Roxane's certification speaks for itself as to its contents. Roxane denies all other allegations contained in paragraph 16 of the Complaint.

17. Roxane admits that by letter dated October 14, 2010 ("Roxane's Notice Letter"), Roxane notified Jazz Pharmaceuticals of its ANDA certification that the patents-in-suit are invalid, unenforceable, and/or will not be infringed by Roxane. Roxane's ANDA speaks for itself as to its contents. Roxane further admits that in Roxane's Notice Letter, Roxane informed Jazz Pharmaceuticals that Roxane seeks FDA approval for Roxane's sodium oxybate oral solution. Roxane denies all other allegations contained in paragraph 17 of the Complaint.

18. Roxane admits that in Roxane's Notice Letter, Roxane made an offer of confidential disclosure pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(1)(cc) and other conditions. Roxane denies that its sodium oxybate oral solution infringes any claims of the patents-in-suit. Roxane admits it received a letter from counsel for Jazz Pharmaceuticals dated October 29, 2010 responding to Roxane's "Offer of Confidential Access to ANDA No. 202090." Further, counsel for Roxane sent a letter dated November 23, 2010 to counsel for Jazz Pharmaceuticals responding to Jazz Pharmaceuticals' October 29, 2010 letter. Roxane denies all other allegations contained in paragraph 18 of the Complaint.

Count I: Infringement of the '889 Patent

19. Roxane repeats, reasserts and incorporates by reference its answers to paragraphs 1-18 of the Complaint above, as if fully set forth herein.

20. Roxane denies the allegations contained in paragraph 20 of the Complaint.

21. Roxane admits the allegations contained in paragraph 21 of the Complaint.

22. Roxane denies the allegations contained in paragraph 22 of the Complaint.

23. Roxane denies the allegations contained in paragraph 23 of the Complaint.

24. Roxane denies the allegations contained in paragraph 24 of the Complaint.

25. Roxane denies the allegations contained in paragraph 25 of the Complaint.

26. Roxane denies the allegations contained in paragraph 26 of the Complaint.

27. Roxane denies the allegations contained in paragraph 27 of the Complaint.

Count II: Infringement of the '219 Patent

28. Roxane repeats, reasserts and incorporates by reference its answers to paragraphs 1-27 of the Complaint above, as if fully set forth herein.

29. Roxane denies the allegations contained in paragraph 29 of the Complaint.

30. Roxane admits the allegations contained in paragraph 30 of the Complaint.

31. Roxane denies the allegations contained in paragraph 31 of the Complaint.

32. Roxane denies the allegations contained in paragraph 32 of the Complaint.

33. Roxane denies the allegations contained in paragraph 33 of the Complaint.

34. Roxane denies the allegations contained in paragraph 34 of the Complaint.

35. Roxane denies the allegations contained in paragraph 35 of the Complaint.

36. Roxane denies the allegations contained in paragraph 36 of the Complaint.

Count III: Infringement of the '730 Patent

37. Roxane repeats, reasserts and incorporates by reference its answers to paragraphs 1-36 of the Complaint above, as if fully set forth herein.

38. Roxane denies the allegations contained in paragraph 38 of the Complaint.

39. Roxane admits the allegations contained in paragraph 39 of the Complaint.

40. Roxane denies the allegations contained in paragraph 40 of the Complaint.

41. Roxane denies the allegations contained in paragraph 41 of the Complaint.

42. Roxane denies the allegations contained in paragraph 42 of the Complaint.

43. Roxane denies the allegations contained in paragraph 43 of the Complaint.

44. Roxane denies the allegations contained in paragraph 44 of the Complaint.

45. Roxane denies the allegations contained in paragraph 45 of the Complaint.

Count IV: Infringement of the '106 Patent

46. Roxane repeats, reasserts and incorporates by reference its answers to paragraphs 1-45 of the Complaint above, as if fully set forth herein.

47. Roxane denies the allegations contained in paragraph 47 of the Complaint.

48. Roxane admits the allegations contained in paragraph 48 of the Complaint.

49. Roxane denies the allegations contained in paragraph 49 of the Complaint.

50. Roxane denies the allegations contained in paragraph 50 of the Complaint.

51. Roxane denies the allegations contained in paragraph 51 of the Complaint.

52. Roxane denies the allegations contained in paragraph 52 of the Complaint.

53. Roxane denies the allegations contained in paragraph 53 of the Complaint.

54. Roxane denies the allegations contained in paragraph 54 of the Complaint.

Count V: Infringement of the '107 Patent

55. Roxane repeats, reasserts and incorporates by reference its answers to paragraphs 1-54 of the Complaint above, as if fully set forth herein.

56. Roxane denies the allegations contained in paragraph 56 of the Complaint.

57. Roxane admits the allegations contained in paragraph 57 of the Complaint.

58. Roxane denies the allegations contained in paragraph 58 of the Complaint.

59. Roxane denies the allegations contained in paragraph 59 of the Complaint.

60. Roxane denies the allegations contained in paragraph 60 of the Complaint.

61. Roxane denies the allegations contained in paragraph 61 of the Complaint.

62. Roxane denies the allegations contained in paragraph 62 of the Complaint.

63. Roxane denies the allegations contained in paragraph 64 of the Complaint.

AFFIRMATIVE DEFENSES

Without prejudice to the denials set forth in its Answer and without admitting any allegations of the Complaint not otherwise admitted, Roxane avers and asserts the following Affirmative Defenses to the Complaint of Plaintiff Jazz Pharmaceuticals, Inc.

FIRST AFFIRMATIVE DEFENSE
(Noninfringement of U.S. Patent No. 6,780,889)

The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that is the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any

validly construed claim of U.S. Patent No. 6,780,889 ("the '889 patent") either literally or under the doctrine of equivalents.

SECOND AFFIRMATIVE DEFENSE
(Invalidity of U.S. Patent No. 6,780,889)

Upon information and belief, the claims of the '889 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

THIRD AFFIRMATIVE DEFENSE
(Noninfringement of U.S. Patent No. 7,262,219)

The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that is the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 7,262,219 ("the '219 patent") either literally or under the doctrine of equivalents.

FOURTH AFFIRMATIVE DEFENSE
(Invalidity of U.S. Patent No. 7,262,219)

Upon information and belief, the claims of the '219 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

FIFTH AFFIRMATIVE DEFENSE
(Noninfringement of U.S. Patent No. 7,668,730)

The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that is the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 7,668,730 ("the '730 patent") either literally or under the doctrine of equivalents.

SIXTH AFFIRMATIVE DEFENSE
(Invalidity of U.S. Patent No. 7,668,730)

Upon information and belief, the claims of the '730 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

SEVENTH AFFIRMATIVE DEFENSE
(Noninfringement of U.S. Patent No. 7,765,106)

The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that are the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 7,765,106 ("the '106 patent") either literally or under the doctrine of equivalents.

EIGHTH AFFIRMATIVE DEFENSE
(Invalidity of U.S. Patent No. 7,765,106)

Upon information and belief, the claims of the '106 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

NINTH AFFIRMATIVE DEFENSE
(Noninfringement of U.S. Patent No. 7,765,107)

The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that is the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 7,765,107 ("the '107 patent") either literally or under the doctrine of equivalents.

TENTH AFFIRMATIVE DEFENSE
(Invalidity of U.S. Patent No. 7,765,107)

Upon information and belief, the claims of the '107 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

COUNTERCLAIMS

1. Counterclaimaint Roxane Laboratories, Inc. ("Roxane") is a corporation organized under the laws of Nevada having a principal place of business at 1809 Wilson Road, Columbus OH 43228-8601.

2. Upon information and belief, Plaintiff and Counterclaim Defendant Jazz Pharmaceuticals Inc. ("Jazz Pharmaceuticals") is a corporation organized under the laws of Delaware having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304.

3. As a consequence of Plaintiff's Complaint against Roxane, there is now an existing, continuing actual controversy between Jazz Pharmaceuticals and Roxane regarding the alleged infringement and validity of U.S. Patent Nos. 6,780,889 ("the '889 patent"), 7,262,219 ("the '219 patent"), 7,668,730 ("the '730 patent"), 7,765,106 ("the '106 patent"), and 7,765,107 ("the '107 patent").

4. This Court has jurisdiction over the subject matter of these counterclaims pursuant to §§ 1331 and 1338(a) of Title 28 of the U.S. Code, as they involve claims arising out of the United States Patent Act, 35 U.S.C. § 1, et. seq.

5. This Court may declare the rights and legal relations for the parties pursuant to §§ 2201 and 2202 of Title 28 of the U.S. Code and § 271(e)(5) of Title 35 of the U.S. Code because Roxane's Counterclaims present an actual controversy within the Court's jurisdiction.

6. Venue for these Counterclaims is proper within this District in which Jazz Pharmaceuticals' Complaint is pending.

Plaintiff's Improper Listing Of the '730, '106 and '107 Patents In The Orange Book

7. The '730, '106 and '107 patents all relate to a "drug distribution system and method [which] utilizes a central pharmacy and database to track all prescriptions for a sensitive drug" and do not claim an approved method of using the drug (21 U.S.C. 355(j)(5)(C)(ii)), *e.g.*, "indications or other conditions of use" required by 21 C.F.R. § 314.53(b)(1).

8. Thus, the '730, '106 and '107 patents were improperly listed in the Orange Book.

9. The listing of the '730, '106 and '107 patents must be removed from the Orange Book because these patents do not claim an approved indication or method of using the drug.

Plaintiff's REMS Program

10. Upon information and belief, Plaintiff submitted a risk evaluation and mitigation strategy as part of its NDA No. 21-196 ("REMS Program"), pursuant to section 355-1 of Title 21 of the United States Code.

11. Upon information and belief, Plaintiff's '730, '106 and/or '107 patents constitute attempts to cover, or claim some or all aspects of Plaintiff's REMS Program.

12. Plaintiff's '730, '106 and '107 patents have all been listed in the Orange Book relating to Plaintiff's XYREM® drug product, thereby improperly serving to block or delay approval of Roxane's ANDA No. 202090 under section 355(j) of Title 21 of the U.S. Code.

COUNT 1
Declaratory Judgment of Noninfringement of the '889 Patent

13. The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that are the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement,

infringe any validly construed claim of U.S. Patent No. 6,780,889 ("the '889 patent") either literally or under the doctrine of equivalents.

COUNT 2
Declaratory Judgment of Invalidity of the '889 Patent

14. Upon information and belief, the claims of the '889 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

COUNT 3
Declaratory Judgment of Noninfringement of the '219 Patent

15. The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that are the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 7,262,219 ("the '219 patent") either literally or under the doctrine of equivalents.

COUNT 4
Declaratory Judgment of Invalidity of the '219 Patent

16. Upon information and belief, the claims of the '219 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

COUNT 5
Declaratory Judgment of Noninfringement of the '730 Patent

17. The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that are the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 7,668,730 ("the '730 patent") either literally or under the doctrine of equivalents.

COUNT 6
Declaratory Judgment of Invalidity of the '730 Patent

18. Upon information and belief, the claims of the '730 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

COUNT 7
Declaratory Judgment of Noninfringement of the '106 Patent

19. The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that are the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 7,765,106 ("the '106 patent") either literally or under the doctrine of equivalents.

COUNT 8
Declaratory Judgment of Invalidity of the '106 Patent

20. Upon information and belief, the claims of the '106 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

COUNT 9
Declaratory Judgment of Noninfringement of the '107 Patent

21. The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that are the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 7,765,107 ("the '107 patent") either literally or under the doctrine of equivalents.

COUNT 10
Declaratory Judgment of Invalidity of the '107 Patent

22. Upon information and belief, the claims of the '107 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

COUNT 11
Order Requiring Removal of the '730 Patent From the Orange Book

23. Counterclaimant Roxane incorporates paragraphs 1-22 of its Counterclaim by reference.

24. Under 21 U.S.C. § 355(j)(5)(C)(ii), Roxane seeks an order requiring Plaintiff to remove the '730 patent from the Orange Book listing for XYREM®.

25. Roxane is entitled to an Order requiring Plaintiff to correct the patent information submitted by Plaintiff for the '730 patent on the ground that the patent does not claim the approved method of using sodium oxybate.

COUNT 12
Order Requiring Removal of the '106 Patent From the Orange Book

26. Counterclaimant Roxane incorporates paragraphs 1-25 of its Counterclaim by reference.

27. Under 21 U.S.C. § 355(j)(5)(C)(ii), Roxane seeks an order requiring Plaintiff to remove the '106 patent from the Orange Book listing for XYREM®.

28. Roxane is entitled to an Order requiring Plaintiff to correct the patent information submitted by Plaintiff for the '106 patent on the ground that the patent does not claim the approved method of using sodium oxybate.

COUNT 13
Order Requiring Removal of the '107 Patent From the Orange Book

29. Counterclaimant Roxane incorporates paragraphs 1-28 of its Counterclaim by reference.

30. Under 21 U.S.C. § 355(j)(5)(C)(ii), Roxane seeks an order requiring Plaintiff to remove the '107 patent from the Orange Book listing for XYREM®.

31. Roxane is entitled to an Order requiring Plaintiff to correct the patent information submitted by Plaintiff for the '107 patent on the ground that the patent does not claim the approved method of using sodium oxybate.

COUNT 14
Declaration of Violation of 21 U.S.C. § 355-1(f)(8)

32. Counterclaimant Roxane incorporates paragraphs 1-31 of its Counterclaim by reference.

33. Roxane is entitled to a declaration that any claim of the '730, '106 or '107 patents that is construed to cover Plaintiff's REMS Program is in violation of 21 U.S.C. § 355-1(f)(8) and is not enforceable to block or delay approval of Roxane's ANDA.

ROXANE'S PRAYER FOR RELIEF

WHEREFORE, Roxane respectfully requests that the Court enter judgment against Jazz Pharmaceuticals as follows:

(A) Declaring that Roxane would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of the '889, '219, '730, '106, and '107 patents either literally or under the doctrine of equivalents by submitting ANDA No. 202090;

(B) Declaring that Roxane's proposed sodium oxybate oral solution that is the subject of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by

inducement, infringe any validly construed claim of the '889 patent either literally or under the doctrine of equivalents;

(C) Declaring that U.S. Patent No. 6,780,889 is invalid for failure to comply with one or more provisions of 35 U.S.C. § 101, 102, 103, and/or 112;

(D) Declaring that Roxane's proposed sodium oxybate oral solution that are the subject of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of the '219 patent either literally or under the doctrine of equivalents;

(E) Declaring that U.S. Patent No. 7,262,219 is invalid for failure to comply with one or more provisions of 35 U.S.C. § 101, 102, 103, and/or 112;

(F) Declaring that Roxane's proposed sodium oxybate oral solution that is the subject of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of the '730 patent either literally or under the doctrine of equivalents;

(G) Declaring that U.S. Patent No. 7,668,730 is invalid for failure to comply with one or more provisions of 35 U.S.C. § 101, 102, 103, and/or 112;

(H) Declaring that Roxane's proposed sodium oxybate oral solution that is the subject of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of the '106 patent either literally or under the doctrine of equivalents;

(I) Declaring that U.S. Patent No. 7,765,106 is invalid for failure to comply with one or more provisions of 35 U.S.C. § 101, 102, 103, and/or 112;

(J) Declaring that Roxane's proposed sodium oxybate oral solution that is the subject of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of the '107 patent either literally or under the doctrine of equivalents;

(K) Declaring that U.S. Patent No. 7,765,107 is invalid for failure to comply with one or more provisions of 35 U.S.C. § 101, 102, 103, and/or 112;

(L) An Order requiring Plaintiff to remove the '730 patent from the Orange Book listing for XYREM®;

(M) An Order requiring Plaintiff to remove the '106 patent from the Orange Book listing for XYREM®;

(N) An Order requiring Plaintiff to remove the '107 patent from the Orange Book listing for XYREM®;

(O) Declaring that Plaintiff's REMS Program for XYREM® is in violation of 21 U.S.C. § 355-1(f)(8) and cannot be used to block or delay approval of Roxane's ANDA;

(P) Awarding Roxane its reasonable costs and attorneys' fees incurred in connection with this action pursuant to 35 U.S.C. § 285;

(Q) Such further and other relief as this Court may deem just and proper.

Dated: December 29, 2010

Respectfully Submitted,

s/Mark S. Olinsky
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CERTIFICATION PURSUANT TO L. CIV. R. 11.2

Pursuant to L. Civ. R. 11.2, I hereby certify that to the best of my knowledge, information, and belief, aside from this action, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: December 29, 2010

s/Mark S. Olinsky
Mark S. Olinsky

CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 201.1(D)(1)

I hereby certify that this action does not fall within the requirement for compulsory arbitration set forth in Local Civil Rule 201(d)(1) because the relief sought consists of non-monetary relief (i.e., permanent injunction).

Dated: December 29, 2010

s/Mark S. Olinsky
Mark S. Olinsky

CERTIFICATE OF SERVICE

I hereby certify that, on December 29, 2010, I electronically filed the attached Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint with the clerk of the Court by using the Court's CM/ECF system, and accordingly served all parties who receive notice of the filing via the Court's CM/ECF system.

s/Mark S. Olinsky
Mark S. Olinsky

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC.,	)	
	)	
Plaintiff,	)	CIVIL ACTION NO.:
	)	2:10-cv-06108 (SDW) (MCA)
vs.	)	
	)	
ROXANE LABORATORIES, INC.,	)	
	)	
Defendant,	)	
	)	

ROXANE LABORATORIES, INC.'S INITIAL INVALIDITY AND NONINFRINGEMENT CONTENTIONS PURSUANT TO LOCAL PATENT RULE 3.6

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ROXANE'S NONINFRINGEMENT CONTENTIONS BEGINNING AT TAB 9 ARE HIGHLY CONFIDENTIAL AND ARE BEING PRODUCED AS OUTSIDE COUNSELS' ATTORNEYS' EYES ONLY UNTIL THE ENTRY OF A DISCOVERY CONFIDENTIALITY ORDER, PURSUANT TO L. PAT. R. 2.2

INDEX

Pursuant to the Court's order at the March 22, 2011 telephonic status conference and Local Patent Rule 3.6, Defendant Roxane Laboratories, Inc. ("Roxane") hereby provides Plaintiff Jazz Pharmaceuticals Inc. ("Plaintiff") with Roxane's initial invalidity contentions regarding U.S. Patent Nos. 6,472,431, 6,780,889, 7,262,219, 7,8,51,506, 7,668,730, 7,765,106, and 7,765,107 ("the patents in suit") pursuant to Local Patent Rule 3.6(b), copies of documents Roxane relies on in support of its invalidity contentions pursuant to Local Patent Rule 3.6(c), Roxane's initial noninfringement contentions regarding the patents in suit pursuant to Local Patent Rule 3.6(d) and copies of documents Roxane relies on in support of its noninfringement contentions pursuant to Local Patent Rule 3.6(e).

GENERAL CONSIDERATIONS

1. Roxane reserves the right to amend, supplement and/or modify these contentions as discovery proceeds in this case and new facts are developed and/or expert discovery proceeds.

2. Roxane reserves the right to amend, supplement and/or modify these contentions upon entry of a claim construction order in this case.

3. Roxane reserves the right to amend, supplement and/or modify these contentions based on Plaintiff's allegations of infringement and validity.

4. These contentions are provided to Plaintiff without any waiver of any privilege or other doctrine of protection, including but not limited to attorney client privilege or work product doctrine.

5. Provision of these contention statements does not prejudice or limit Roxane's rights to pursue discovery of any other defenses, including, but not limited to, other invalidity or noninfringement defenses.

6. Roxane does not take any particular position on any claim construction issues in these contention statements and nothing in these contentions shall be construed to limit Roxane's

rights to assert the same or a different claim construction during that portion of these proceedings.

7. These invalidity and noninfringement contentions are not set forth in any particular order and the order of presentation shall not be construed to limit Roxane's right to present all, more or none of these contentions at any hearing or trial in this matter.

8. Roxane's noninfringement contentions are HIGHLY CONFIDENTIAL and are being produced on an OUTSIDE COUNSEL'S ATTORNEYS' EYES ONLY until the entry of a Discovery Confidentiality Order pursuant to L. Pat. R. 2.2.

INVALIDITY CONTENTIONS

A. The claims of United States Patent No. 6,472,431 are invalid:

1. Roxane contends that claims 1-7 of United States Patent No. 6,472,431 ("the '431 patent") are invalid for violating 35 U.S.C. § 112 ¶¶ 1, 2, 4, and 5 for at least the reasons set forth below.

2. Claims 1-7 of the '431 patent are invalid under 35 U.S.C. § 112, ¶¶ 1 and 2 as lacking written description and being indefinite at least because it is unclear if the claim element "the medium" refers to the original aqueous medium or the final medium after all of the claim steps have been performed.

3. Claim 1, and all claims depending from claim 1, are invalid under 35 U.S.C. § 112, ¶ 2 as being indefinite at least because there is no antecedent basis for "the gamma-hydroxybutyrate." *See* MPEP § 2173.05(e).

4. Claim 4 is invalid as an improper multiple dependent claim, because it is a multiple dependent claim that depends from a multiple dependent claim (claim 3). Accordingly, claim 4 violates 35 U.S.C. § 112, ¶ 5.

5. Claim 4 is invalid under 35 U.S.C § 112, ¶¶ 1 and 2 as lacking written description and being indefinite because the claim contradicts itself. Specifically, claim 4 requires the addition of gamma-hydroxybutyrate and a pH adjusting agent, both of which function as preservatives in the claimed composition.

6. Claim 7 is invalid under 35 U.S.C § 112, ¶¶ 2 and 4. Claim 7 depends from claim 6, which requires the pH adjusting agent to be an "organic acid;" however, claim 7 recites five (5) inorganic acids (*i.e.*, HCl, H3PO4, H2SO4, HS(=O)2–OH, and HNO3).

7. Roxane contends that claims 1-7 of the '431 patent are invalid under 35 U.S.C § 112 for at least the reasons set forth above. Additionally, and without prejudice or admitting that the claims are definite and/or capable of construction, Roxane further contends that claims 1-7 of the '431 patent are invalid over one or more of the following references, alone (for anticipation and/or obviousness) or in combination (for obviousness): United States Patent No. 5,840,331 ("the '331 patent") (ROXGHB002548-ROXGHB002569); United States Patent No. 4,983,632 ("the '632 patent") (ROXGHB002570-ROXGHB002575); United States Patent No. 3,051,619 ("the '619 patent") (ROXGHB002576-ROXGHB002578); Chem Abstract ES302338 (Accession Number 1966:481550, CAN 65:81550, CAPLUS) ("CA 338") (ROXGHB002579); R.H. Roth, et al. "γ-butyrolactone and γ-hydroxybutyric acid-II. The Pharmacologically active form, *Int. J. Neuropharmacol.*, 5, 421-428 (1966) ("Roth") (ROXGHB002580-ROXGHB002590); M.D. Vickers, "Gammahydroxybutyric acid" *International Anesthesiology Clinics*: Spring 1969 - Volume 7 - Issue 1 – pp. 75-90 ("Vickers") (ROXGHB002591-ROXGHB002609); Morrison and Boyd,ORGANIC CHEMISTRY, 3RD EDITION, 1973 ("Morrison") (ROXGHB002610-ROXGHB002618); USP 23/NF18, 1995 ("1995 USP") (ROXGHB002619-ROXGHB002621); 21 CFR 184 (1998); and the HANDBOOK OF PHARMACEUTICAL EXCIPIENTS, (2nd. Ed., 1994) ("1994 HPE") (ROXGHB002622-ROXGHB002626).

8. More specifically, and subject to Roxane's rights to seek amendment, modification or supplementation of these contentions, Roxane provides the following claim

charts demonstrating Roxane's preliminary initial contentions as to how the references render the claims of the '431 patent unpatentable over the prior art.

'431 Patent Claims	Prior art
1. A method of rendering an aqueous medium resistant to microbial growth, comprising	The preamble is not a limitation as it merely is result of practicing the claimed method. However, if the Court were to construe the preamble as a limitation, then the preamble limitation is shown by CA 338 (ROXGHB 002579); the '632 patent (ROXGHB002570-ROXGHB002575); Vickers (ROXGHB002591-ROXGHB002609); the '331 patent (ROXGHB002548-ROXGHB002569), and the '619 patent (ROXGHB002576-ROXGHB002578).
adding the gamma-hydroxybutyrate salt to the aqueous medium,	The '632 patent teaches adding a gamma-hydroxybutyrate sodium salt to water. *See e.g.,* Examples 1, 2, and the "injectable preparation" below Example 5 (ROXGHB002574). Vickers describes "a solution containing 2.42 gm. sodium 4-hydroxybutyrate in 10 ml. water." Vickers, p. 75 (ROXGHB002594). A person of ordinary skill in the art would have known that the solution described in Vickers could be obtained by adding gamma-hydroxybutyrate salt to an aqueous medium. *See, also* the '331 patent (ROXGHB002548-ROXGHB002569).
adjusting the concentration of the gamma-hydroxybutyrate salt in the aqueous medium to a final concentration of at least about 250 mg/ml,	The "adjusting the concentration" limitation is taught by CA 338 in view of the '632 patent and Vickers. CA 338 (ROXGHB002579) teaches solutions of gamma-hydroxybutyric acid salts for injections at a concentration of 20% (200 mg/ml). A person of ordinary skill in the art would have been motivated to adjust the concentration of the solution taught by CA 338 to arrive at a concentration of at least about 250 mg/ml based on the teachings of the '632 patent (ROXGHB 002574) and Vickers

'431 Patent Claims	Prior art
	(ROXGHB 002594), which teach concentrations of about 250 mg/ml or greater. *See also*, the '619 patent teaching that "[s]odium 4-hydroxy-butyrate… is highly soluble in water and which, in aqueous solution, has a pH slightly in excess of 7." (ROXGHB002576; Col. 1, lns. 61-66.) Accordingly, it would have been obvious to a person of ordinary skill in the art that the concentration of gamma-hydroxybutyrate could have been adjusted to concentrations of at least about 250 mg/ml.
and adjusting the pH of the medium to a final pH of about 6 to about 10,	The "adjusting the pH" limitation is taught by Vickers in view of CA 338 and further in view of 1995 USP and 1994 HPE. Vickers teaches "[g]ammahydroxybutyric acid is marketed for intravenous injection as a solution containing 2.42 gm. sodium 4-hydroxybutyrate in 10 ml. water. This is equivalent to 2 gm. of gammahydroxybutyric acid per ampule, or 20 percent solution. The pH lies between 8.2 and 8.9." Vickers, at p. 75 (ROXGHB002594). CA 338 teaches that a pH range of 7.2 to 7.7 is preferred. (ROXGHB002579). A person of ordinary skill in the art would have known that the pH solutions of gamma-hydroxybutyrate with acidulant pH adjusting agents as taught by 1995 USP, p.2205 (ROXGHB002621) and 1994 HPE, pp. 285-86 (ROXGHB002624-ROXGHB002626).
so that the medium is chemically stable	Not a claim limitation. *See*, *e.g.*, M.P.E.P. § 2111.04. However, if the Court were to construe this clause as a claim limitation, then the limitation of the clause is shown in the prior art as follows. A person of ordinary skill in the art would have understood that aqueous compositions of sodium gamma-hydroxybutyrate at an adjusted pH within the range of about 6 to about 10 would be chemically stable based on the prior art teachings to prepare stable, aqueous

'431 Patent Claims	Prior art
	pharmaceutical compositions. *See* CA 338 (ROXGHB002579) and Vickers (ROXGHB002591-ROXGHB002609).
and resistant to microbial growth.	Not a claim limitation. *See*, *e.g.*, M.P.E.P. § 2111.04. However, if the Court were to construe this clause as a claim limitation, then the limitation of the clause is shown in the prior art as follows. Stable, preservative-free, aqueous pharmaceutical compositions of sodium gamma-hydroxybutyrate at an adjusted pH within the range of about 6 to 10 were known in the prior art. *See* CA 338 (ROXGHB002579) and Vickers (ROXGHB002591-ROXGHB002609). A person of ordinary skill in the art would have understood stable, preservative-free pharmaceutical compositions to be resistant to microbial growth. *See also, e.g.,* the "injectable preparation" that does not contain any preservatives described in the '632 patent (ROXGHB002574; col. 8, lns. 57-60); and the '619 patent (ROXGHB002577; examples 1-3).

'431 Patent Claims	Prior art
2. The method of claim 1 wherein the salt is sodium gamma-hydroxybutyrate.	The '632 patent teaches adding sodium gamma-hydroxybutyrate to an aqueous solution. *See* Col. 7, lns. 32-34 and Examples 1, 2, and the "injectable preparation" below Example 5 (ROXGHB002574). Also, Vickers teaches a solution containing "sodium 4-hydroxybutyrate". Vickers, p. 75 (ROXGHB002594), which a person of ordinary skill in the art would have known could have been obtained by adding sodium gamma-hydroxybutyrate to water. *See also* the '619 patent, teaching that "Sodium

'431 Patent Claims	Prior art
	4-hydroxy-butyrate… is highly soluble in water and which, in aqueous solution, has a pH slightly in excess of 7." (ROXGHB002576; Col. 1, lns. 61-66.)

'431 Patent Claims	Prior art
3. The method of claim 1 or 2 wherein the final concentration is from about 310 to about 750 mg/ml,	CA 338 (ROXGHB002579) teaches solutions of gamma-hydroxybutyric acid salts for injections at a concentration of 20% (200 mg/ml). A person of ordinary skill in the art would have been motivated to adjust the concentration of the solution taught by CA 338 to arrive at a concentration of between about 310 and 750 mg/ml based on the teachings of the '632 patent, which teaches concentrations in the range of about 310 to 500 mg/ml. *See also*, the '619 patent teaching that "Sodium 4-hydroxy-butyrate … is highly soluble in water and which, in aqueous solution, has a pH slightly in excess of 7." (ROXGHB002574; Col. 7, lns. 48-50). Therefore, it would have been obvious to a person of ordinary skill in the art that the concentration of sodium gamma-hydroxybutyrate could have been adjusted to a concentration between about 310 and 750 mg/ml.
and the pH is about 6 to about 9.	The "adjusting the pH" limitation is taught by Vickers in view of CA 338 and further in view of 1995 USP and 1994 HPE. Vickers teaches "[g]ammahydroxybutyric acid is marketed for intravenous injection as a solution containing 2.42 gm. sodium 4-hydroxybutyrate in 10 ml. water. This is equivalent to 2 gm. of gammahydroxybutyric acid per ampule, or 20 percent solution. The pH lies between 8.2 and 8.9." Vickers, at p. 75 (ROXGHB002594). CA 338 teaches that a pH range of 7.2 to 7.7 is preferred. (ROXGHB 002579). A person of ordinary skill in the art would have known that the pH solutions of gamma-hydroxybutyrate with acidulant pH adjusting agents as taught by

'431 Patent Claims	Prior art
	1995 USP p.2205 (ROXGHB 002621) and 1994 HPE, pp. 285-86 (ROXGHB 002624-ROXGHB 002626).

'431 Patent Claims	Prior art
4. The method of claim 1, 2, or 3 wherein the medium does not contain a preservative.	If gamma-hydroxybutyrate were not considered a preservative, then the method would be obvious because the prior art teaches preparation of stable, preservative-free, aqueous pharmaceutical compositions of gamma-hydroxybutyrate. *See* CA 338 (ROXGHB002579) and Vickers (ROXGHB002591-ROXGHB002609). *See also, e.g.,* Morrison, p. 674 (ROXGHB002612); the '331 patent (ROXGHB002548-ROXGHB002569); and the '632 patent (ROXGHB002570-ROXGHB002575).

'431 Patent Claims	Prior art
5. The method of claim 1, wherein the concentration of said gamma-hydroxybutyrate is from about 250 to about 750 mg/ml.	CA 338 (ROXGHB002579) teaches solutions of gamma-hydroxybutyric acid salts for injections at a concentration of 20% (200 mg/ml). A person of ordinary skill in the art would have been motivated to adjust the concentration of the solution taught by CA 338 to arrive at a concentration of between about 250 and 750 mg/ml based on the teachings of the '632 patent (ROXGHB002574) and Vickers (ROXGHB002594), which teach concentrations in the range of about 250 to 750 mg/ml. *See also*, the '619 patent teaching that "[s]odium 4-hydroxy-butyrate… is highly soluble in water and which, in aqueous solution, has a pH slightly in excess of 7." Col. 1, lns. 61-66 (ROXGHB002576). Accordingly, it would have been obvious to a

'431 Patent Claims	Prior art
	person of ordinary skill in the art that the concentration of sodium gamma-hydroxybutyrate could have been adjusted to a concentration in the range of about 250 to about 750 mg/ml.

'431 Patent Claims	Prior art
6. The method of claim 1, wherein said pH-adjusting agent is an organic acid.	Adding organic acids, such as malic acid, citric acid, acetic acid, and propionic, to adjust the pH of an aqueous solution was well known to those of ordinary skill in the art. For example, the United States Pharmacopeia lists these acids among a list of thirteen (13) acidifying agents. 1995 USP. p. 2205 (ROXGHB002621). Adding organic acids, such as malic acid, citric acid, acetic acid, lactic acid, propionic acid and tartaric acid, to adjust the pH of pharmaceutical compositions was also well known. 21 C.F.R. §§ 184.1005, 184.1033, 184.1061, 184.1069, 184.1081, 184.1099 (1998). *See also,* 1994 HPE. pp. 285-286, 633 (ROXGHB002624-ROXGHB002626) (describing malic acid, lactic acid, and tartaric acid among only four (4) "acidulants" and malic, citric, lactic, tartaric acids among a list of thirteen (13) "acids").

'431 Patent Claims	Prior art
7. The method of claim 6, wherein said acid is selected from the group consisting of malic acid, citric acid, acetic acid, boric acid, lactic acid, hydrochloric acid, phosphoric acid, sulfuric acid, sulfonic acid and nitric acid.	Adding malic acid, citric acid, and acetic acid to adjust the pH of an aqueous solution was well known to those of ordinary skill in the art. For example, the United States Pharmacopeia lists these acids among a list of thirteen (13) acidifying agents. 1995 USP. p. 2205 (ROXGHB002621). Adding malic acid, citric acid, acetic acid, and

'431 Patent Claims	Prior art
	lactic acid to adjust the pH of pharmaceutical compositions was also well known. 21 C.F.R. §§ 184.1005, 184.1033, 184.1061, 184.1069, 184.1081, 184.1099 (1998). *See also,* 1994 HPE. pp. 285-286, 633 (ROXGHB002624-ROXGHB002626) (describing malic acid and lactic acid among only four (4) "acidulants" and malic, citric, and lactic acids among a list of thirteen (13) "acids"). Although boric acid, hydrochloric acid, phosphoric acid, sulfuric acid, sulfonic acid and nitric acid are not organic acids and, thus, are improperly claimed, these acids were well known to those of ordinary skill in the art for at least the reasons set forth below. Hydrochloric acid, phosphoric acid, sulfuric acid, and nitric acid were well known pH adjusting agent to those of ordinary skill in the art. For example, the United States Pharmacopeia lists these acids among only thirteen (13) acidifying agents. 1995 USP. p. 2205 (ROXGHB002621). Sulfuric acid was also known as an acid appropriate for use in pharmaceutical compositions. 21 C.F.R. § 184.1095 (1998). *See also,* 1994 HPE. pp. 285-286, 633 (ROXGHB002624-ROXGHB002626) (describing hydrochloric acid as one of thirteen (13) "acids").

B. The single claim of United States Patent No. 6,780,889 is invalid:

1. Roxane contends that claim 1 of United States Patent No. 6,780,889 ("the '889 patent") is invalid under 35 U.S.C § 112, ¶¶ 1 and 2 as lacking written description and being indefinite because the claim contradicts itself. Specifically, claim 1 requires gamma-hydroxybutyrate and a pH adjusting agent, both of which function as preservatives in the claimed composition.

2. Roxane contends that claim 1 of the '889 patent is invalid under 35 U.S.C § 112 for at least the reasons set forth above. Additionally, and without prejudice or admitting that the claims are definite and/or capable of construction, Roxane further contends that claim 1 of the '889 patent is invalid over one or more of the following references, alone (for anticipation and/or obviousness) or in combination (for obviousness): United States Patent No. 5,840,331 (the '331 patent"), (ROXGHB002548-ROXGHB002569); United States Patent No. 4,983,632 (the '632 patent") (ROXGHB002570-ROXGHB002575); United States Patent No. 3,051,619 ("the '619 patent") (ROXGHB002576-ROXGHB002578); Chem Abstract ES302338 (Accession Number 1966:481550, CAN 65:81550, CAPLUS) ("CA 338") (ROXGHB002579); R.H. Roth, et al. "γ-butyrolactone and γ-hydroxybutyric acid-II. The Pharmacologically active form," *Int. J. Neuropharmacol.*, 5, 421-428 (1966) ("Roth") (ROXGHB002580-ROXGHB002590); M.D. Vickers, "Gammahydroxybutyric acid," *International Anesthesiology Clinics*: Spring 1969 - Volume 7 - Issue 1 – pp. 75-90 ("Vickers") (ROXGHB002591-ROXGHB002609); Morrison and Boyd, ORGANIC CHEMISTRY, 3RD EDITION, 1973 ("Morrison") (ROXGHB002610-ROXGHB002618); USP 23/NF18, 1995 ("1995 USP") (ROXGHB002619-ROXGHB002621);

21 CFR 184 (1998); and the HANDBOOK OF PHARMACEUTICAL EXCIPIENTS, (2nd. Ed., 1994) ("1994 HPE") (ROXGHB002622-ROXGHB002626).

3. More specifically, and subject to Roxane's rights to seek amendment, modification or supplementation of these contentions, Roxane provides the following claim chart demonstrating Roxane's preliminary initial contentions as to how the references render claim 1 of the '889 patent unpatentable.

'889 Patent Claims	**Prior art**
1. A pharmaceutical composition,	A number of references described gamma-hydroxybutyrate in a pharmaceutical composition. *see e.g.*, Vickers, pp. 75-90 (ROXGHB002591-ROXGHB002609); the '632 patent (ROXGHB002570-ROXGHB002575) and the '331 patent (ROXGHB002548-ROXGHB002569).
consisting essentially of	This is a transitional phrase that limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52 (CCPA 1976). *See* MPEP § 2111.03.
an aqueous solution of 500 mg/ml sodium gamma-hydroxybutyrate,	The '632 patent teaches the use of gamma-hydroxybutyrate in an aqueous solution and that the "GHB salt content of the compositions according to the present invention can vary from 12.5 to 50% by weight." (ROXGHB002574; col. 7, lns. 48-50). A person of ordinary skill in the art would have known that a composition containing 50% by weight of GHB (as taught by the '632 patent) is equivalent to 500 mg/ml. *See also*, the '619 patent teaching that "[s]odium 4-hydroxy-butyrate… is highly soluble in water and which, in aqueous solution, has a pH slightly in excess of 7." (ROXGHB002576; col. 1, lns. 61-66.)

'889 Patent Claims	Prior art
and malic acid as a pH adjusting agent,	Malic acid was a well known pH adjusting agent to those of ordinary skill in the art. For example, the United States Pharmacopeia lists malic acid as one of a mere thirteen (13) acidifying agents. 1995 USP, p. 2205 (ROXGHB002621). Malic acid was also known as an acid appropriate for use in pharmaceutical compositions. 21 C.F.R. § 184.1005 (1998). *See also,* 1994 HPE, pp. 285-286, 633 (ROXGHB002624-ROXGHB002626) (describing malic acid as one of four (4) "acidulants").
wherein the composition has a pH of about 7.5,	Stable, preservative-free, aqueous, pharmaceutical compositions of sodium gamma-hydroxybutyrate at pH 7.5 were well-known. *See* CA 338 (ROXGHB002579).
and wherein the composition is chemically stable	Not a claim limitation. *See*, *e.g.*, M.P.E.P. § 2111.04. However, if the Court were to construe this clause as a claim limitation, then the limitation of the clause is shown in the prior art as follows. Stable, preservative-free, aqueous pharmaceutical compositions of sodium gamma-hydroxybutyrate at pH 7.5 were known in the prior art. *See* CA 338 (ROXGHB002579). *See also, e.g.,* the "injectable preparation" described in the '632 patent at col. 8, lns. 57-60 (ROXGHB002574); and the '619 patent, Examples 1-3 (ROXGHB002577).
and resistant to microbial growth,	Not a claim limitation. *See*, *e.g.*, M.P.E.P. § 2111.04. However, if the Court were to construe this clause as a claim limitation, then the limitation of the clause is shown in the prior art as follows. Stable, preservative-free, aqueous

'889 Patent Claims	Prior art
	pharmaceutical compositions of sodium gamma-hydroxybutyrate at pH 7.5 were known in the prior art. *See* CA 338 (ROXGHB002579). A person of ordinary skill in the art would have understood stable, preservative-free pharmaceutical compostions to be resistant to microbial growth. *See also, e.g.,* the "injectable preparation" that does not contain any preservatives described in the '632 patent at col. 8, lns. 57-60 (ROXGHB002574); and Examples 1-3, the '619 patent (ROXGHB002577).
and wherein the composition is free of preservatives.	Not a claim limitation. *See*, *e.g.*, M.P.E.P. § 2111.04. However, if the Court were to construe this clause as a claim limitation, then the limitation of the clause is shown in the prior art as set forth below. Stable, preservative-free, aqueous pharmaceutical compositions of gamma-hydroxybutyrate at pH 7.5 were known in the prior art. *See* CA 338 (ROXGHB002579). *See also, e.g.,* the '632 patent; Vickers, pp. 75-90 (ROXGHB002591-ROXGHB002609); Morrison, p. 674 (ROXGHB002612); and the '331 patent (ROXGHB002548-ROXGHB002569).

C. The claims of United States Patent No. 7,262,219 are invalid:

1. Roxane contends that claims 1-4 of United States Patent No. 7,262,219 ("the '219 patent") are invalid under 35 U.S.C § 112, ¶¶ 1 and 2 as lacking written description and being indefinite because the claims contradict themselves. Specifically, independent claims 1 and 4 require gamma-hydroxybutyrate and a pH adjusting agent, both of which function as preservatives in the claimed composition.

2. Roxane contends that claims 1-4 of the '219 patent are invalid under 35 U.S.C § 112 for at least the reasons set forth above. Additionally, and without prejudice or admitting that the claims are definite and/or capable of construction, Roxane further contends that the claims of the '219 patent are invalid over one or more of the following references, alone (for anticipation and/or obviousness) or in combination (for obviousness): United States Patent No. 5,840,331 ("the '331 patent") (ROXGHB002548-ROXGHB002569); United States Patent No. 4,983,632 ("the '632 patent") (ROXGHB002570-ROXGHB002575); and United States Patent No. 3,051,619 ("the '619 patent") (ROXGHB002576-ROXGHB002578); Chem Abstract ES302338 (Accession Number 1966:481550, CAN 65:81550, CAPLUS) ("CA 338") (ROXGHB002579); R.H. Roth, et al. "γ-butyrolactone and γ-hydroxybutyric acid-II. The Pharmacologically active form," *Int. J. Neuropharmacol.*, 5, 421-428 (1966) ("Roth") (ROXGHB002580-ROXGHB002590); M.D. Vickers, "Gammahydroxybutyric acid," *International Anesthesiology Clinics*: Spring 1969 - Volume 7 - Issue 1 – pp. 75-90 ("Vickers") (ROXGHB002591-ROXGHB002609); Morrison and Boyd, ORGANIC CHEMISTRY, 3RD EDITION, 1973 ("Morrison") (ROXGHB002610-ROXGHB002618); USP 23/NF18, 1995 ("1995 USP") (ROXGHB002619-ROXGHB002621); 21 CFR 184 (1998); and the HANDBOOK OF PHARMACEUTICAL EXCIPIENTS, (2nd. Ed., 1994) ("1994 HPE")(ROXGHB002622-ROXGHB002626).

Tab 4-1

3. More specifically, and subject to Roxane's rights to seek amendment, modification or supplementation of these contentions, Roxane provides the following claim charts demonstrating Roxane's preliminary initial contentions as to how the references render claims 1-4 of the '219 patent unpatentable over the prior art.

'219 Patent Claims	**Prior art**
1. A pharmaceutical composition,	A number of references described gamma-hydroxybutyrate in a pharmaceutical composition. *see e.g.*, Vickers, (ROXGHB002591-ROXGHB002609); the '632 patent (ROXGHB002570-ROXGHB002575) and the '331 patent (ROXGHB002548-ROXGHB002569).
consisting essentially of	This is a transitional phrase that limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52 (CCPA 1976). *See* MPEP § 2111.03.
an aqueous solution of about 350-750 mg/ml sodium gamma-hydroxybutyrate,	The '632 patent teaches the use of gamma-hydroxybutyrate in an aqueous solution and that the "GHB salt content of the compositions according to the present invention can vary from 12.5 to 50% by weight." (ROXGHB002574; col. 7, lns. 48-50). A person of ordinary skill in the art would have known that a composition containing 35-50% by weight of GHB (as taught by the '632 patent) is equivalent to 350-500 mg/ml, all of which are in the claimed 350-750 mg/ml range. *See also*, the '619 patent teaching that "[s]odium 4-hydroxy-butyrate… is highly soluble in water and which, in aqueous solution, has a pH slightly in excess of 7." (ROXGHB002576; col. 1, lns. 61-66.)
and a pH adjusting agent, wherein the pH adjusting agent is malic acid, citric acid, acetic acid, lactic acid, carbonic acid, formic acid,	Each of malic acid, citric acid, acetic acid, and propionic were well known pH adjusting agents to those of ordinary skill in the art. For example, the United States Pharmacopeia lists

'219 Patent Claims	Prior art
propionic acid or tartaric acid	these acids among a list of thirteen (13) acidifying agents. 1995 USP, p. 2205 (ROXGHB002621). Each of malic acid, citric acid, acetic acid, lactic acid, propionic acid and tartaric acid were also known as acids appropriate for use in pharmaceutical compositions. 21 C.F.R. §§ 184.1005, 184.1033, 184.1061, 184.1069, 184.1081, 184.1099 (1998). *See also,* 1994 HPE, pp. 285-286, 633 (ROXGHB002624-ROXGHB002626) (describing malic acid, lactic acid, and tartaric acid among only four (4) "acidulants" and malic, citric, lactic, tartaric acids among a list of thirteen (13) "acids").
wherein the composition has a pH of about 6-7.5,	Stable, preservative-free, aqueous, pharmaceutical compositions of sodium gamma-hydroxybutyrate at least pH 7.2-7.5 were well-known. *See* CA 338 (ROXGHB002579).
and wherein the composition is chemically stable	Not a claim limitation. *See*, *e.g.*, M.P.E.P. § 2111.04. However, if the Court were to construe this clause as a claim limitation, then the limitation of the clause is shown in the prior art as follows. Stable, preservative-free, aqueous pharmaceutical compositions of sodium gamma-hydroxybutyrate at pH 7.5 were known in the prior art. *See* CA 338 (ROXGHB002579). *See also, e.g.,* the "injectable preparation" described in the '632 patent at col. 8, lns. 57-60 (ROXGHB002574); and the '619 patent, Examples 1-3 (ROXGHB002577).
and resistant to microbial growth,	Not a claim limitation. *See*, *e.g.*, M.P.E.P. § 2111.04. However, if the Court were to construe this clause as a claim limitation, then the limitation of the clause is shown in the

'219 Patent Claims	Prior art
	prior art as follows. Stable, preservative-free, aqueous pharmaceutical compositions of sodium gamma-hydroxybutyrate at pH 7.5 were known in the prior art. *See* CA 338 (ROXGHB002579). A person of ordinary skill in the art would have understood stable, preservative-free pharmaceutical compositions to be resistant to microbial growth. *See also, e.g.,* the "injectable preparation" that does not contain any preservatives described in the '632 patent at col. 8, lns. 57-60 (ROXGHB002574); and Examples 1-3 in the '619 patent (ROXGHB002577).
and wherein the composition is free of preservatives.	Not a claim limitation. *See*, *e.g.*, M.P.E.P. § 2111.04. However, if the Court were to construe this clause as a claim limitation, then the limitation of this clause is shown in the prior art as set forth below. Stable, preservative- free, aqueous pharmaceutical compositions of sodium gamma-hydroxybutyrate at pH 7.5 were known in the prior art. *See* CA 338 (ROXGHB002579). *See also, e.g.,* the '632 patent (ROXGHB002570-ROXGHB002575); Vickers, pp. 75-90 (ROXGHB002591-ROXGHB002609); Morrison, p. 674 (ROXGHB002612); and the '331 patent (ROXGHB002548-ROXGHB002569).

'219 Patent Claims	Prior art
2. The pharmaceutical composition of claim 1 wherein the aqueous solution contains about 400-650 mg/ml of sodium gamma-hydroxybutyrate.	The '632 patent teaches the use of gamma-hydroxybutyrate in an aqueous solution and that the "GHB salt content of the compositions according to the present invention can vary from 12.5 to 50% by weight." (ROXGHB002574; col. 7, lns. 48-50.) A person of ordinary skill in the art would have

'219 Patent Claims	Prior art
	known that a composition containing 40-50% by weight of GHB (as taught by the '632 patent) is equivalent to 400-500 mg/ml, all of which are in the claimed 400-650 mg/ml range. *See also*, the '619 patent teaching that "[s]odium 4-hydroxy-butyrate… is highly soluble in water and which, in aqueous solution, has a pH slightly in excess of 7." Col. 1, lns. 61-66 (ROXGHB002576).

'219 Patent Claims	Prior art
3. The pharmaceutical composition of claim 1, wherein the pH adjusting agent is malic acid.	Malic acid was a well known pH adjusting agent to those of ordinary skill in the art. For example, the United States Pharmacopeia lists malic acid as one of a mere thirteen (13) acidifying agents. 1995 USP, p. 2205 (ROXGHB002621). Malic acid was also known as an acid appropriate for use in pharmaceutical compositions. 21 C.F.R. § 184.1005 (1998). *See also,* 1994 HPE, pp. 285-286, 633 (ROXGHB002624-ROXGHB002626) (describing malic acid as one of four (4) "acidulants").

'219 Patent Claims	Prior art
4. A pharmaceutical composition,	A number of references described gamma-hydroxybutyrate in a pharmaceutical composition. *see e.g.*, Vickers, pp. 75-90 (ROXGHB002591-ROXGHB002609); the '632 patent (ROXGHB002570-ROXGHB002575) and the '331 patent (ROXGHB002548-ROXGHB002569).
consisting essentially of	This is a transitional phrase that limits the scope of a claim to the specified materials or steps "and those that do not materially affect

'219 Patent Claims	Prior art
	the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52 (CCPA 1976). *See* MPEP § 2111.03.
an aqueous solution of about 350-750 mg/ml sodium gamma-hydroxybutyrate,	The '632 patent teaches the use of gamma-hydroxybutyrate in an aqueous solution and that the "GHB salt content of the compositions according to the present invention can vary from 12.5 to 50% by weight." (ROXGHB002574; col. 7, lns. 48-50). A person of ordinary skill in the art would have known that a composition containing 35-50% by weight of GHB (as taught by the '632 patent) is equivalent to 350-500 mg/ml, all of which are in the claimed 350-750 mg/ml range. *See also*, the '619 patent teaching that "Sodium 4-hydroxy-butyrate… is highly soluble in water and which, in aqueous solution, has a pH slightly in excess of 7." Col. 1, lns. 61-66 (ROXGHB002576).
and a pH adjusting agent, wherein the pH adjusting agent is hydrochloric acid, phosphoric acid, sulphuric acid, boric acid or nitric acid,	Hydrochloric acid, phosphoric acid, sulfuric acid, and nitric acid were well known pH adjusting agent to those of ordinary skill in the art. For example, the United States Pharmacopeia lists these acids among only thirteen (13) acidifying agents. 1995 USP, p. 2205 (ROXGHB002621). Sulfuric acid was also known as an acid appropriate for use in pharmaceutical compositions. 21 C.F.R. § 184.1095 (1998). *See also,* 1994 HPE, pp. 285-286, 633 (ROXGHB002624-ROXGHB002626) (describing hydrochloric acid as one of thirteen (13) "acids").
wherein the composition has a pH of about 6-7.5,	Stable, preservative-free, aqueous, pharmaceutical compositions of sodium gamma-hydroxybutyrate at least pH 7.2-7.5 were well-known. *See* CA 338 (ROXGHB002579).

'219 Patent Claims	Prior art
and wherein the composition is chemically stable	Not a claim limitation. *See*, *e.g.*, M.P.E.P. § 2111.04. However, if the Court were to construe this clause as a claim limitation, then the limitation of this clause is shown in the prior art as follows. Stable, preservative-free, aqueous pharmaceutical compositions of sodium gamma-hydroxybutyrate at pH 7.5 were known in the prior art. *See* CA 338 (ROXGHB002579). *See also, e.g.,* the "injectable preparation" described in the '632 patent at col. 8, lns. 57-60 (ROXGHB002574); and the '619 patent, Examples 1-3 (ROXGHB002577).
and resistant to microbial growth,	Not a claim limitation. *See*, *e.g.*, M.P.E.P. § 2111.04. However, if the Court were to construe this clause as a claim limitation, then the limitation of this clause is shown in the prior art as follows. Stable, preservative-free, aqueous pharmaceutical compositions of sodium gamma-hydroxybutyrate at pH 7.5 were known in the prior art. *See* CA 338 (ROXGHB002579). A person of ordinary skill in the art would have understood stable, preservative-free pharmaceutical compositions to be resistant to microbial growth. *See also, e.g.,* the "injectable preparation" that does not contain any preservatives described in the '632 patent at col. 8, lns. 57-60 (ROXGHB002574); and Examples 1-3 in the '619 patent (ROXGHB002577).
and wherein the composition is free of preservatives.	Not a claim limitation. *See*, *e.g.*, M.P.E.P. § 2111.04. However, if the Court were to construe this clause as a claim limitation, then the limitation of the clause is shown in the prior art as shown below. Stable, preservative-free, aqueous

'219 Patent Claims	Prior art
	pharmaceutical compositions of sodium gamma-hydroxybutyrate at pH 7.5 were known in the prior art. *See* CA 338 (ROXGHB002579). *See also, e.g.,*, the '632 patent (ROXGHB002570-ROXGHB002575); Vickers, pp. 75-90 (ROXGHB002591-ROXGHB002609); Morrison, p. 674 (ROXGHB002612); and the '331 patent (ROXGHB002548-ROXGHB002569).

D. The claims of United States Patent No. 7,851,506 are invalid:

1. Roxane contends that at least claim 3 of United States Patent No. 7,851,506 ("the '506 patent") is invalid for violating 35 U.S.C. § 112 ¶¶ 1, 2, and 4 for at least the reasons set forth below.

2. Claim 3 of the '506 patent is invalid under 35 U.S.C. § 112, ¶ 4 because claim 3 does not specify a further limitation of the subject matter claimed in claim 1. Specifically, "catalepsy" is not a condition that appears in claim 1.

3. Claim 3 of the '506 patent is also invalid under 35 U.S.C. § 112, ¶¶ 1 and 2 because the specification does not provide any written description or enablement for the condition "catalepsy." Furthermore, the '506 patent does not teach or suggest that catalepsy is a condition that is responsive to treatment with sodium gamma-hydroxybutyrate.

4. Roxane contends that at least claim 3 of the '506 patent is invalid under 35 U.S.C § 112 for at least the reasons set forth above. Additionally, and without prejudice or admitting that the claims are definite and/or capable of construction, Roxane further contends that claims 1-3 of the '506 patent are invalid over one or more of the following references, alone (for anticipation and/or obviousness) or in combination (for obviousness): United States Patent No. 5,840,331 ("the '331 patent") (ROXGHB002548-ROXGHB002569); United States Patent No. 4,983,632 ("the '632 patent") (ROXGHB002570-ROXGHB002575); United States Patent No. 3,051,619 ("the '619 patent") (ROXGHB002576-ROXGHB002578); Chem Abstract ES302338 (Accession Number 1966:481550, CAN 65:81550, CAPLUS) ("CA 338") (ROXGHB002579); R.H. Roth, et al. "γ-butyrolactone and γ-hydroxybutyric acid-II. The Pharmacologically active

form," *Int. J. Neuropharmacol.*, 5, 421-428 (1966) ("Roth") (ROXGHB002580-ROXGHB002590); M.D. Vickers, "Gammahydroxybutyric acid," *International Anesthesiology Clinics*: Spring 1969 - Volume 7 - Issue 1 – pp. 75-90 ("Vickers") (ROXGHB002591-ROXGHB002609); L. Scrima, et al. "The effects of γ-hydroxybutyrate on the sleep of narcolepsy patients: a double-blind study," *Sleep*., 13(6):479-490 ("Scrima") (ROXGHB002627-ROXGHB002638); Morrison and Boyd,. ORGANIC CHEMISTRY, 3RD EDITION, 1973 ("Morrison") (ROXGHB002610-ROXGHB002618); USP 23/NF18, 1995 ("1995 USP") (ROXGHB002619-ROXGHB002621); 21 CFR 184 (1998); and the HANDBOOK OF PHARMACEUTICAL EXCIPIENTS, (2nd. Ed., 1994) ("1994 HPE") (ROXGHB002622-ROXGHB002626).

5. More specifically, and subject to Roxane's rights to seek amendment or modification of these contentions, Roxane provides the following claim charts demonstrating Roxane's preliminary initial contentions as to how the references render claims 1-3 of the '506 patent unpatentable over the prior art.

'506 Patent Claims	**Prior art**
1. A method of treating a condition responsive to sodium gamma-hydroxybutyrate, comprising	The prior art disclosed a method of treating a condition responsive to sodium gamma-hydroxybutyrate. *See,* Scrima, 479-490 (ROXGHB002627-ROXGHB002638).
orally administering to a patient afflicted with the condition an aqueous composition comprising	Scrima discloses orally administering an aqueous composition to a patient afflicted with a condition (*i.e.*, narcolepsy). Scrima at p. 480 (ROXGHB002628).
a first dose of about 4.5 to about 10 grams of sodium gamma-hydroxybutyrate within an hour prior to initial sleep onset	Scrima discloses administering a first dose of gamma-hydroxybutyrate prior to the initial sleep onset. Scrima at p. 482 (ROXGHB002630). The '632 patent teaches that "[t]he typical dosage for a GHB salt is from 0.025 to 0.10 g/kg…" (ROXGHB002574; Col. 7, lns. 44-

'506 Patent Claims	Prior art
	46). Accordingly, a person of ordinary skill in the art would understand that a patient weighing between 45 kg (100 lbs) to 100 kg (220 lbs) (*See e.g.,* Scrima at p. 481; ROXGHB002629) would be given a dose between 4.5 to 10 grams if the dose was 0.10 g/kg as taught by the '632 patent.
and an aqueous composition comprising a second dose of about 4.5 to about 10 grams within 2 to 5 hours following initial sleep onset,	Scrima discloses administering a second dose of gamma-hydroxybutyrate 3 hours after the first dose is administered. Scrima at p. 482 (ROXGHB002630). The '632 patent teaches that "[t]he typical dosage for a GHB salt is from 0.025 to 0.10 g/kg…" (ROXGHB002574; Col. 7, lns. 44-46). Accordingly, a person of ordinary skill in the art would understand that a patient weighing between 45 kg (100 lbs) to 100 kg (220 lbs) (*See e.g.,* Scrima at p. 481; ROXGHB002629) would be given a dose between 4.5 to 10 grams if the dose was 0.10 g/kg as taught the '632 patent.
wherein the aqueous composition of the first dose and the aqueous composition of the second dose each comprises a respective concentration of sodium gamma-hydroxybutyrate of greater than about 500 mg/mL,	The '632 patent teaches the use of gamma-hydroxybutyrate in an aqueous solution and that the "GHB salt content of the compositions according to the present invention can vary from 12.5 to 50% by weight." (ROXGHB002574; col. 7, lns. 48-50). A person of ordinary skill in the art would have known that a composition containing 50% by weight of GHB (as taught by the '632 patent) is equivalent to 500 mg/ml, which is in the claimed range. *See also*, the '619 patent teaching that "[s]odium 4-hydroxy-butyrate… is highly soluble in water and which, in aqueous solution, has a pH slightly in excess of 7." (ROXGHB002576; col. 1, lns. 61-66.) Therefore, a person of ordinary skill in the art would have known that the concentration of sodium gamma-hydroxybutyrate in the aqueous compositions of the first and second

'506 Patent Claims	Prior art
	dose could have been adjusted to a concentration within the claimed greater than about 500 mg/ml limitation.
wherein the condition is selected from the group consisting of apnea, sleep time disturbances, narcolepsy, cataplexy, sleep paralysis, hypnagogic hallucination, sleep arousal, insomnia, and nocturnal myoclonus.	The prior art disclosed the treatment of the claimed conditions with sodium gamma-hydroxybutyrate. *See e.g.,* Scrima (ROXGHB002627-ROXGHB002638).

'506 Patent Claims	Prior art
2. The method of claim 1, wherein the condition is narcolepsy.	The prior art disclosed the treatment of narcolepsy with sodium gamma-hydroxybutyrate. *See e.g.,* Scrima (ROXGHB002627-ROXGHB002638).

'506 Patent Claims	Prior art
3. The method of claim 1, wherein the condition is a catalepsy.	If Jazz were to contend that claim 3 should recite cataplexy instead of catalepsy and if the Court were to revise the claim in accordance with Jazz's contention, then the limitation of this claim would be met by the prior art disclosure of the treatment of cataplexy with sodium gamma-hydroxybutyrate. *See e.g.,* Scrima (ROXGHB002627-ROXGHB002638)

E. The claims of United States Patent No. 7,668,730 are invalid:

1. The method claims of the '730 patent are invalid on the ground that the claimed subject matter is not encompassed by 35 U.S.C. § 101. The patent claims are invalid because the patentee admittedly seeks to patent an algorithm or an abstract idea, *see Bilski v. Kappos*, 130 S.Ct. 3218, 3229-30 (2010), and the claims do not satisfy the machine-or-transformation test, *see In re Bilski*, 545 F.3d 943, 962-63 (Fed. Cir. 2008).

2. First, the claims of the distribution patents are directed to functions or algorithms that are implemented in computer software or a combination of software and human implemented procedures. (*See*, *e.g.*, '730 patent at col. 2, line 66-col. 3, line 13.) The Supreme Court has repeatedly rejected patents that claim a formula or an algorithm. *See*, *e.g.*, *Gottschalk v. Benson*, 409 U.S. 63, 71 (1972); *Parker v. Flook*, 437 U.S. 584, 594 (1978); *In re Grams*, 888 F.2d 835, 837, n.1 (Fed. Cir. 1989) ("It is of no moment that the algorithm is not expressed in terms of a mathematical formula. Words used in a claim operating on data to solve a problem can serve the same purpose as a formula."); *Bilski v. Kappos*, 130 S.Ct. at 3231. The claims are also directed to a patent ineligible, abstract idea, *i.e.*, the concept of checking for potential abuse of a prescription drug by a patient or the prescribing doctor and applying that concept to a specific drug, GHB.

3. Second, the method claims of the distribution patents are not patent-eligible because the claimed methods do not transform an article into a different state or thing. The patents merely claim a method of distributing sensitive drugs that does not transform or make the drugs any less sensitive. And while the methods arguably include a "data-gathering step," wherein the pharmacy technician, specialist or pharmacist must "confirm[] with a patient that educational material has been read" or "confirm[] receipt by the patient of the prescription drug,"

the Federal Circuit has noted that "gathering data would not constitute a transformation of any article." *Bilski*, 545 F.3d at 963. And while the claimed methods refer to periodic reports that are generated "to evaluate potential diversion patterns" or "potential for abuse, misuse, or diversion," this is merely an addition of "non-essential post-solution activity" that will not save the claims from invalidity. *See Bilski*, 545 F.3d at 962-63. Generating a report containing data to be analyzed later is not the main purpose of the claimed process—distributing sensitive drugs in a manner to minimize risk and protect against abuse. (*See*, *e.g.*, '730 patent at col. 1, lines 6-7.)

4. Third, the claims of the distribution patents are not tied to a particular machine. While many of the steps require uses of so-called "exclusive computer system under the control of an exclusive central pharmacy," "exclusive central computer system," "computer processor" or "exclusive central pharmacy that maintains a central database," the specification does not require any specific type of computer system—the software can be executed "on a digital signal processor, ASIC, microprocessor, or other type of possessor operating on a computer system, such as a personal computer, server or other computer system." (*See*, *e.g.*, '730 patent at col. 3, lines 10-14.) The Supreme Court in *Gottschalk* rejected a claimed process that utilized any general-purpose digital computer of any type. *See Gottschalk*, 409 U.S. at 71-72. The Board of Patent Appeals and Interferences has followed the Gottschalk approach and has rejected applications that are not tied to a specific computer system. *See*, *e.g.*, *Ex Parte Kuno, et al.*, Appeal No. 2009-006896 (B.P.A.I. Dec. 13, 2010); *Ex Parte Monk, et al.*, Appeal No. 2009-013250 (B.P.A.I. Dec. 30, 2010).

5. Finally, no patent can be obtained for a method an essential component of which consists of human mental participation. If a method necessarily involves human judgment and

choice, then the method will not meet the standard of definiteness required for patent protection. *See, e.g., Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1356 (Fed. Cir. 2005) ("The scope of claim language cannot depend solely on the unrestrained, subjective opinion of a particular individual purportedly practicing the invention. *See Application of Musgrave*, 57 C.C.P.A. 1352, 431 F.2d 882, 893 (1970)."). The claims of the distribution patents are invalid for indefiniteness because they require someone, for example, a pharmacy specialist, technician or pharmacist, to make certain subjective judgment calls as to whether the patient indeed received and read the program materials or whether there is potential for abuse of the prescription drug by the patient. The applicants repeatedly argued to the PTO that the claimed methods of distribution or distribution models "analyse[] (sic) for and determine[] potential abuse situations and current and anticipated patterns of potential adverse reactions." (*See*, *e.g.*, '730 PH, 9/30/04 Petition to Make Special at ROXGHB004395.) Neither the claims nor the specifications of the distribution patents, however, provide objective steps or criteria for evaluating the potential for abuse or on how to verify whether the patient has indeed truthfully reviewed the program materials—the technician could accept what the patient says or could exercise his or her own judgment to determine whether the patient is being truthful or not. Because the claimed methods seek to address the problems associated with the abuse and illegal distribution of sensitive prescription drugs like GHB, pharmacy specialists, technicians and pharmacists must be given authority to act on their "gut" feeling as to whether a certain patient is being deceitful or untrustworthy. Patent claims that require such human mental participation are indefinite and not proper patent-eligible subject matter.

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	Borsand (U.S. Patent Application Publication No. 2003/0074225), ROXGHB004109-36, ("Borsand"), **Califano (U.S. Patent Application Publication No. 2003/0033168), ROXGHB004137-70, ("Califano"),** **"An Interview with Orphan Medical about Xyrem" ("An Interview with Orphan Medical about Xyrem," Feb. 12, 2001, http://www.talkaboutsleep.com/sleepdisorders/archives/Narcolepsy_xyrem_interview.htm), ROXGHB004250-52 ("An Interview with Orphan Medical about Xyrem"),** **Lilly (U.S. Patent Application Publication No. 2004/0176985), ROXGHB004253-64 ("Lilly"),** **Melker (U.S. Patent Application Publication No. 2002/0177232), ROXGHB004265-81 ("Melker"),** **Moradi (U.S. Patent Application Publication No. 2004/0019794), ROXGHB004282-312 ("Moradi"),** **Ukens ("Specialty Pharmacy," Jun. 5, 2000, Drug Topics, v. 144, p. 40), ROXGHB004313-20 ("Ukens"), and** **Williams (U.S. Patent No. 6,315,720), ROXGHB004321-31 ("Williams")**
(preamble) 1. A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising: a "method of distributing" a drug "under exclusive control of an exclusive central pharmacy, the method comprising"	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a claim limitation, then it is disclosed in the prior art as follows: The preamble limitations are disclosed in at least Moradi and Ukens. The June 19, 2006 Office Action, ROXGHB004525-ROXGHB004545 ("the 6/19/06 OA") and the October 3, 2007 Examiner's Answer, ROXGHB004708-ROXGHB004725 ("the Examiner's Answer") each found "a method of distributing a drug under exclusive control of an exclusive central pharmacy, the method comprising" disclosed among paragraphs 3 (ROXGHB004295) and 24 (ROXGHB004296) of Moradi. Also, the October 18, 2006 Office Action, ROXGHB004586-ROXGHB004600 ("the 10/18/06 OA") and the Examiner's Answer each found an exclusive central pharmacy disclosed among page 3,

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	paragraphs 3-5 of Ukens (ROXGHB004315). The August 31, 2009 Decision on Appeal, ROXGHB004750-ROXGHB004763 ("BPAI Decision") decided August 31, 2009, stated: "But for the Examiner's finding, that Moradi and Lilly disclose 'exclusive' computer databases, the Examiner's remaining findings characterizing the scope and content of the cited references as well as the differences between the claimed subject matter and the prior art have not been rebutted. Accordingly, as to these findings, they are accepted as being undisputed" (BPAI Decision, p. 6, ROXGHB004756).
distributing a "prescription" drug	Disclosed in at least paragraph [0003] of Moradi: "This invention generally relates to the field of ***prescription delivery systems***, and more particularly to the field of automated prescription handling." (*See* Moradi paragraph [0003]; emphasis added, ROXGHB004295).
a "computerized" method	Disclosed in at least paragraph [0022] of Moradi: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022]; emphasis added, ROXGHB004296). One skilled in the art would have been motivated to modify Moradi to include the exclusive central pharmacy of Ukens. *See* 10/18/06 OA and Examiner's Answer ("limit access to dangerous drugs (page 3, paragraph 5 of Ukens)".)
(clause a) receiving in a computer processor all prescription requests, for any and all patients being prescribed the prescription drug, only at the	In the Examiner's Answer, the Examiner found that "receiving all prescription requests at the exclusive central pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
exclusive central pharmacy from any and all medical doctors allowed to prescribe the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the any and all medical doctors;	doctor" is disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi, paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly, and page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision, held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"receiving in a computer processor all prescription requests . . ."	As noted above in connection with the preamble, *supra*, at least paragraph [0022] of Moradi states that: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022]; emphasis added, ROXGHB004296).
"for any and all patients being prescribed" the drug, "only at the exclusive central pharmacy from any and all medical doctors allowed to prescribe" the drug, and "various credentials of the any and all medical doctors "	Ukens discloses this feature at least by describing, *inter alia*, "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed." (*See* Ukens p. 3, para. 1, ROXGHB004315). Thus, Ukens teaches that all prescription requests, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all medical doctors allowed to prescribe it. Moreover, such discussion by Ukens teaches that the various doctor credentials recognized by the Examiner disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi would, in the context of the one pharmacy of Ukens, correspond to the any and all medical doctors allowed to prescribe the specialty medication.

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
(clause b) requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;	
requiring " entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations"	In the 6/19/06 OA, the 10/18/06 OA, and the Examiner's Answer, the Examiner found that "requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations" is disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly, and page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly stating: "To one of ordinary skill in the art reading Lilly, Lilly's data storage is 'exclusive' in that it is the sole data storage that 'contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information.'" (Decision, p. 10, ROXGHB004760). The BPAI Decision holds all other findings of the Examiner to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"such that all prescriptions for" the drug are "processed only by the exclusive central pharmacy "	Ukens teaches "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)), which also indicates that such specialty medications are "prescribed." (*See* Ukens p. 3, para. 1, ROXGHB004315).

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
processing all prescriptions "using only the exclusive computer database"	This feature is shown by Borsand. Borsand describes storing ***all*** pharmaceutical-related information ***only once*** and in a ***single*** database 62 and, thus, discloses an exclusive computer database and processing prescriptions using only the exclusive computer database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). Moreover, at least Fig. 3 of Borsand indicates the pharmaceutical-related information stored in single database 62 to include pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, ***patient*** information, and ***provider*** information. Borsand further indicates that such a provider can be a ***physician***: "A ***health care provider 30*** includes any person capable of issuing a pharmaceutical 32 prescription 28 such as a ***physician***, physician's assistant, or veterinarian."

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	(*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). One skilled in the art at the time would have been motivated to modify Moradi and Ukens to include the exclusive computer database of Lilly at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "ensure that prescribers have an accurate view of their patients' use of prescription drugs and to help protect professionals from lawsuits and other potential liabilities (para. 58 of Lilly)." One would have been further motivated to modify Moradi, Ukens and Lilly to process prescriptions using ***only*** an exclusive computer database as taught by Borsand at least to allow all pharmaceutical-related information to be stored on a single database that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines. (*See* Borsand paragraph [0043], ROXGHB004127.)
(clause c) checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the prescription drug; checking doctor "credentials" checking the doctor "credentials" with a computer processor	In the 6/19/06 OA and the Examiner's Answer, the Examiner found "checking the credentials of the doctor" disclosed by paragraph 118 of Moradi (ROXGHB004304). The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Also disclosed in Moradi. *See*, for example, paragraph [0022] of Moradi which states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)).

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
checking the doctor "credentials" to determine doctor "eligibility" to "prescribe" the drug checking the "credentials" of the "<u>any and all doctors</u>"	At least Moradi paragraph [0118] (ROXGHB004304) discloses checking the doctor's credentials ("DEA number" and "license number") to determine the eligibility of the doctor to prescribe the prescription drug. As noted, *supra*, in connection with clause "a," at least by discussing "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3 para. 3, ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed" (*see* Ukens p. 3 para. 1, ROXGHB004315), Ukens teaches that all prescription requests, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all medical doctors allowed to prescribe the specialty medication. Checking the credentials of the doctor, as the Examiner recognized was disclosed in paragraph 118 of Moradi (ROXGHB004304), would, in the context of Ukens' single pharmacy, correspond to the any and all doctors allowed to prescribe the specialty medication.
(clause d) confirming with a patient that educational material has been read prior to shipping the prescription drug; confirming "with a patient that educational material has been read prior to shipping" the drug	 In the 6/19/06 OA and the Examiner's Answer, the Examiner found that "confirming with the patient that educational material has been read prior to shipping the drug" is disclosed by paragraph [0084] of Califano (ROXGHB004163). The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). One skilled in the art at the time would have been motivated to modify one or more of Moradi, Ukens, Lilly, and Borsand to implement Califano's teaching of confirming, prior to shipping a drug, that a patient has read educational material at least to, as found by the Examiner in the 6/19/06 OA and the Examiner's Answer, "ensure that the patient knows about the risks and dangers associated with the drug (para. 43 of Califano)."

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	See also, Williams, col. 8, line 57 to col. 9, line 2 and col. 10, lines 23-46, ROXGHB004325-26. One skilled in the art at the time would have been further motivated to modify one or more of Moradi, Ukens, Lilly, Borsand, and Califano to implement Williams' teaching regarding educational material at least to ensure patient compliance with taking a drug. (*See* Williams col. 3 ln. 56-59, ROXGHB004323.)
(clause e) checking the exclusive computer database for potential abuse of the prescription drug;	
checking the "computer database for potential abuse of" the drug	In the Examiner's Answer, the Examiner found the feature of clause "e" of "checking the … computer database for potential abuse of the … drug" among paragraphs 6 (ROXGHB004295), 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi. The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
an "exclusive computer database"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found this feature among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the findings of the Examiner. (BPAI Decision, p. 6, ROXGHB004756).
(clause f) mailing the prescription drug to the patient only if no potential abuse is found by the patient to whom the prescription drug is prescribed and the doctor prescribing the prescription drug;	
mailing the drug to the patient "only if no	In the 10/18/06 OA and the Examiner's Answer, the Examiner found the feature of "only mailing the drug to the patient if no potential abuse is found …" to be

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
potential abuse is found"	disclosed among paragraphs 6 (ROXGHB004295), 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi. The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." *See also* Borsand paragraph [0120], ROXGHB004134.
mailing the drug to the patient "only if no potential abuse is found by the patient … and the doctor"	Borsand discloses checking, both before and after prescription 28 is filled, for evidence of fraud or misuse by ***provider 30*** and evidence of fraud or misuse by ***patient 22***. Borsand further explains that prescription 28 is canceled where such fraud or misuse is detected: "The system 20 facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 ***even*** after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the ***cancellation*** or modification of a ***prescription 28***. The modification of a prescription at 132 is an event triggered process. There must be an event that triggers the modification or cancellation of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a ***provider 30***, pharmacist 40, or ***patient 22***." (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)). "A ***health care provider 30*** includes . . . a ***physician***, physician's assistant, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). It would have been obvious to modify the prior art teachings to only mail the drug to the patient if no potential abuse is found by both the patient and the doctor in view of Borsand's teaching to check for fraud and abuse before and after filling the prescription and to cancel a prescription if evidence is found of fraud or misuse by either the patient or the doctor.
(clause g) confirming receipt by the patient of the	

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
prescription drug; and "confirming receipt by the patient of" the drug	In the 6/19/06 OA and the Examiner's Answer, the Examiner found that "confirming receipt by the patient of the drug" is disclosed by the abstract of Moradi. The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause h) generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns. generating the periodic reports "with the computer processor"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found that "generating periodic reports via the exclusive computer database to evaluate potential diversion patterns" is disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the Examiner's finding of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Taught at least in paragraph [0051] of Lilly: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)).

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
(preamble) 2. A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a claim limitation, then it is disclosed in the prior art as follows:
a "method of distributing" a drug "under exclusive control of an exclusive central pharmacy, the method comprising"	The preamble limitations are disclosed in at least Moradi and Ukens. The 6/19/06 OA, and the Examiner's Answer, each found "a method of distributing a drug under exclusive control of an exclusive central pharmacy, the method comprising" to be disclosed among paragraphs 3 (ROXGHB004295) and 24 (ROXGHB004296) of Moradi. Also, the 10/18/06 OA, and the Examiner's Answer each found an exclusive central pharmacy disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision, held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
distributing a "prescription" drug	Disclosed in at least paragraph [0003] of Moradi: "This invention generally relates to the field of ***prescription delivery systems***, and more particularly to the field of automated prescription handling." (*See* Moradi paragraph [0003], ROXGHB004295 (emphasis added)).
a "computerized" method	Disclosed in at least paragraph [0022] of Moradi: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). One skilled in the art would have been motivated to modify Moradi to include the exclusive central pharmacy of Ukens. *See* 10/18/06 OA and Examiner's Answer ("limit access to dangerous drugs (page 3, paragraph 5 of Ukens)").

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
(clause a) receiving in a computer processor all prescription requests, for any and all patients being prescribed the prescription drug, only at the exclusive central pharmacy from any and all medical doctors allowed to prescribe the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the any and all medical doctors;	In the Examiner's Answer, the Examiner found that "receiving all prescription requests at the exclusive central pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor" is disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi, paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly, and page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"receiving in a computer processor all prescription requests . . ."	As noted above in connection with the preamble, *supra*, at least paragraph [0022] of Moradi states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)).
"for any and all patients being prescribed" the drug, "only at the exclusive central pharmacy from any and all medical doctors allowed to prescribe" the drug, and "various credentials of the any and all medical doctors"	Ukens discloses this feature at least by describing, *inter alia*, "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed." (*See* Ukens p. 3, para. 1, ROXGHB004315). Thus, Ukens teaches that all prescription requests, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all medical doctors allowed to prescribe it. Moreover, such discussion by Ukens teaches that the various doctor credentials recognized by the Examiner was disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi would, in the context of the one pharmacy of Ukens, correspond to the any and all medical

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	doctors allowed to prescribe the specialty medication.
(clause b) entering the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;	
"entering the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found that "entering the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations" is disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"such that all prescriptions for" the drug "are processed only by the exclusive central pharmacy"	Ukens teaches "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)), which also indicates that such specialty medications are "prescribed." (*See* Ukens p. 3, para. 1, ROXGHB004315).
processing all prescriptions "using only the exclusive computer database"	This feature is shown by Borsand. Borsand discusses storing ***all*** pharmaceutical-related information ***only once*** and in a ***single*** database 62, and, thus discloses an exclusive computer database and

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	processing prescriptions using only the exclusive computer database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). Moreover, at least Fig. 3 of Borsand (ROXGHB004112) indicates the pharmaceutical-related information stored in single database 62 to include pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, ***patient*** information, and ***provider*** information. Borsand further indicates that such a provider can be a ***physician***: "A ***health care provider 30*** includes any person capable of issuing a pharmaceutical 32 prescription 28 such as a ***physician***, physician's assistant, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). One skilled in the art at the time would have been motivated to modify Moradi and Ukens to include the exclusive computer database of Lilly at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	Answer "ensure that prescribers have an accurate view of their patients' use of prescription drugs and to help protect professionals from lawsuits and other potential liabilities (para. 58 of Lilly)." One would have been further motivated to modify Moradi, Ukens and Lilly to process prescriptions using ***only*** an exclusive computer database as taught by Borsand at least to allow all pharmaceutical-related information to be stored on a single database that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines. (*See* Borsand paragraph [0043], ROXGHB004127).
(clause c) checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the prescription drug;	
checking doctor "credentials"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found that "checking the credentials of the doctor" is disclosed by paragraph 118 of Moradi. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
checking the doctor "credentials" with a computer processor	Also disclosed in Moradi. *See*, for example, paragraph [0022] of Moradi which states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)).
checking the doctor "credentials" to determine doctor "eligibility" to "prescribe" the drug	At least Moradi paragraph [0118] discloses checking the doctor's credentials ("DEA number" and "license number") to determine the eligibility of the doctor to prescribe the prescription drug. (ROXGHB004304)
checking the "credentials" of the "any and all	As noted, *supra*, in connection with clause "a," at least Ukens' disclosure of

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
doctors"	"restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3 para. 3, ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed" (*see* Ukens p. 3 para. 1, ROXGHB004315), teaches that all prescription requests, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all medical doctors allowed to prescribe it. Checking doctor credentials, as the Examiner recognized was disclosed in paragraph 118 of Moradi (ROXGHB004304), would, in the context of Ukens' single pharmacy, corresponds to the any and all doctors allowed to prescribe the specialty medication.
(clause d) checking the exclusive computer database for potential abuse of the prescription drug;	
checking the "computer database for potential abuse of" the drug	In the Examiner's Answer, the Examiner found the feature of clause "d" of "checking the … computer database for potential abuse of the … drug" among paragraphs 6 (ROXGHB004295), 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
an "exclusive computer database"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found this feature among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the findings of the Examiner.
(clause e) mailing the prescription drug to a patient only if no potential abuse is found by the patient to whom the prescription drug is prescribed and the doctor prescribing the prescription drug;	

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
mailing the drug to a patient "only if no potential abuse is found"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed the feature of "only mailing the drug to the patient if no potential abuse is found …" in paragraphs 6 (ROXGHB004295), 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). *See also* Borsand paragraph [0120], ROXGHB004134.
mailing the drug to a patient "only if no potential abuse is found by the patient … and the doctor"	Borsand discloses checking, both before and after prescription 28 is filled, for evidence of fraud or misuse by ***provider 30*** and evidence of fraud or misuse by ***patient 22***. Borsand further explains that prescription 28 is canceled where such fraud or misuse is detected: "The system 20 facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 ***even*** after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the ***cancellation*** or modification of a ***prescription 28***. The modification of a prescription at 132 is an event triggered process. There must be an event that triggers the modification or cancellation of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a ***provider 30***, pharmacist 40, or ***patient 22***." (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)). "A ***health care provider 30*** includes . . . a ***physician***, physician's assistant, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). It would have been obvious to modify the prior art teachings to only mail the drug to the patient if no potential abuse is found by both the patient and the doctor in view of Borsand's teaching to check for fraud and abuse before and after filling the prescription and to cancel a prescription if evidence is found of fraud or misuse by either the patient or the doctor.

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
(clause f) confirming receipt by the patient of the prescription drug; and "confirming receipt by the patient of" the drug	In the 6/19/06 OA and the Examiner's Answer, the Examiner found that "confirming receipt by the patient of the drug" is disclosed by the abstract of Moradi (ROXGHB004282). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause g) generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns. generating the periodic reports "with the computer processor"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found that Lilly disclosed "generating periodic reports via the exclusive computer database to evaluate potential diversion patterns" in paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263). The BPAI Decision affirmed the Examiner's finding of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." Taught at least in paragraph [0051] of Lilly: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)).
3. The method of claim 2 wherein the exclusive central pharmacy controls the exclusive computer database.	

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
the "exclusive central pharmacy" controls the "computer database"	In the 6/19/06 OA, the 10/18/06 OA, and the Examiner's Answer, the Examiner found that "wherein the exclusive central pharmacy controls the … computer database" is disclosed among paragraphs 7 (ROXGHB004295) and 43 (ROXGHB004299) of Moradi. Moreover, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
an "exclusive computer database"	The 6/19/06 OA, the 10/18/06 OA, and the Examiner's Answer each found an exclusive computer database disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly.
4. The method of claim 2 and further comprising selectively blocking shipment of the prescription drug to a patient.	
selectively blocking shipment of the drug to a patient	The 6/19/06 OA and the Examiner's Answer each found that "selectively blocking shipment of the drug to a patient" disclosed among paragraphs 45 and 46 of Moradi (ROXGHB004299-4300). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
5. The method of claim 2 wherein an abuse pattern is associated with a patient, and shipment is blocked upon such association.	The 6/19/06 OA and the Examiner's Answer each found that "wherein an abuse pattern is associated with a patient, and shipment is blocked upon such association" is disclosed among paragraphs 45 and 46 of Moradi (ROXGHB004299-4300), and paragraph 58 of Lilly (ROXGHB004261). The

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	BPAI Decision held the Examiner's findings "accepted as being undisputed."
6. The method of claim 2 wherein the prescription drug comprises gamma hydroxy butyrate (GHB). the drug is gamma hydroxy butyrate (GHB)	The 6/19/06 OA and the Examiner's Answer each found this feature disclosed by paragraph 3 of Melker (ROXGHB004272). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). One skilled in the art at the time would have been motivated to modify one or more of Moradi, Ukens, Lilly, and Borsand to implement Melker's teaching of the drug being gamma hydroxy butyrate (GHB) at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "include drugs of recent concern, such as GHB (para. 3 of Melker)."

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
(preamble) 7. A computerized method of distributing a prescription drug under control of an exclusive central pharmacy, the method comprising:	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a claim limitation, then it is disclosed in the prior art as follows:
a "method of distributing" a drug "under control of an exclusive central pharmacy, the method comprising"	The preamble limitations are disclosed in at least Moradi and Ukens. The 10/18/06 OA and the Examiner's Answer each found "a method of distributing a drug under control of an exclusive central pharmacy, the method comprising" to be disclosed among paragraphs 3 (ROXGHB004295) and 24 (ROXGHB004296) of Moradi. Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
distributing a "prescription" drug	Disclosed in at least paragraph [0003] of Moradi: "This invention generally relates to the field of ***prescription delivery systems***, and more particularly to the field of automated prescription handling." (*See* Moradi paragraph [0003], ROXGHB004295 (emphasis added)).
a "computerized" method	Disclosed in at least paragraph [0022] of Moradi: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). One skilled in the art would have been motivated to modify Moradi to include the exclusive central pharmacy of Ukens. *See* 10/18/06 OA and Examiner's

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	Answer ("limit access to dangerous drugs (page 3, paragraph 5 of Ukens)").
(clause a) receiving in a computer processor prescription requests, for any and all patients being prescribed the prescription drug, only at the central pharmacy from any and all authorized prescribers allowed to prescribed the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the any and all authorized prescribers;	In the 10/18/06 OA and the Examiner's Answer, the Examiner found that "receiving prescription requests at the central pharmacy from an authorized prescriber containing information identifying a patient, the sensitive drug, and various credentials of the authorized prescriber" is disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi, paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy to be disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). As noted above in connection with the preamble, *supra*, at least paragraph [0022] of Moradi states that: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). Ukens discloses this feature at least by describing, *inter alia*, "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed." (*See* Ukens p. 3, para. 1, ROXGHB004315). Thus, Ukens teaches that prescription requests, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all authorized prescribers allowed to prescribe it.
"receiving in a computer processor prescription requests …"	
"for any and all patients being prescribed" the drug, "only at the central pharmacy from any and all authorized prescribers allowed to prescribe" the drug, and "various credentials of the any and all authorized prescribers"	

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	Moreover, Ukens' teaching that the various authorized prescriber credentials, recognized by the Examiner to be disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi, would, in the context of the one pharmacy of Ukens, correspond to the any and all authorized prescribers allowed to prescribe the specialty medication.
(clause b) entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of the prescription drug such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;	
"entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of" the drug	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of the sensitive drug" disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly, and page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision affirmed the Examiner's finding of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"such that all prescriptions for" the drug are "processed only by the exclusive central pharmacy"	Ukens teaches "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added), which also indicates that such specialty medications are "prescribed." (*See* Ukens p. 3,

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
processing all prescriptions "using only the exclusive computer database"	para. 1, ROXGHB004315). Borsand discloses this feature. Borsand discusses storing ***all*** pharmaceutical-related information ***only once*** and in a ***single*** database 62 and thus discloses an exclusive computer database and processing prescriptions using only the exclusive computer database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). Moreover, at least Fig. 3 of Borsand indicates the pharmaceutical-related information stored in single database 62 to include pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, ***patient*** information, and ***provider*** information. Borsand further indicates that such a provider can be a ***physician***: "A ***health care provider 30*** includes any person capable of issuing a pharmaceutical 32 prescription 28 such as a ***physician***, physician's assistant,

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). One skilled in the art at the time would have been motivated to modify Moradi and Ukens to include the exclusive computer database of Lilly at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "ensure that prescribers have an accurate view of their patients' use of prescription drugs and to help protect professionals from lawsuits and other potential liabilities (para. 58 of Lilly)." One would have been further motivated to modify Moradi, Ukens, and Lilly to process prescriptions using ***only*** an exclusive computer database as taught by Borsand at least to allow all pharmaceutical-related information to be stored on a single database that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines. (*See* Borsand paragraph [0043], ROXGHB004127).
(clause c) checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe the prescription drug; checking authorized prescriber "credentials" checking the authorized prescriber "credentials" with a computer processor	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "checking of the credentials of the authorized prescriber" disclosed by paragraph 118 of Moradi (ROXGHB004304). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Also disclosed in Moradi. *See*, for example, paragraph [0022] of Moradi which states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet."

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	(ROXGHB004296 (emphasis added)).
checking the authorized prescriber "credentials" to determine authorized prescriber "eligibility" to "prescribe" the drug	At least Moradi paragraph [0118] (ROXGHB004304) discloses checking the prescriber's credentials ("DEA number" and "license number") to determine the eligibility of the prescriber to prescribe the prescription drug.
checking the "credentials" of the "any and all authorized prescribers"	As noted, *supra*, in connection with clause "a," at least Ukens describes "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3 para. 3, ROXGHB004315 (emphasis added)) and indicates that such specialty medications are "prescribed" (*see* Ukens p. 3 para. 1, ROXGHB004315). Ukens further teaches that all prescription requests, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all prescribers allowed to prescribe it. Checking the credentials of the authorized prescriber, as the Examiner recognized was disclosed in paragraph 118 of Moradi (ROXGHB004304), would, in the context of Ukens' single pharmacy, correspond to the any and all authorized prescribers allowed to prescribe the specialty medication.
(clause d) confirming with a patient that educational material has been read prior to providing the prescription drug to the patient;	
confirming "with a patient that educational material has been read prior to providing" the drug "to the patient"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found that "confirming with the patient that educational material has been read prior to providing the drug to the patient" is disclosed by paragraph [0084] of Califano (ROXGHB004163). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). One skilled in the art at the time would have been motivated to modify one or more of Moradi, Ukens, Lilly, and Borsand to implement Califano's teaching of confirming with the patient that educational material has been read prior to providing the drug to the patient at least to, as found by the Examiner in the 10/18/06 OA and the Examiner's Answer, "ensure that the patient knows about

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	the risks and dangers associated with the drug (para. 43 of Califano)." *See also*, Williams, col. 8, line 57 to col. 9, line 2 and col. 10, lines 23-46 (ROXGHB004325-26). One skilled in the art at the time would have been further motivated to modify one or more of Moradi, Ukens, Lilly, Borsand, and Califano to implement Williams' teaching regarding educational material at least to ensure patient compliance with taking a drug. (*See* Williams col. 3 ln. 56-59, ROXGHB004323).
(clause e) requiring checking of the exclusive computer database for potential abuse associated with the patient and the authorized prescriber;	In the 10/18/06 OA and the Examiner's Answer, the Examiner found that "requiring checking of the … computer database for potential abuse associated with the patient and/or the authorized prescriber" to be disclosed among 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi. The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
an "exclusive computer database,"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found this feature among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the findings of the Examiner.
the "potential abuse" is associated with the patient "and" the authorized prescriber	Borsand discloses checking, both before and after prescription 28 is filled, for evidence of fraud or misuse by ***provider 30*** and evidence of fraud or misuse by ***patient 22***. Borsand further explains that prescription 28 is canceled where such fraud or misuse is detected: "The system 20 facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 ***even*** after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the ***cancellation*** or modification of a ***prescription 28***. The modification of a prescription at 132 is an event

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	triggered process. There must be an event that triggers the modification or cancellation of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a ***provider 30***, pharmacist 40, or ***patient 22***." (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)). "A ***health care provider 30*** includes . . . a ***physician***, physician's assistant, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)).
(clause f) providing the prescription drug to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom the prescription drug is prescribed and the authorized prescriber of the prescription drug;	
providing the drug to the patient "only provided information in" the computer database "is not indicative of potential abuse"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found the feature of "only providing the drug to the patient provided information in the … computer database is not indicative of potential abuse" disclosed among paragraphs 43 and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi. The BPAI Decision held the Examiner's findings "accepted as being undisputed." *See also* Borsand paragraph [0120], ROXGHB004134).
an "exclusive computer database"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found this feature among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the findings of the Examiner.
the "potential abuse" is "by the patient to	Borsand discloses checking, both before and after prescription 28 is filled, for

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
whom" the drug "is prescribed" and "the authorized prescriber of" the drug	evidence of fraud or misuse by ***provider 30*** and evidence of fraud or misuse by ***patient 22***. Borsand further explains that prescription 28 is ***canceled where such fraud or misuse is detected***: "The system 20 facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 ***even*** after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the ***cancellation*** or modification of a ***prescription 28***. The modification of a prescription at 132 is an event triggered process. There must be an event that triggers the modification or cancellation of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a ***provider 30***, pharmacist 40, or ***patient 22***." (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)). "A ***health care provider 30*** includes … a ***physician***, ***physician's assistant***, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). It would have been obvious to modify the prior art teachings to provide the drug to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom the drug is prescribed and the authorized prescriber of the drug in view of Borsand's teaching to check for fraud and abuse before and after filling the prescription and to cancel a prescription if evidence is found of fraud or misuse by either the patient or the doctor.
(clause g) confirming receipt by the patient of the prescription drug; and "confirming receipt by the patient of" the drug	In the 10/18/06 OA and the Examiner's Answer, the Examiner found that "confirming receipt by the patient of the drug" is disclosed by the abstract of

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	Moradi. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause h) generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns. generating the periodic reports "with the computer processor"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "generating periodic reports via the exclusive computer database to evaluate potential diversion patterns" disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the Examiner's finding of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Taught at least in paragraph [0051] of Lilly: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)).

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
(preamble) 8. A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a claim limitation, then it is disclosed in the prior art as follows:
a "method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising"	The preamble limitations are disclosed in at least Moradi, Ukens, and "An Interview with Orphan Medical about Xyrem." The 10/18/06 OA and the Examiner's Answer each found "a method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising" disclosed among paragraphs 3 (ROXGHB004295) and 24 (ROXGHB004296) of Moradi and "An Interview with Orphan Medical about Xyrem" (ROXGHB004250-52). Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy to be disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
a "computerized" method,	Disclosed in at least paragraph [0022] of Moradi: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). One skilled in the art would have been motivated to modify Moradi to implement the "An Interview with Orphan Medical about Xyrem" teaching of the drug being gamma hydroxy butyrate (GHB). *See* 10/18/06 OA and Examiner's Answer ("provide this medicine to patients that need it in a responsible manner (see 'An Interview with Orphan Medical about Xyrem,' talkaboutsleep.com))." One would have been further motivated to modify Moradi and "An Interview with Orphan Medical about Xyrem" to include the exclusive central pharmacy of Ukens. *See* 10/18/06 OA and Examiner's Answer ("limit access to dangerous

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	drugs (page 3, paragraph 5 of Ukens)").
(clause a), receiving in a computer processor prescription requests for GHB, for any and all patients being prescribed GHB, only at the central pharmacy from any and all authorized prescribers allowed to prescribe GHB, the prescription requests for GHB containing information identifying patients, and various credentials of the any and all authorized prescribers;	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "receiving prescription requests for GHB at the central pharmacy from an authorized prescriber containing information identifying a patient and various credentials of the authorized prescriber" disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi and "An Interview with Orphan Medical about Xyrem" (ROXGHB004250-52). Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
the prescription requests are received "in a computer processor"	As noted above in connection with the preamble, *supra*, at least paragraph [0022] of Moradi states that: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022]; emphasis added) (ROXGHB004296).
the prescription requests are for "any and all patients being prescribed" the drug the prescription requests are received "only" at the central pharmacy the prescription requests are from "any and all authorized prescribers allowed to prescribe" the drug	Ukens discloses this feature at least by describing, *inter alia*, "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed." (*See* Ukens p. 3, para. 1, ROXGHB004315). Thus, Ukens teaches that prescription requests for the specialty medication, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all authorized prescribers allowed to prescribe it.

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
the prescription requests contain various credentials of the "any and all" authorized prescribers	Moreover, Ukens' teaching that the various authorized prescriber credentials, recognized by the Examiner to be disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi, would, in the context of the one pharmacy of Ukens, correspond to the any and all authorized prescribers allowed to prescribe the specialty medication.
(clause b) entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB, such that all prescriptions for GHB are processed only by the exclusive central pharmacy using only the exclusive computer database;	
"entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB" disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly and"An Interview with Orphan Medical about Xyrem" (ROXGHB004250-52). Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"such that <u>all</u> <u>prescriptions</u> for" the drug are	Ukens teaches "restricting distribution of a specialty medication to only ***one***

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
"processed only by the exclusive central pharmacy"	pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)), which also indicates that such specialty medications are "prescribed." (*See* Ukens p. 3, para. 1, ROXGHB004315).
processing all prescriptions "using only the exclusive computer database"	This feature is shown by Borsand. Borsand discusses storing ***all*** pharmaceutical-related information ***only once*** and in a ***single*** database 62 and thus discloses an exclusive computer database and processing prescriptions using only the exclusive computer database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). Moreover, at least Fig. 3 of Borsand (ROXGHB004112) indicates the pharmaceutical-related information stored in single database 62 to include pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, ***patient*** information, and ***provider*** information. Borsand further indicates that such a provider can be a ***physician***:

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	"A ***health care provider 30*** includes any person capable of issuing a pharmaceutical 32 prescription 28 such as a ***physician***, physician's assistant, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). One skilled in the art at the time would have been motivated to modify Moradi, "An Interview with Orphan Medical about Xyrem," and Ukens to include the exclusive computer database of Lilly at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "ensure that prescribers have an accurate view of their patients' use of prescription drugs and to help protect professionals from lawsuits and other potential liabilities (para. 58 of Lilly)." One would have been further motivated to modify Moradi, "An Interview with Orphan Medical about Xyrem," Ukens, and Lilly to process prescriptions using ***only*** an exclusive computer database as taught by Borsand at least to allow all pharmaceutical-related information to be stored on a single database that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines. (*See* Borsand paragraph [0043], ROXGHB004127).
(clause c) checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the authorized prescribers to prescribe GHB; checking authorized prescriber "credentials" checking the authorized prescriber "credentials" with a computer processor	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "checking the credentials of the authorized prescriber" disclosed by paragraph 118 of Moradi. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Also disclosed in Moradi. *See*, for example, paragraph [0022] of Moradi which states: "The system 100 includes several processing components that are located at

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)).
checking the authorized prescriber "credentials" to determine authorized prescriber "eligibility" to "prescribe" the drug	At least Moradi paragraph [0118] discloses checking the prescriber's credentials ("DEA number" and "license number") to determine the eligibility of the prescriber to prescribe the drug. (ROXGHB004304).
checking the "credentials" of the "any and all authorized prescribers"	As noted, *supra*, in connection with clause "a," at least by discussing "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3 para. 3, ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed" (*see* Ukens p. 3 para. 1, ROXGHB004315), Ukens teaches that all prescription requests, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all prescribers allowed to prescribe it. Checking the credentials of the authorized prescriber, as the Examiner recognized was disclosed in paragraph 118 of Moradi (ROXGHB004304), would, in the context of Ukens' single pharmacy, correspond to the any and all authorized prescribers allowed to prescribe the specialty medication.
(clause d) confirming with the patient that GHB educational material has been read prior to providing GHB to the patient a first time;	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "confirming with the patient that GHB educational material has been read prior to providing GHB to the patient a first time" disclosed among paragraph [0084] of Califano (ROXGHB004163) and "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). *See also*, paragraph [0006] of Moradi, ROXGHB004295. One skilled in the art at the time would have been motivated to modify one or more of Moradi, "An Interview with Orphan Medical about Xyrem," Ukens, Lilly, and Borsand to implement Califano's teaching of confirming with the patient that educational material has been read prior to providing a drug to the

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	patient a first time at least to, as found by the Examiner in the 10/18/06 OA and the Examiner's Answer, "ensure that the patient knows about the risks and dangers associated with the drug (para. 43 of Califano)." *See also*, Williams, col. 8, line 57 to col. 9, line 2 and col. 10, lines 23-46, ROXGHB004325-26. One skilled in the art at the time would have been further motivated to modify one or more of Moradi, "An Interview with Orphan Medical about Xyrem," Ukens, Lilly, Borsand, and Califano to implement Williams' teaching regarding educational material at least to ensure patient compliance with taking a drug. (*See* Williams col. 3 ln. 56-59, ROXGHB004323).
(clause e) requiring checking of the exclusive computer database for potential GHB abuse associated with the patient; "requiring checking of" of the "computer database for potential GHB abuse associated with the patient"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found the feature of clause "e" of "requiring checking of the … computer database for potential GHB abuse associated with the patient" among paragraphs 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi, and "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
an "exclusive computer database"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found this feature among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the findings of the Examiner.
(clause f) providing GHB to the patient only provided information in the exclusive computer	

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
database is not indicative of potential abuse by the patient to whom GHB is prescribed and the authorized prescriber of the GHB;	
"providing GHB to the patient only provided information in" the computer database "is not indicative of potential abuse"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found the feature of "only providing GHB to the patient provided information in the … computer database is not indicative of potential abuse" disclosed among paragraphs 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi, and "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (*See also* Borsand paragraph [0120], ROXGHB004134).
an "exclusive computer database"	In the 6/19/06 OA and the Examiner's Answer the Examiner found this feature among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the findings of the Examiner.
the "potential abuse" is "by the patient to whom" the drug "is prescribed" and "the authorized prescriber of" the drug	Borsand discloses checking, both before and after prescription 28 is filled, for evidence of fraud or misuse by ***provider 30*** and evidence of fraud or misuse by ***patient 22***. Borsand further explains that prescription 28 is canceled where such fraud or misuse is detected: "The system 20 facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 ***even*** after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the ***cancellation*** or modification of a ***prescription 28***. The modification of a prescription at 132 is an event triggered process. There must be an event that triggers the modification or cancellation of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a ***provider 30***, pharmacist 40, or ***patient 22***."

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	(*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)). "A ***health care provider 30*** includes . . . a ***physician***, ***physician's assistant***, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). It would have been obvious to modify the prior art teachings to only provide the drug to the patient if no potential abuse is found by both the patient and the prescriber in view of Borsand's teaching to check for fraud and abuse before and after filling the prescription and to cancel a prescription if evidence is found of fraud or misuse by either the patient or the prescriber.
(clause g) confirming receipt by the patient of the GHB; and	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "confirming receipt by the patient of the GHB" disclosed among the abstract of Moradi and "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause h) generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns. generating the periodic reports "with the computer processor"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "generating periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns" disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly and "An Interview with Orphan Medical about Xyrem." The BPAI Decision affirmed the Examiner's finding of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Taught at least in paragraph [0051] of Lilly: "Referring now to the drawings and, more particularly to FIG. 1, there is

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)).

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
(preamble) 9. A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a claim limitation, then it is disclosed in the prior art as follows:
a "method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising"	The preamble limitations are disclosed in at least Moradi, Ukens, and "An Interview with Orphan Medical about Xyrem." The 10/18/06 OA and the Examiner's Answer each found "a method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising" disclosed among paragraphs 3 (ROXGHB004295) and 24 (ROXGHB004296) of Moradi and "An Interview with Orphan Medical about Xyrem" (ROXGHB004250-52). Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy to be disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
a "computerized" method,	Disclosed in at least paragraph [0022] of Moradi: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). One skilled in the art would have been motivated to modify Moradi to implement the "An Interview with Orphan Medical about Xyrem" teaching of the drug being gamma hydroxy butyrate (GHB). *See* 10/18/06 OA and Examiner's Answer ("provide this medicine to patients that need it in a responsible manner (see 'An Interview with Orphan Medical about Xyrem,' talkaboutsleep.com))." One would have been further motivated to modify Moradi and "An Interview with Orphan Medical about Xyrem" to include the exclusive central pharmacy of Ukens. *See* 10/18/06 OA and Examiner's Answer ("limit access to dangerous

	drugs (page 3, paragraph 5 of Ukens)").
(clause a) receiving in a computer processor prescription requests for GHB, for any and all patients being prescribed GHB, only at the central pharmacy from any and all authorized prescribers allowed to prescribe GHB, the prescription requests containing information identifying patients, and various credentials of the any and all authorized prescribers;	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "receiving prescription requests for GHB at the central pharmacy from an authorized prescriber containing information identifying a patient and various credentials of the authorized prescriber" disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi and "An Interview with Orphan Medical about Xyrem." Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
the prescription requests are received "in a computer processor"	As noted above in connection with the preamble, *supra*, at least paragraph [0022] of Moradi states that: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022] ROXGHB004296 (emphasis added)).
the prescription requests are for "any and all patients being prescribed" the drug the prescription requests are received "only" at the central pharmacy the prescription requests are from "any and all authorized prescribers allowed to prescribe" the drug	Ukens discloses this feature at least by describing, *inter alia*, "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed." (*See* Ukens p. 3, para. 1, ROXGHB004315). Thus, Ukens teaches that prescription requests for the specialty medication, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all authorized prescribers allowed to prescribe it.
the prescription requests contain various	Moreover, Ukens' teaching that the various authorized prescriber credentials,

credentials of the "any and all" authorized prescribers	recognized by the Examiner to be disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi, would, in the context of the one pharmacy of Ukens, correspond to the any and all authorized prescribers allowed to prescribe the specialty medication.
(clause b) entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB, such that all prescriptions for GHB are processed only by the exclusive central pharmacy using only the exclusive computer database;	
"entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB" disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly and "An Interview with Orphan Medical about Xyrem." Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"such that <u>all</u> <u>prescriptions</u> for" the drug are "processed only by the exclusive central	Ukens teaches "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)), which also indicates that such specialty medications are "prescribed." (*See* Ukens p. 3,

pharmacy" processing all prescriptions "using only the exclusive computer database"	para. 1, ROXGHB004315). Borsand discloses this feature. Borsand discusses storing ***all*** pharmaceutical-related information ***only once*** and in a ***single*** database 62 and thus discloses an exclusive computer database and processing prescriptions using only the exclusive computer database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). Moreover, at least Fig. 3 of Borsand indicates the pharmaceutical-related information stored in single database 62 to include pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, ***patient*** information, and ***provider*** information. Borsand further indicates that such a provider can be a ***physician***: "A ***health care provider 30*** includes any person capable of issuing a pharmaceutical 32 prescription 28 such as a ***physician***, physician's assistant, or veterinarian."

	(*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). One skilled in the art at the time would have been motivated to modify Moradi, "An Interview with Orphan Medical about Xyrem," and Ukens to include the exclusive computer database of Lilly at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "ensure that prescribers have an accurate view of their patients' use of prescription drugs and to help protect professionals from lawsuits and other potential liabilities (para. 58 of Lilly)." One would have been further motivated to modify Moradi, "An Interview with Orphan Medical about Xyrem," Ukens, and Lilly to process prescriptions using ***only*** an exclusive computer database as taught by Borsand at least to allow all pharmaceutical-related information to be stored on a single database that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines. (*See* Borsand paragraph [0043], ROXGHB004127).
(clause c) checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the authorized prescribers to prescribe GHB; checking authorized prescriber "credentials" checking the authorized prescriber "credentials" with a computer processor	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "checking the credentials of the authorized prescriber" disclosed by paragraph 118 of Moradi. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Also disclosed in Moradi. *See*, for example, paragraph [0022] of Moradi, which states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet."

	(*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)).
checking the authorized prescriber "credentials" to determine authorized prescriber "eligibility" to "prescribe" the drug checking the "credentials" of the "<u>any and all authorized prescribers</u>"	At least Moradi paragraph [0118] discloses checking the prescriber's credentials ("DEA number" and "license number") to determine the eligibility of the prescriber to prescribe the drug. (ROXGHB004304) As noted, *supra*, in connection with clause "a," at least by discussing "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3 para. 3, ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed" (*see* Ukens p. 3 para. 1, ROXGHB004315), Ukens teaches that all prescription requests, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all prescribers allowed to prescribe it. Checking the credentials of the authorized prescriber, as the Examiner recognized was disclosed in paragraph 118 of Moradi, would, in the context of Ukens' single pharmacy, correspond to the any and all authorized prescribers allowed to prescribe the specialty medication.
(clause d) confirming with the patient that GHB educational material has been read prior to providing GHB to the patient a first time;	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "confirming with the patient that GHB educational material has been read prior to providing GHB to the patient a first time" disclosed among paragraph [0084] of Califano (ROXGHB004163) and "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). *See also*, paragraph [0006] of Moradi, ROXGHB004295. One skilled in the art at the time would have been motivated to modify one or more of Moradi, "An Interview with Orphan Medical about Xyrem," Ukens, Lilly, and Borsand to implement Califano's teaching of confirming with the patient that educational material has been read prior to providing a drug to the patient a first time at least to, as found by the Examiner in the 10/18/06 OA and the Examiner's Answer, "ensure that the patient knows about the risks and dangers associated with the drug (para. 43 of Califano)." *See also*, Williams, col. 8, line 57 to col. 9, line 2 and col. 10, lines 23-46,

	ROXGHB004325-26. One skilled in the art at the time would have been further motivated to modify one or more of Moradi, "An Interview with Orphan Medical about Xyrem," Ukens, Lilly, Borsand, and Califano to implement Williams' teaching regarding educational material at least to ensure patient compliance with taking a drug. (*See* Williams col. 3 ln. 56-59, ROXGHB004323).
(clause e) requiring checking of the exclusive computer database for potential GHB abuse associated with the patient; "requiring checking of" of the "computer database for potential GHB abuse associated with the patient" an "exclusive computer database"	 In the 10/18/06 OA and the Examiner's Answer, the Examiner found the feature of clause "e" of "requiring checking of the … computer database for potential GHB abuse associated with the patient" disclosed among paragraphs 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi, and "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). In the 6/19/06 OA and the Examiner's Answer, the Examiner found this feature among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the findings of the Examiner. (BPAI Decision, p. 6, ROXGHB004756).
(clause f) mailing GHB to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom GHB is prescribed and the authorized prescriber of the GHB; "mailing GHB to the patient only provided information in" the computer database "is not	 In the 10/18/06 OA and the Examiner's Answer, the Examiner found the feature of "mailing GHB to the patient provided information in the … computer

indicative of potential abuse"	database is not indicative of potential abuse" disclosed among paragraphs 6 (ROXGHB004295), 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi, and "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). *See also* Borsand paragraph [0120], ROXGHB004134.
an "exclusive computer database"	In the 6/19/06 OA and the Examiner's Answer the Examiner found this feature among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the findings of the Examiner.
the "potential abuse" is "by the patient to whom" the drug "is prescribed" and "the authorized prescriber of" the drug	Borsand discloses checking, both before and after prescription 28 is filled, for evidence of fraud or misuse by ***provider 30*** and evidence of fraud or misuse by ***patient 22***. Borsand further explains that prescription 28 is canceled where such fraud or misuse is detected: "The system 20 facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 ***even*** after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the ***cancellation*** or modification of a ***prescription 28***. The modification of a prescription at 132 is an event triggered process. There must be an event that triggers the modification or cancellation of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a ***provider 30***, pharmacist 40, or ***patient 22***." (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)). "A ***health care provider 30*** includes . . . a ***physician***, ***physician's assistant***, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). It would have been obvious to modify the prior art teachings to only provide the

	drug to the patient if no potential abuse is found by both the patient and the prescriber in view of Borsand's teaching to check for fraud and abuse before and after filling the prescription and to cancel a prescription if evidence is found of fraud or misuse by either the patient or the prescriber.
(clause g) confirming receipt by the patient of the GHB; and	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "confirming receipt by the patient of the GHB" disclosed among the abstract of Moradi and "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause h) generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns. generating the periodic reports "with the computer processor"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "generating periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns" disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly and "An Interview with Orphan Medical about Xyrem." The BPAI Decision affirmed the Examiner's finding of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Taught at least in paragraph [0051] of Lilly: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)).

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
(preamble) 10. A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a claim limitation, then it is disclosed in the prior art as follows:
a "method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising"	The preamble limitations are disclosed in at least Moradi, Ukens, and "An Interview with Orphan Medical about Xyrem." The 10/18/06 OA and the Examiner's Answer each found "a method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising" disclosed among paragraphs 3 (ROXGHB004295) and 24 (ROXGHB004296) of Moradi and "An Interview with Orphan Medical about Xyrem" (ROXGHB004250-52). Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy to be disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
a "computerized" method	Disclosed in at least paragraph [0022] of Moradi: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). One skilled in the art would have been motivated to modify Moradi to implement the "An Interview with Orphan Medical about Xyrem" teaching of the drug being gamma hydroxy butyrate (GHB). *See* 10/18/06 OA and Examiner's Answer ("provide this medicine to patients that need it in a responsible manner (see 'An Interview with Orphan Medical about Xyrem,' talkaboutsleep.com))." One would have been further motivated to modify Moradi and "An Interview with Orphan Medical about Xyrem" to include the exclusive central pharmacy of Ukens. *See* 10/18/06 OA and Examiner's Answer ("limit access to dangerous

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	drugs (page 3, paragraph 5 of Ukens)").
(clause a) manufacturing GHB;	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "manufacturing GHB" disclosed by "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause b) providing manufactured GHB only to the exclusive central pharmacy;	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "only providing manufactured GHB to the exclusive central pharmacy" disclosed by "An Interview with Orphan Medical about Xyrem." Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy disclosed among page 3, paragraphs 3-5 of Ukens. *See also* Ukens p. 3, para. 3, ROXGHB004315. The BPAI Decision held the Examiner's findings "accepted as being undisputed."(BPAI Decision, p. 6, ROXGHB004756).
(clause c) receiving in a computer processor all prescription requests for GHB, for any and all patients being prescribed GHB, only at the central pharmacy from any and all authorized prescribers allowed to prescribe GHB, the prescription requests containing information identifying patients, and various credentials of the any and all authorized prescribers; the prescription requests are received "in a	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "receiving prescription requests for GHB at the central pharmacy from an authorized prescriber containing information identifying a patient and various credentials of the authorized prescriber" disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi and "An Interview with Orphan Medical about Xyrem" (ROXGHB004250-52). Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). As noted above in connection with the preamble, *supra*, at least paragraph

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
computer processor"	[0022] of Moradi states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)).
receiving "all" prescription requests the prescription requests are for "any and all patients being prescribed" the drug the prescription requests are received "only" at the central pharmacy the prescription requests are from "any and all authorized prescribers allowed to prescribe" the drug	Ukens discloses these features at least by describing, *inter alia*, "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added) and indicating that such specialty medications are "prescribed." (*See* Ukens p. 3, para. 1, ROXGHB004315). Thus, Ukens teaches that all prescription requests for the specialty medication, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all authorized prescribers allowed to prescribe it.
the prescription requests contain various credentials of the "any and all" authorized prescribers	Moreover, such discussion by Ukens teaches that the various authorized prescriber credentials recognized by the Examiner to be disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi would, in the context of the one pharmacy of Ukens, correspond to the any and all authorized prescribers allowed to prescribe the specialty medication. The authorized prescriber credentials recognized by the Examiner to be disclosed by Moradi would, in view at least of paragraph [0022] of Moradi at ROXGHB004296, be received in the computer processor.
(clause d) entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the	

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
exclusive computer database is required for distribution of GHB, such that all prescriptions for GHB are processed only by the exclusive central pharmacy using only the exclusive computer database;	
"entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB" disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly and "An Interview with Orphan Medical about Xyrem." Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy to be disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"such that all prescriptions for" the drug are "processed only by the exclusive central pharmacy"	Ukens teaches "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)), which also indicates that such specialty medications are "prescribed." (*See* Ukens p. 3, para. 1, ROXGHB004315).
processing all prescriptions "using only the exclusive computer database"	This feature is shown by Borsand. Borsand discusses storing ***all*** pharmaceutical-related information ***only once*** and in a ***single*** database 62 and thus discloses an exclusive computer database and processing prescriptions using only the exclusive computer database:

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	"FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). Moreover, at least Fig. 3 of Borsand (ROXGHB004112) indicates the pharmaceutical-related information stored in single database 62 to include pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, ***patient*** information, and ***provider*** information. Borsand further indicates that such a provider can be a ***physician***: "A ***health care provider 30*** includes any person capable of issuing a pharmaceutical 32 prescription 28 such as a ***physician***, physician's assistant, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). One skilled in the art at the time would have been motivated to modify Moradi, "An Interview with Orphan Medical about Xyrem," and Ukens to include the exclusive computer database of Lilly at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "ensure that prescribers have an accurate view of their patients' use of prescription drugs and

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	to help protect professionals from lawsuits and other potential liabilities (para. 58 of Lilly)." One would have been further motivated to modify Moradi, "An Interview with Orphan Medical about Xyrem," Ukens, and Lilly to process prescriptions using ***only*** an exclusive computer database as taught by Borsand at least to allow all pharmaceutical-related information to be stored on a single database that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines. (*See* Borsand paragraph [0043], ROXGHB004127).
(clause e) checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the authorized prescribers to prescribe GHB;	
checking authorized prescriber "credentials"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "checking the credentials of the authorized prescriber" disclosed by paragraph [0118] of Moradi (ROXGHB004304). The BPAI Decision held the Examiner's findings "accepted as being undisputed."
checking the authorized prescriber "credentials" with a computer processor	Also disclosed in Moradi. *See*, for example, paragraph [0022] of Moradi which states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)).
checking the authorized prescriber "credentials" to determine authorized prescriber "eligibility" to "prescribe" the drug	At least Moradi paragraph [0118], ROXGHB004304, discloses checking the prescriber's credentials ("DEA number" and "license number") to determine the eligibility of the prescriber to prescribe the drug.
checking the "credentials" of the "any and all	As noted, *supra*, in connection with clause "c," at least by discussing "restricting

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
authorized prescribers"	distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3 para. 3, ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed" (*see* Ukens p. 3 para. 1, ROXGHB004315), Ukens teaches that all prescription requests, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all prescribers allowed to prescribe it. Checking the credentials of the authorized prescriber, as the Examiner recognized was disclosed in paragraph 118 of Moradi (ROXGHB004304), would, in the context of Ukens' single pharmacy, correspond to the any and all authorized prescribers allowed to prescribe the specialty medication.
(clause f) confirming with the patient that GHB educational material has been read prior to providing GHB to the patient a first time;	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "confirming with the patient that GHB educational material has been read prior to providing GHB to the patient a first time" disclosed among paragraph [0084] of Califano (ROXGHB004163) and "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." *See also*, paragraph [0006] of Moradi, ROXGHB004295. One skilled in the art at the time would have been motivated to modify one or more of Moradi, "An Interview with Orphan Medical about Xyrem," Ukens, Lilly, and Borsand to implement Califano's teaching of confirming with the patient that educational material has been read prior to providing a drug to the patient a first time at least to, as found by the Examiner in the 10/18/06 OA and the Examiner's Answer, "ensure that the patient knows about the risks and dangers associated with the drug (para. 43 of Califano)." *See also*, Williams, col. 8, line 57 to col. 9, line 2 and col. 10, lines 23-46, ROXGHB004325-26. One skilled in the art at the time would have been further motivated to modify one or more of Moradi, "An Interview with Orphan Medical about Xyrem," Ukens, Lilly, Borsand, and Califano to implement Williams' teaching regarding educational material at least to ensure patient compliance with taking a drug.

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	(*See* Williams col. 3 ln. 56-59, ROXGHB004323).
(clause g) requiring checking of the exclusive computer database for potential GHB abuse associated with the patient;	
"requiring checking of" of the "computer database for potential GHB abuse associated with the patient"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found the feature of clause "g" of "requiring checking of the … computer database for potential GHB abuse associated with the patient" disclosed among paragraphs 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi, and "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
an "exclusive computer database"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found this feature among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the findings of the Examiner.
(clause h) mailing GHB to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom GHB is prescribed and the doctor prescribing the GHB;	
"mailing GHB to the patient only provided information in" the computer database "is not indicative of potential abuse"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found the feature of "mailing GHB to the patient provided information in the … computer database is not indicative of potential abuse" disclosed among paragraphs 6 (ROXGHB004295), 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi, and "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). *See also* Borsand

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	paragraph [0120], ROXGHB004134.
an "exclusive computer database"	In the 6/19/06 OA and the Examiner's Answer the Examiner found this feature among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the findings of the Examiner.
the "potential abuse" is "by the patient to whom" the drug "is prescribed" and "the doctor prescribing" the drug	Borsand discloses checking, both before and after prescription 28 is filled, for evidence of fraud or misuse by ***provider 30*** and evidence of fraud or misuse by ***patient 22***. Borsand further explains that prescription 28 is canceled where such fraud or misuse is detected: "The system 20 facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 ***even*** after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the ***cancellation*** or modification of a ***prescription 28***. The modification of a prescription at 132 is an event triggered process. There must be an event that triggers the modification or cancellation of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a ***provider 30***, pharmacist 40, or ***patient 22***." (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)). "A ***health care provider 30*** includes . . . a ***physician***, physician's assistant, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). It would have been obvious to modify the prior art teachings to only provide the drug to the patient if no potential abuse is found by both the patient and the doctor in view of Borsand's teaching to check for fraud and abuse before and after filling the prescription and to cancel a prescription if evidence is found of

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	fraud or misuse by either the patient or the doctor.
(clause i) confirming receipt by the patient of the GHB; and	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "confirming receipt by the patient of the GHB" disclosed among the abstract of Moradi and "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause j) generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns. generating the periodic reports "with the computer processor"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "generating periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns" disclosed among paragraphs 11, 33, 54, 57, 58, 61, and 69 of Lilly and "An Interview with Orphan Medical about Xyrem." The BPAI Decision affirmed the Examiner's finding of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Taught at least in paragraph [0051] of Lilly: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)).

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
(preamble) 11. A computerized method of distributing a prescription drug under control of an exclusive central pharmacy, the method comprising:	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a claim limitation, then it is disclosed in the prior art as follows:
a "method of distributing" a drug "under control of an exclusive central pharmacy, the method comprising"	The preamble limitations are disclosed in at least Moradi and Ukens. The 10/18/06 OA and the Examiner's Answer each found "a method of distributing a drug under control of an exclusive central pharmacy, the method comprising" disclosed among paragraphs 3 (ROXGHB004295) and 24 (ROXGHB004296) of Moradi. Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy to be disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
distributing a "prescription" drug	Disclosed in at least paragraph [0003] of Moradi: "This invention generally relates to the field of ***prescription delivery systems***, and more particularly to the field of automated prescription handling." (*See* Moradi paragraph [0003], ROXGHB004295 (emphasis added)).
a "computerized" method	Disclosed in at least paragraph [0022] of Moradi: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). One skilled in the art would have been motivated to modify Moradi to include the exclusive central pharmacy of Ukens. *See* 10/18/06 OA and Examiner's

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	Answer ("limit access to dangerous drugs (page 3, paragraph 5 of Ukens)").
(clause a) receiving in a computer processor all prescription requests, for any and all patients being prescribed the prescription drug, only at the central pharmacy from any and all authorized prescribers allowed to prescribed the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the any and all authorized prescribers;	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "receiving prescription requests at the central pharmacy from an authorized prescriber containing information identifying a patient, the sensitive drug, and various credentials of the authorized prescriber" disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi and paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. Also, the 10/18/06 OA and the Examiner's Answer each found an exclusive central pharmacy to be disclosed among page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"receiving in a computer processor prescription requests . . ."	As noted above in connection with the preamble, *supra*, at least paragraph [0022] of Moradi states that: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)).
"… all prescription requests, for any and all patients being prescribed" the drug, "only at the central pharmacy from any and all authorized prescribers allowed to prescribe" the drug, and "various credentials of the any and all authorized prescribers"	Ukens discloses this feature at least by describing, *inter alia*, "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed." (*See* Ukens p. 3, para. 1, ROXGHB004315). Thus, Ukens teaches that all prescription requests, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all authorized prescribers allowed to prescribe it.

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	Moreover, such discussion by Ukens teaches that the various authorized prescriber credentials recognized by the Examiner to be disclosed among paragraphs 35 (ROXGHB004297-98), 116 and 117 (ROXGHB004303) of Moradi would, in the context of the one pharmacy of Ukens, correspond to the any and all authorized prescribers allowed to prescribe the specialty medication.
(clause b) entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of the prescription drug such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;	
"entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of" the drug	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of the sensitive drug" disclosed among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly and page 3, paragraphs 3-5 of Ukens (ROXGHB004315). The BPAI Decision affirmed the Examiner's finding of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"such that all prescriptions for" the drug are "processed only by the exclusive central pharmacy"	Ukens teaches "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)), which also indicates that such specialty medications are "prescribed." (*See* Ukens p. 3,

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
processing all prescriptions "using only the exclusive computer database"	para. 1, ROXGHB004315). Borsand discloses this feature. Borsand discusses storing ***all*** pharmaceutical-related information ***only once*** and in a ***single*** database 62 and thus discloses an exclusive computer database and processing prescriptions using only the exclusive computer database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127; emphasis added). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). Moreover, at least Fig. 3 of Borsand (ROXGHB004112) indicates the pharmaceutical-related information stored in single database 62 to include pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, ***patient*** information, and ***provider*** information. Borsand further indicates that such a provider can be a ***physician***: "A ***health care provider 30*** includes any person capable of issuing a pharmaceutical 32 prescription 28 such as a ***physician***, physician's assistant,

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). One skilled in the art at the time would have been motivated to modify Moradi and Ukens to include the exclusive computer database of Lilly at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "ensure that prescribers have an accurate view of their patients' use of prescription drugs and to help protect professionals from lawsuits and other potential liabilities (para. 58 of Lilly)." One would have been further motivated to modify Moradi, Ukens, and Lilly to process prescriptions using ***only*** an exclusive computer database as taught by Borsand at least to allow all pharmaceutical-related information to be stored on a single database that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines. (*See* Borsand paragraph [0043], ROXGHB004127).
(clause c) checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe the prescription drug; checking authorized prescriber "credentials" checking the authorized prescriber "credentials" with a computer processor	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "checking of the credentials of the authorized prescriber" disclosed by paragraph 118 of Moradi (ROXGHB004304). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Also disclosed in Moradi. *See*, for example, paragraph [0022] of Moradi, which states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet."

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	(*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)).
checking the authorized prescriber "credentials" to determine authorized prescriber "eligibility" to "prescribe" the drug	At least Moradi paragraph [0118] (ROXGHB004304) discloses checking the prescriber's credentials ("DEA number" and "license number") to determine the eligibility of the prescriber to prescribe the prescription drug.
checking the "credentials" of the "any and all authorized prescribers"	As noted, *supra*, in connection with clause "a," at least by discussing "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3 para. 3 ROXGHB004315 (emphasis added)) and indicating that such specialty medications are "prescribed" (*see* Ukens p. 3 para. 1, ROXGHB004315), Ukens teaches that all prescription requests, for any and all patients being prescribed the specialty medication are received only at the one pharmacy from any and all prescribers allowed to prescribe it. Checking the credentials of the authorized prescriber, as the Examiner recognized was disclosed in paragraph 118 of Moradi (ROXGHB004304), would, in the context of Ukens' single pharmacy, correspond to the any and all authorized prescribers allowed to prescribe the specialty medication.
(clause d) confirming with the patient that educational material has been read prior to providing the prescription drug to the patient;	
confirming "with the patient that educational material has been read prior to providing" the drug "to the patient"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "confirming with the patient that educational material has been read prior to providing the drug to the patient" disclosed by paragraph [0084] of Califano (ROXGHB004163). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). One skilled in the art at the time would have been motivated to modify one or more of Moradi, Ukens, Lilly, and Borsand to implement Califano's teaching of confirming with the patient that educational material has been read prior to providing the drug to the patient at least to, as found by the Examiner in the 10/18/06 OA and the Examiner's Answer, "ensure that the patient knows about

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	the risks and dangers associated with the drug (para. 43 of Califano)." *See also*, Williams, col. 8, line 57 to col. 9, line 2 and col. 10, lines 23-46, ROXGHB004325-26. One skilled in the art at the time would have been further motivated to modify one or more of Moradi, Ukens, Lilly, Borsand, and Califano to implement Williams' teaching regarding educational material at least to ensure patient compliance with taking a drug. (*See* Williams col. 3 ln. 56-59, ROXGHB004323).
(clause e) requiring checking of the exclusive computer database for potential abuse by the patient to whom the prescription drug is prescribed and the authorized prescriber allowed to prescribe the prescription drug; an "exclusive computer database," the "potential abuse" is by the patient to whom the prescription drug is prescribed "and" the authorized prescriber	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "requiring checking of the … computer database for potential abuse associated with the patient and/or the authorized prescriber" disclosed among paragraphs 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). In the 6/19/06 OA and the Examiner's Answer, the Examiner found this feature among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the findings of the Examiner. Borsand discloses checking, both before and after prescription 28 is filled, for evidence of fraud or misuse by ***provider 30*** and evidence of fraud or misuse by ***patient 22***. Borsand further explains that prescription 28 is canceled where such fraud or misuse is detected: "The system 20 facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 ***even*** after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the ***cancellation*** or modification of a ***prescription 28***. The modification of a prescription at 132 is an event

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	triggered process. There must be an event that triggers the modification or cancellation of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a ***provider 30***, pharmacist 40, or ***patient 22***." (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)). "A ***health care provider 30*** includes . . . a ***physician***, physician's assistant, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)).
(clause f) providing the prescription drug to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom the prescription drug is prescribed and the authorized prescriber allowed to prescribe the prescription drug; and	
providing the drug to the patient "only provided information in" the computer database "is not indicative of potential abuse"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found the feature of "only providing the drug to the patient provided information in the … computer database is not indicative of potential abuse" disclosed among paragraphs 43, and 45 (ROXGHB004299), and Fig. 3 items 318 and 322 (ROXGHB004285) of Moradi. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). *See also* Borsand paragraph [0120], ROXGHB004134.
an "exclusive computer database"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found this feature among paragraphs 11 (ROXGHB004256), 33 (ROXGHB004259), 54 (ROXGHB004260-61), 57, 58 (ROXGHB004261), 61 (ROXGHB004262), and 69 (ROXGHB004263) of Lilly. The BPAI Decision affirmed the findings of the Examiner.
that the "potential abuse" is "by the patient to	Borsand discloses checking, both before and after prescription 28 is filled, for

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
whom" the drug "is prescribed" and "the authorized prescriber of" the drug	evidence of fraud or misuse by ***provider 30*** and evidence of fraud or misuse by ***patient 22***. Borsand further explains that prescription 28 is ***canceled where such fraud or misuse is detected***: "The system 20 facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 ***even*** after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the ***cancellation*** or modification of a ***prescription 28***. The modification of a prescription at 132 is an event triggered process. There must be an event that triggers the modification or cancellation of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a ***provider 30***, pharmacist 40, or ***patient 22***." (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)). "A ***health care provider 30*** includes … a ***physician***, ***physician's assistant***, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)). It would have been obvious to modify the prior art teachings to provide the drug to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom the drug is prescribed and the authorized prescriber of the drug in view of Borsand's teaching to check for fraud and abuse before and after filling the prescription and to cancel a prescription if evidence is found of fraud or misuse by either the patient or the doctor.
(clause g) confirming receipt by the patient of the prescription drug. "confirming receipt by the patient of" the drug	In the 10/18/06 OA and the Examiner's Answer, the Examiner found "confirming receipt by the patient of the drug" disclosed by the abstract of

Claims of U.S. Patent No. 7,668,730	Description in Prior Art:
	Moradi. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).

F. The claims of United States Patent No. 7,765,106 are invalid:

1. The method claims of the '106 patent are invalid on the ground that the claimed subject matter is not encompassed by 35 U.S.C. § 101. The patent claims are invalid because the patentee admittedly seeks to patent an algorithm or an abstract idea, *see Bilski v. Kappos*, 130 S.Ct. 3218, 3229-30 (2010), and the claims do not satisfy the machine-or-transformation test, *see In re Bilski*, 545 F.3d 943, 962-63 (Fed. Cir. 2008).

2. First, the claims of the distribution patents are directed to functions or algorithms that are implemented in computer software or a combination of software and human implemented procedures. (*See, e.g.*, '106 patent at col. 3, lines 5-19.) The Supreme Court has repeatedly rejected patents that claim a formula or an algorithm. *See, e.g.*, *Gottschalk v. Benson*, 409 U.S. 63, 71 (1972); *Parker v. Flook*, 437 U.S. 584, 594 (1978); *In re Grams*, 888 F.2d 835, 837, n.1 (Fed. Cir. 1989) ("It is of no moment that the algorithm is not expressed in terms of a mathematical formula. Words used in a claim operating on data to solve a problem can serve the same purpose as a formula."); *Bilski v. Kappos*, 130 S.Ct. at 3231. The claims are also directed to a patent ineligible, abstract idea, *i.e.*, the concept of checking for potential abuse of a prescription drug by a patient or the prescribing doctor and applying that concept to a specific drug, GHB.

3. Second, the method claims of the distribution patents are not patent-eligible because the claimed methods do not transform an article into a different state or thing. The patents merely claim a method of distributing sensitive drugs that does not transform or make the drugs any less sensitive. And while the methods arguably include a "data-gathering step," wherein the pharmacy technician, specialist or pharmacist must "confirm[] with a patient that educational material has been read" or "confirm[] receipt by the patient of the prescription drug,"

the Federal Circuit has noted that "gathering data would not constitute a transformation of any article." *Bilski*, 545 F.3d at 963. And while the claimed methods refer to periodic reports that are generated "to evaluate potential diversion patterns" or "potential for abuse, misuse, or diversion," this is merely an addition of "non-essential post-solution activity" that will not save the claims from invalidity. *See Bilski*, 545 F.3d at 962-63. Generating a report containing data to be analyzed later is not the main purpose of the claimed process—distributing sensitive drugs in a manner to minimize risk and protect against abuse. (*See*, *e.g.*, '106 patent at col. 1, lines 13-14.)

4. Third, the claims of the distribution patents are not tied to a particular machine. While many of the steps require uses of so-called "exclusive computer system under the control of an exclusive central pharmacy," "exclusive central computer system," "computer processor" or "exclusive central pharmacy that maintains a central database," the specification does not require any specific type of computer system—the software can be executed "on a digital signal processor, ASIC, microprocessor, or other type of possessor operating on a computer system, such as a personal computer, server or other computer system." (*See*, *e.g.*, '106 patent at col. 3, lines 16-19.) The Supreme Court in *Gottschalk* rejected a claimed process that utilized any general-purpose digital computer of any type. *See Gottschalk*, 409 U.S. at 71-72. The Board of Patent Appeals and Interferences has followed the Gottschalk approach and has rejected applications that are not tied to a specific computer system. *See*, *e.g.*, *Ex Parte Kuno, et al.*, Appeal No. 2009-006896 (B.P.A.I. Dec. 13, 2010); *Ex Parte Monk, et al.*, Appeal No. 2009-013250 (B.P.A.I. Dec. 30, 2010).

5. Finally, no patent can be obtained for a method an essential component of which consists of human mental participation. If a method necessarily involves human judgment and

choice, then the method will not meet the standard of definiteness required for patent protection. *See, e.g., Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1356 (Fed. Cir. 2005) ("The scope of claim language cannot depend solely on the unrestrained, subjective opinion of a particular individual purportedly practicing the invention. *See Application of Musgrave*, 57 C.C.P.A. 1352, 431 F.2d 882, 893 (1970)."). The claims of the distribution patents are invalid for indefiniteness because they require someone, for example, a pharmacy specialist, technician or pharmacist, to make certain subjective judgment calls as to whether the patient indeed received and read the program materials or whether there is potential for abuse of the prescription drug by the patient. The applicants repeatedly argued to the PTO that the claimed methods of distribution or distribution models "analyse[] (sic) for and determine[] potential abuse situations and current and anticipated patterns of potential adverse reactions." (*See*, *e.g.*, '730 PH, 9/30/04 Petition to Make Special at ROXGHB004395.) Neither the claims nor the specifications of the distribution patents, however, provide objective steps or criteria for evaluating the potential for abuse or on how to verify whether the patient has indeed truthfully reviewed the program materials—the technician could accept what the patient says or could exercise his or her own judgment to determine whether the patient is being truthful or not. Because the claimed methods seek to address the problems associated with the abuse and illegal distribution of sensitive prescription drugs like GHB, pharmacy specialists, technicians and pharmacists must be given authority to act on their "gut" feeling as to whether a certain patient is being deceitful or untrustworthy. Patent claims that require such human mental participation are indefinite and not proper patent-eligible subject matter.

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	Borsand (U.S. Patent Application Publication No. 2003/0074225), ROXGHB004109-36, ("Borsand"), **Califano (U.S. Patent Application Publication No. 2003/0033168), ROXGHB004137-70, ("Califano"),** **"An Interview with Orphan Medical about Xyrem" ("An Interview with Orphan Medical about Xyrem," Feb. 12, 2001, http://www.talkaboutsleep.com/sleepdisorders/archives/Narcolepsy_xyrem_interview.htm), ROXGHB004250-52 ("An Interview with Orphan Medical about Xyrem"),** **Lilly (U.S. Patent Application Publication No. 2004/0176985), ROXGHB004253-64 ("Lilly"),** **Melker (U.S. Patent Application Publication No. 2002/0177232), ROXGHB004265-81 ("Melker"),** **Moradi (U.S. Patent Application Publication No. 2004/0019794), ROXGHB004282-312 ("Moradi"),** **Ukens ("Specialty Pharmacy," Jun. 5, 2000, Drug Topics, v. 144, p. 40), ROXGHB004313-20 ("Ukens"), and** **Williams (U.S. Patent No. 6,315,720), ROXGHB004321-31 ("Williams").**
(preamble) 1. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising: a "therapeutic" method for "treating" a "patient" with a drug	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a claim limitation, then it is disclosed in the prior art as follows: Moradi discloses at least at paragraph [0008] delivering a drug to a patient: "Briefly, according to an aspect of the present invention, a method and system for delivering prescription medicine provides method of performing prescription medicine delivery that issues a prescription to a person and also accepts an identification of that person … The method then delivers the medicine that was prescribed by the prescription to the person."

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	(*See* Moradi paragraph [0008], ROXGHB004295). Borsand also discloses that the drug is "effective for therapeutic purposes": "The process of creating a prescription 28, canceling a prescription 28, or accessing patient-related information is done in the context of a particular patient 22. ***Patient 22*** attributes include the patient's medical ***condition to be remedied or mitigated with a pharmaceutical*** 32." (*See* Borsand paragraph [0053], ROXGHB004128 (emphasis added)).
the drug is a "prescription" drug	Moradi discloses at least in paragraph [0003]: "This invention generally relates to the field of ***prescription*** delivery systems, and more particularly to the field of automated prescription handling." (*See* Moradi paragraph [0003], ROXGHB004295 (emphasis added)).
the drug "has potential to be abused, misused, or diverted"	Moradi discloses at least in paragraph [0006]: "Delivery of prescription medication by mail is also possible … This technique is also open to ***fraud*** since the individual patient typically does not personally present his or her prescription to the pharmacy. This technique can also lead to ***an improper person receiving the prescription***, such as when a child that is living with the recipient retrieves mail that contains the mailed prescription." (*See* Moradi paragraph [0006], ROXGHB004295 (emphasis added)).
(clause a) receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and from any and all doctors allowed to prescribe the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is prescribing the prescription	

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
drug; "all" prescriptions are received and contain information identifying the "patient," the "drug," and "various credentials" of the doctor	U.S. Patent No. 7,765,106 is a divisional application of U.S. Patent No. 7,668,730 ("the '730 patent"). In the October 3, 2007 Examiner's Answer, ROXGHB004708-ROXGHB004725 ("the Examiner's Answer"), the Examiner found that Moradi, Lilly and Ukens disclosed "receiving ***all*** prescription requests at the exclusive central pharmacy from a medical doctor ***containing information identifying a patient, the sensitive drug, and various credentials of the doctor.***" *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The August 31, 2009 Decision on Appeal, ROXGHB004750-ROXGHB004763 ("BPAI Decision") stated: "But for the Examiner's finding, that Moradi and Lilly disclose 'exclusive' computer databases, the Examiner's remaining findings characterizing the scope and content of the cited references as well as the differences between the claimed subject matter and the prior art have not been rebutted. Accordingly, as to these findings, they are accepted as being undisputed" (BPAI Decision, p. 6, ROXGHB004756). In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving all prescription requests at the exclusive central pharmacy ***from*** a medical ***doctor*** containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"all prescriptions" are "only" received, "all prescriptions" are "for any and all patients being prescribed" the drug, and "from any and all doctors allowed to prescribe" the drug, and the various credentials are of the medical doctor "who is prescribing" the drug	Ukens describes "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)) and indicates that such specialty medications are "prescribed" (*see* Ukens p. 3, para. 1, ROXGHB004315). Thus, Ukens teaches receiving only at the one pharmacy all prescriptions for any and all patients being prescribed the specialty medication and from any and all doctors allowed to prescribe it. In the Examiner's Answer the Examiner found Moradi disclosed various doctor credentials. *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303. Such various doctor credentials, in view of the one pharmacy of Ukens, correspond to the medical doctor who is prescribing the specialty medication.
receipt is into an "exclusive central computer system"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclose "receiving all prescription requests at the ***exclusive central*** pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Further, Moradi paragraph [0022] states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). Further, Lilly paragraph [0051] states: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)). Either the Moradi or Lilly computer would, in the context of the exclusive central pharmacy of Ukens, constitute an ***exclusive central*** computer. One skilled in the art at the time would have been motivated to modify Moradi or Lilly to include the exclusive central pharmacy of Ukens in light of Ukens' teaching to "limit access to dangerous drugs (page 3, paragraph 5 of Ukens)." *See* the October 18, 2006 Office Action, ROXGHB004586-ROXGHB004600 ("the 10/18/06 OA") and Examiner's Answer.
(clause b) requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database; "requiring entering" of "the information into an exclusive computer database associated with the exclusive central computer system for	In the June 19, 2006 Office Action, ROXGHB004525-ROXGHB004545 ("the 6/19/06 OA"), the 10/18/06 OA and the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
analysis of potential abuse, misuse, or diversion"	computer database associated with the exclusive central pharmacy for analysis of potential abuse situations." *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly stating: "To one of ordinary skill in the art reading Lilly, Lilly's data storage is 'exclusive' in that it is the sole data storage that 'contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information'" (BPAI Decision, p. 10, ROXGHB004760). The BPAI Decision also held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). The previously discussed exclusive central computer system of Lilly (or Moradi) is associated with the exclusive central database of Lilly when viewed in the context of Ukens' exclusive central pharmacy. *See* clause a, *supra*.
the "abuse" is "of" the drug	Lilly discloses: "All of these entities can have immediate access to potential medication abuse by identification of needless prescription duplications, potential drug interactions, and multi-source interstate ***prescriptive medication abuse.***" (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)).
"all" prescriptions for the drug are processed "only" using the "exclusive central computer system" and the "exclusive computer database"	Borsand discusses storing ***all*** pharmaceutical-related information -- including prescription information -- ***only once*** and in a ***single*** database 62 and, thus, discloses an ***exclusive computer database***. Database 62 is the only location where processing can access the all pharmaceutical-related information, thus, ***all***

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	prescriptions are processed ***only*** using the exclusive computer database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). Moreover, at least Fig. 3 at ROXGHB004112 of Borsand indicates the pharmaceutical-related information stored in single database 62 includes pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, patient information, and provider information. At least Fig. 3 at ROXGHB004112 and paragraph [0043] at ROXGHB004127 of Borsand disclose exclusive computer database 62 to be ***associated with single computer 26*** of Borsand. *See also* Borsand paragraph [0031] stating: "The computer 26 can be a ***single centralized*** computer or server, a single network, a series of interconnected networks, a series of devices capable of accessing the Internet or World Wide Web including an application server, or

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	any other configuration which supports the ability of different entities to communicate with one another." (*See* Borsand paragraph [0031], ROXGHB004125-26 (emphasis added)).
processing is "for authorization"	Lilly discloses: "For instance, if a pharmacist is checking on a prescriptive medication ***prior to dispensing*** the prescriptive medication, a red flag as indicated at 140 may be issued if the prescription presents a problem, e.g., is a conflicting type of drug (contraindicated prescriptive medication) or perhaps a similar type of drug which in combination with a previous prescriptive medication might be harmful to the consumer. Red flags may be issued as a result of automatic or manual operation. ***System 100*** and/or the pharmacist and/or the doctor ***may require or suggest declining or approving the prescriptive medication***, and otherwise add notes, comments, and flags, as desired." (*See* Lilly paragraph [0070], ROXGHB004263 (emphasis added)). A person of ordinary skill in the art would be motivated to combine the single exclusive database of Borsand with one or more of Moradi and Lilly in view of Ukens because these references relate to storing pharmaceutical related information using a computer. (*See* 6/19/06 OA, Examiner's Answer and Borsand paragraph [0043], ROXGHB004127).
(clause c) controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the	

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and	
"controlling the distribution" of the drug	In the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed "***only mailing*** the drug to the patient ***if*** no potential abuse is found …" *See* Moradi, paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"controlling the distribution" of the drug uses the "exclusive central computer system"	As noted above in connection with clause a, *supra*, a computer of Moradi or Lilly would, in the context of the exclusive central pharmacy of Ukens, constitute an exclusive central computer. Additionally, as discussed above, Borsand also discloses an exclusive central computer.
the exclusive central computer system "tracks all prescriptions" of the drug	As noted, Lilly or Moradi in the context of Ukens, or Borsand alone, provide an exclusive central computer. Lilly discloses at least via paragraphs [0009], [0050], and [0054] that such exclusive central computer tracks prescriptions: "The industry has widely recognized a need for better efficiencies, but without notable success in many areas, including prescription abuse. For instance, the Healthcare Information Portability and Accountability Act (HIPAA) mandates making the exchange of information more ubiquitous, secure, and efficient but does not provide a solution with respect to ***prescription tracking*** and abuse." (*See* Lilly paragraph [0009], ROXGHB004256 (emphasis added)). "In accord with the method of the present invention, a secure, private, independent, network-based, centralized method operable for ***tracking*** and managing ***prescriptive medication information*** in aggregate is provided which allows electronic querying and real-time notification of patients' prescriptive

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	medication history at the time of prescriptive medication creation." (*See* Lilly paragraph [0050], ROXGHB004260 (emphasis added)). "All of these entities can have immediate access to potential medication abuse by ***identification*** of needless ***prescription duplications***, potential drug interactions, and multi-source interstate prescriptive medication abuse." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)).
the exclusive central computer system "analyzes for the potential abuse, misuse, or diversion" of the drug	As noted above in connection with clause b, *supra*, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer database associated with the ***exclusive central*** pharmacy for ***analysis of potential abuse*** situations." (Emphasis added). *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). It would have been obvious to perform the potential abuse analysis in an exclusive central computer system in Ukens' exclusive central pharmacy in view of the teachings of Moradi, Lilly or Borsand.
determining of patterns of "potential prescription abuse, misuse, or diversion" of the drug from "periodic reports"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found Lilly disclosed "generating ***periodic reports*** via the exclusive computer database to evaluate ***potential diversion*** patterns." *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263. The BPAI Decision affirmed the Examiner's finding that Lilly disclosed an "exclusive computer database" and held all other findings of the Examiner to be "accepted as being undisputed" (see clause b, *supra*). Moreover, as additionally

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	noted in connection with clause b, *supra*, Lilly discloses abuse of the drug.
the "exclusive computer database" generates the periodic reports	In the 6/19/06 OA and the Examiner's Answer, the Examiner found Lilly disclosed "generating periodic reports via the ***exclusive computer database*** to evaluate potential diversion patterns." *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263 (emphasis added). The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (*See* clause b, *supra*).
"the exclusive central computer system" generates the periodic reports	As noted in connection with clause b, *supra*, the computer of Moradi or Lilly, in the context of the exclusive central pharmacy of Ukens, or the computer of Borsand alone, would correspond to an ***exclusive central*** computer system.
the determined potential diversion patterns are "current and anticipated" diversion patterns	Lilly teaches: "Pharmacies 26 may check to personally verify the drug usage of each purchaser to ***immediately*** detect problems related to ***abuse, fraud, and misuse*** of medications … Pharmacists are constantly challenged to circumvent duplication, ***abuse, fraud, and misuse*** of these medications while providing a cost effective medication delivery system. In the present health system the wide availability of pharmaceuticals from different pharmacies raises the risks of negative drug interactions and its associated destructive medical outcome. ***Pharmaceutical information control organization 12 can flag these issues*** in real time, thereby ***completely preventing*** or at least minimizing their occurrences." (*See* Lilly paragraph [0057], ROXGHB004261 (emphasis added)). "FIG. 2 discloses a presently preferred pharmaceutical information flow diagram 100 for a method of operation of ***pharmaceutical information control organization 12*** in accord with the present invention. A plurality of entities,

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	networks, organizations may be utilized in accord with the present invention including doctors 102. Pharmacies 104 include pharmacies that are affiliated with each other as well as pharmacies that are unaffiliated with each other. Other entities include hospitals 106, pharmaceutical companies 108, insurance companies 110 (which may include health or life insurance companies or any other type of insurance companies), government agencies 112, health care informatics companies 114, health researchers 116, managed care organizations 118, and other healthcare providers 120 … In a preferred embodiment, the present invention provides that ***data storage 122*** is able to access the ***databases*** of the above-listed entities and/or other member organizations as needed and/or store the corresponding pharmaceutical data in data storage 122 which is external to each entity's database(s) … Data storage 122 preferably has the ability to allow the software schemas to be changed without disruption of system 100." (See Lilly paragraph [0061], ROXGHB004262 (emphasis added)). *See also* Lilly, paragraph [0058], ROXGHB004261.
the periodic reports are generated based on prescription data from a medical doctor	Lilly teaches: "All of these entities can have immediate access to potential medication abuse by ***identification*** of needless ***prescription duplications***, potential drug interactions, and multi-source interstate prescriptive medication abuse." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)). "The display may be made by a patient identifier, patient name, date, drug name, ***doctor prescribing the medication***, pharmacy, geography (city, state, zip code), by phone number, and/or by aberrant use flag." (*See* Lilly paragraph [0069], ROXGHB004263 (emphasis added)).
the prescription data contain "information identifying the patient, the drug prescribed, and	As noted in connection with clause a, *supra*, in the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclose "receiving all ***prescription*** requests at the exclusive central pharmacy from a medical doctor containing

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
credentials of the doctor"	information identifying a ***patient***, the sensitive ***drug***, and various ***credentials of the doctor***." (Emphasis added). *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added).
(clause d) selecting multiple controls for distribution using said exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the	

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;	
"selecting" of "multiple controls," the controls "selected from the group consisting of … identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; … [and] obtaining patient information …"	Moradi discloses selecting the control of identifying the physician's name, license, and Drug Enforcement Agency registration information at least by indicating the control is required. Moradi discloses selecting the control of obtaining patient information at least by disclosing registering the patient where it is determined that the patient is not registered. "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by the automated prescription delivery system 100. The data includes the physician's ***name***, address, practice information, ***DEA number, license numbers***, e-mail, phone number and web site address." (*See* Moradi paragraph [0118], ROXGHB004304; emphasis added). "This module allows a physician to complete an online registration form for access to the automated prescription delivery system 100. This module is part of the Registration module 218. This module is used for entering ***required*** physician registration information and does not grant access to the system.

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	Access is granted the system by another module controlled and used by authorized employees. Entries and editing of registration data is tracked via an automated audit trail." (*See* Moradi paragraph [0109], ROXGHB004303 (emphasis added)). "If the POC System 104 is in a physician's office, the processing begins instead with the physician completing, at step 302, the prescription form. The prescription can be a new prescription or a prescription for a refill. The processing next ***determines, at step 304, whether the patient is registered*** with the automated prescription delivery system 100. The exemplary embodiment of the present invention has the patient tell the physician's office staff whether or not he or she is registered with the system. If the patient is registered, the processing continues with the POCP operator's entering the patient's identification into the POC system 104. The patient's identification in the exemplary embodiment of the present invention is the patient's name and social security number. Alternative embodiments utilize different patient identification techniques, including identification cards encoded with printed or magnetically readable identification numbers or data, biometric identification devices and other identification devices that provide a unique identification of the patient. ***If the patient is not registered***, the processing continues instead by ***registering the patient***, at step 308, by collecting patient information and entering it into the POC system 104 and relaying it to the CSS 102. The patient information can be entered either manually into the POC system 104 or by scanning a form that is completed by the patient, as is described below." (*See* Moradi paragraph [0035], ROXGHB004297-98 (emphasis added)). Further, in the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all prescription requests at the exclusive central pharmacy from a medical doctor containing ***information identifying a patient***, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." The Examiner's Answer found Moradi, Lilly, and Ukens disclosed receipt of prescription requests containing patient information. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260.
the selected "controls" are "for distribution"	Moradi discloses the control of identifying the physician's name, license, and Drug Enforcement Agency registration information to be for distribution at least by indicating it to be for the automated prescription ***delivery*** system: "This module allows a physician to complete an online registration form for access to the automated prescription ***delivery*** system 100. This module is part of the Registration module 218. This module is used for entering required physician registration information and does not grant access to the system. Access is granted the system by another module controlled and used by authorized employees. Entries and editing of registration data is tracked via an automated audit trail." (*See* Moradi paragraph [0109], ROXGHB004303 (emphasis added)). Moradi discloses the control of obtaining patient information to be for distribution at least by indicating the corresponding registration of steps 304, 306, and 308 to precede step 322 of "giv[ing] ordered medicine to delivery person for hand ***delivery.***" (*See* Moradi Fig. 3 at ROXGHB004285 (emphasis added)): "After the patient is either registered or has his or her identification entered into the system, the POCP operator then scans and submits, at step 310, the prescription for the patient. The prescription is scanned by an image scanner that is part of the POC system 104." (*See* Moradi paragraph [0036], ROXGHB004298).

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	"The PMS system assigns the prescription a prescription number, and the pharmacist enters that prescription number and the number of refills into the PODP 216, which then communicates that data back to the CSS 102 with an identification of the prescription. The pharmacist then gives, at step 322, the ordered medicine and a copy of the prescription image to a prescription deliverer, which is a delivery person in the exemplary embodiments, for delivery to the patient." (*See* Moradi paragraph [0043], ROXGHB004299). Moreover, the 6/19/06 OA and the Examiner's Answer each found Moradi disclosed "a method of ***distributing a drug under exclusive control of an exclusive central pharmacy***." *See* Moradi, paragraphs [0003] at ROXGHB004295 and [0024] at ROXGHB004296. Also, the 10/18/06 OA and the Examiner's Answer each found Ukens disclosed an exclusive central pharmacy at page 3, paragraphs 3-5. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). The noted ***controls*** would, in the context of such distribution under ***control*** of such exclusive central pharmacy, be ***controls*** for distribution .
selecting control for the "distribution" uses the "exclusive central computer system"	As noted above in connection with clause b, *supra*, Moradi or Lilly in the context of Ukens, or Borsand alone, provides an exclusive central computer, and Moradi discloses that the exclusive central computer controls distribution of the drug (*see* clause c, *supra*).
(clause e) authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;	
"the exclusive central computer system"	As noted above in connection with clause b, *supra*, Lilly or Moradi in the context of Ukens, or Borsand alone, provides an exclusive central computer. Lilly

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
authorizes the filling of the prescription	discloses that such exclusive central computer authorizes the filling of a prescription for a prescriptive medication: "For instance, if a pharmacist is checking on a prescriptive medication ***prior to dispensing*** the prescriptive medication, a red flag as indicated at 140 may be issued if the prescription presents a problem, e.g., is a conflicting type of drug (contraindicated prescriptive medication) or perhaps a similar type of drug which in combination with a previous prescriptive medication might be harmful to the consumer. Red flags may be issued as a result of automatic or manual operation. ***System 100*** and/or the pharmacist and/or the doctor may require or suggest ***declining or approving*** the ***prescriptive medication***, and otherwise add notes, comments, and flags, as desired." (*See* Lilly paragraph [0070], ROXGHB004263 (emphasis added)).
the drug has been subjected to said multiple controls	At least paragraphs [0118] and [0035] of Moradi teach subjecting the drug to the multiple controls of identifying the physician's name, license, and Drug Enforcement Agency registration information; and obtaining patient information: "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by the automated prescription delivery system 100. The data includes the physician's ***name***, address, practice information, ***DEA number, license numbers***, e-mail, phone number and web site address." (*See* Moradi paragraph [0118], ROXGHB004304 (emphasis added)). "If the POC System 104 is in a physician's office, the processing begins instead with the physician completing, at step 302, the prescription form. The prescription can be a new prescription or a prescription for a refill. The processing next determines, at step 304, whether the patient is registered with the automated prescription delivery system 100. The exemplary embodiment of the present invention has the patient tell the physician's office staff whether or not he or she is registered with the system. If the patient is registered, the processing continues with the POCP operator's entering the patient's

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	identification into the POC system 104. The patient's identification in the exemplary embodiment of the present invention is the patient's name and social security number. Alternative embodiments utilize different patient identification techniques, including identification cards encoded with printed or magnetically readable identification numbers or data, biometric identification devices and other identification devices that provide a unique identification of the patient. If the patient is not registered, the processing continues instead by ***registering the patient***, at step 308, by collecting patient information and entering it into the POC system 104 and relaying it to the CSS 102. The patient information can be entered either manually into the POC system 104 or by scanning a form that is completed by the patient, as is described below." (*See* Moradi paragraph [0035], ROXGHB004297-98 (emphasis added)).
the drug "has been approved for shipment to the patient"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed "only ***mailing*** the drug to the patient ***if no potential abuse is found*** …" *See* Moradi, paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause f) noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and	
noting that there is patient potential for "abuse, misuse, or diversion"	Borsand discloses checking, both before and after prescription 28 is filled, for evidence of fraud or misuse by provider 30 and ***evidence of fraud or misuse by patient 22***. Borsand further explains that prescription 28 is canceled where such fraud or misuse is detected: "The system 20 facilitates communication between a payor 60, a PBM 50, a

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	pharmacist 40, and a provider 30 even after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the cancellation or modification of a prescription 28. The modification of a prescription at 132 is an event triggered process. There must be an event that triggers the modification or cancellation of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a provider 30, pharmacist 40, or ***patient 22.***" (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)).
noting is "based on <u>one or</u> more of the analysis of the potential abuse, misuse, or diversion" of the drug and the periodic reports	As is discussed in connection with clause b, *supra*, in the 6/19/06 OA, the 10/18/06 OA and the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy ***for analysis of potential abuse*** situations." (Emphasis added). *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. Further, the BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly, and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause g) delivering the prescription drug to the patient in order to treat the patient with the prescription drug. the drug is delivered to the patient	As is discussed in connection with clause e, *supra*, in the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed the feature of "only ***mailing the drug to the patient*** if no potential abuse is found …" (Emphasis added). *See* Moradi paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	Decision, p. 6, ROXGHB004756).
"in order to treat the patient" with the drug	Borsand teaches: "The process of creating a prescription 28, canceling a prescription 28, or accessing patient-related information is done in the context of a particular patient 22. Patient 22 attributes include the patient's medical ***condition to be remedied or mitigated with a pharmaceutical 32***; medical history such as allergies and medication history; eligibility and other coverage information relating to payor's 60 health plan; refill behavior; and any other characteristic or attribute that could affect the desirability of a pharmaceutical 32 or prescription 28 with respect to a particular patient 22." (*See* Borsand paragraph [0053], at ROXGHB004128 (emphasis added)).
2. The method of claim 1, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically. the "control" of "communicating prescriptions from a physician to the exclusive central computer system" that the "prescriptions" are communicated	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all ***prescription requests*** at the exclusive central pharmacy ***from*** a

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
"from a physician"	***medical doctor*** containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
communication is to the "exclusive central computer system"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving all prescription requests at the ***exclusive central*** pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Further, Moradi paragraph [0022] states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). *See also* Lilly paragraph [0051], ROXGHB004260. Either the Moradi or Lilly computer would, in the context of the exclusive central

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	pharmacy of Ukens, constitute an ***exclusive central*** computer.
that the "control" of "communicating prescriptions from a physician to the exclusive central computer system" is selected	In the Examiner's Answer, the Examiner found Moradi, Lilly, and Ukens disclosed prescription request receipt. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260.
the "control" of "identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information"	Moradi discloses: "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by the automated prescription delivery system 100. The data includes the physician's ***name, address, practice information, DEA number, license numbers***, e-mail, phone number and web site address." (*See* Moradi paragraph [0118] at ROXGHB004304; emphasis added).
selecting the "control" of "identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information"	Moradi describes: "This module allows a physician to complete an online registration form for access to the automated prescription delivery system 100. This module is part of the Registration module 218. This module is used for entering required physician registration information and does not grant access to the system." (*See* Moradi paragraph [0109] at ROXGHB004303).
the "control" of "verifying the prescription"	Moradi discloses: "Once the POD system 106 at the pharmacy has received the image of the prescription from the CSS 102, the data are decrypted and the processing continues by using a software based data authenticator to ***verify***, at step 316, ***the prescription*** at the POD system 106. This step includes operating a software based digital signature authenticator to ensure that a valid digital signature has been added to the prescription. This step also requires that if the prescription is not refillable, or if the prescription is refillable but the number of

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	digital signatures added to the prescription image is equal to or greater than the number of refills, the operator is to check the order for cancellations of previous submissions to the POD 106." (*See* Moradi paragraph [0042] ROXGHB004299 (emphasis added)).
selecting the "control" of "verifying the prescription"	Moradi discloses verifying the prescription with a computer or processing device, which can correspond to PODP software 212 of that computer or processing device. (*See* Moradi paragraph [0028] at ROXGHB004297).
the "control" of "obtaining patient information"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all prescription requests at the exclusive central pharmacy from a medical doctor containing ***information identifying a patient***, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). *See also* Moradi paragraph [0035] at ROXGHB004297-98.
selecting the "control" of "obtaining patient information"	In the Examiner's Answer, the Examiner found Moradi, Lilly, and Ukens disclosed prescription request receipt. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260. *See also* Moradi paragraph [0031] at ROXGHB004297.
the "control" of "verifying patient registry information"	Moradi discloses server-side validation of patient registration data: "If the 'Continue' button was pressed, the processing continues by determining, at step 814, if there is successful client-side validation. If there is not successful client side validation, the processing displays, at step 816, an error message that indicates which field is in error. If there is successful client side validation, the

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	patient registration data is securely sent, at step 812, to the CSS 102. The exemplary embodiment uses an HTTPS communications link to securely communicate all data. Once the CSS 102 receives the data, the ***processing determines***, at step 818, ***if there is successful server-side validation***. If there is not successful server-side validation, the processing displays, at step 820, an error message indicating which data field is in error." (*See* Moradi paragraph [0161] at ROXGHB004305 (emphasis added)).
selecting the control of "verifying patient registry information"	Moradi discloses effecting server-side validation with a computer or processing device that can correspond to registration software component 218 of such computer or processing device. (*See* Moradi paragraphs [0031] at ROXGHB004297 and [0161] at ROXGHB004305).
the "control" of "providing comprehensive education information to the patient"	Williams discloses: "Preferably the patient is provided ***full*** disclosure of ***all*** the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such ***counsel*** may be provided verbally, as well as in ***written form***. In preferred embodiments, the prescriber provides the patient with ***literature materials*** on the drug for which a prescription is contemplated, such ***as product information, educational brochures, continuing education monographs, and the like***." (*See* Williams col. 8 ln. 57 - col. 9 ln. 2, ROXGHB004325-26 (emphasis added)). *See also* the 6/19/06 OA and the Examiner's Answer wherein the Examiner found Califano disclosed "confirming with the patient that educational material has been read prior to shipping the drug." *See*, Califano, paragraph [0084] at ROXGHB004163. The BPAI Decision held the Examiner's findings "accepted as

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "providing comprehensive education information to the patient"	As noted above in connection with clauses a and b of claim 1, *supra*, Moradi, Borsand, and Lilly each disclose a computer processor. Additionally, Williams' discussion of a "computer readable storage medium" (*see* Williams' col. 2 ln. 50-60 at ROXGHB004322) describes or suggests a computer processor. *See also* Califano's paragraph [0052] at ROXGHB004159 for disclosure of a computer processor. Williams discloses the control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, ***in order to become registered in the computer readable storage medium, the prescriber may be required*** to comply with various aspects of the methods described herein including, for example, ***providing patient education and counseling***, and the like, as described in detail below." (*See* Williams col. 4 ln. 43-54, ROXGHB004323 (emphasis added)). *See also* Califano paragraphs [0052] at ROXGHB004159 and [0084] at ROXGHB004163. One skilled in the art at the time would have been motivated to modify one or more of Lilly, Moradi, Ukens, and Borsand to have selected with a computer processor the control of providing comprehensive education information to the patient as taught by Williams at least to ensure patient compliance with taking a drug. (*See* Williams col. 3 ln. 56-59, ROXGHB004323). One skilled in the art at the time would have been motivated to modify one or

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	more of Lilly, Moradi, Ukens, Borsand, and Williams to have selected with a computer processor the control of providing comprehensive education information to the patient as taught by Califano at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "ensure that the patient knows about the risks and dangers associated with the drug (para. 43 of Califano)."
the "control" of "verifying the patient has received and/or reviewed the educational materials"	Williams discloses: "In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the ***patient to fill out an informed consent form*** which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. ***Verification that the patient*** has given his/her informed consent may also be registered in the computer readable storage medium … By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. ***In the informed consent form***, the patient preferably ***agrees to*** comply with the risk avoidance measures provided, and to ***behave in a manner which is consistent with the prescriber's counsel***." (*See* Williams col. 10 ln. 23-46, ROXGHB004326 (emphasis added)). *See also* the 6/19/06 OA and the Examiner's Answer wherein the Examiner found paragraph [0084] of Califano disclosed "confirming with the patient that educational material has been read prior to shipping the drug." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "verifying the patient has received and/or reviewed the	Williams discloses:

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
educational materials"	"In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. ***Verification*** that the patient has given his/her informed consent may also be registered ***in the computer readable storage medium.***" *(See* Williams col. 10 ln. 23-32, ROXGHB004326 (emphasis added)). *See also* Califano paragraphs [0084] and [0086] at ROXGHB004163-64.
the "control" of "requiring rewriting of the prescription periodically"	Williams discloses: "In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will ***not be permitted*** without a ***renewal prescription from the prescriber***, as discussed in detail below." (*See* Williams col. 12 ln. 3-8 at ROXGHB004327 (emphasis added)). *See also* Moradi paragraph [0098] at ROXGHB004302.
selecting the control of "requiring rewriting of the prescription periodically"	Williams discloses this control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, ***in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein*** including, for example, providing patient education

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	and counseling, and the like, as described in detail below." (*See* Williams col. 4 ln. 43-54 at ROXGHB004323 (emphasis added)).

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
(preamble) 3. A therapeutic method for treating a narcoleptic patient with sodium oxybate for daytime cataplexy comprising:	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a claim limitation, then it is disclosed in the prior art as follows:
a "therapeutic" method for "treating" a "narcoleptic patient" with a drug	Paragraphs 1 and 13 of "An Interview with Orphan Medical about Xyrem" teach: "***Persons with narcolepsy***, especially those who experience cataplexy, are anxiously awaiting the decision by the Food and Drug Administration (FDA) on the approval of Xyrem as a ***treatment*** for the ***symptoms*** of narcolepsy, A decision is expected later this spring, as the Xyrem New Drug Application has been given Priority Review Status." (*See* "An Interview with Orphan Medical about Xyrem" paragraph 1, ROXGHB004250 (emphasis added)). "TalkAboutSleep: What is the estimated cost to ***Narcolepsy patients***? Is it likely that the drug will be covered by health insurers? Will Orphan Medical provide assistance to persons with narcolepsy in getting Insurance coverage? Will Xyrem be available free or at reduced cost to low-income individuals without insurance? How will this be done?" (*See* "An Interview with Orphan Medical about Xyrem" paragraph 13, ROXGHB004251 (emphasis added)).
the treatment is for "cataplexy"	"An Interview with Orphan Medical about Xyrem" discloses: "***Persons with narcolepsy, especially those who experience cataplexy***, are anxiously awaiting the decision by the Food and Drug Administration (FDA) on the approval of Xyrem as ***a treatment for the symptoms of narcolepsy***, A decision is expected later this spring, as the Xyrem New Drug Application has been given Priority Review Status." (*See* "An Interview with Orphan Medical about Xyrem" paragraph 1, ROXGHB004250 (emphasis added)). "How Does Xyrem Work?

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	TalkAboutSleep: Originally Xyrem was expected to be a drug for the ***control of cataplexy for people who have Narcolepsy***. We know from personal experiences that it can also help alleviate Excessive Daytime Sleepiness (EDS). Does Orphan Medical know exactly how Xyrem alleviates cataplexy? Is it a chemical effect or does it occur purely by improving sleep?" (*See* "An Interview with Orphan Medical about Xyrem" paragraph 16, ROXGHB004251 (emphasis added)).
the "cataplexy" is "daytime" cataplexy	"An Interview with Orphan Medical about Xyrem" teaches treatment of "daytime" cataplexy by teaching overall treatment of cataplexy: "Persons with narcolepsy, especially those who experience cataplexy, are anxiously awaiting the decision by the Food and Drug Administration (FDA) on the approval of Xyrem as a treatment for the symptoms of narcolepsy, A decision is expected later this spring, as the Xyrem New Drug Application has been given Priority Review Status." (*See* "An Interview with Orphan Medical about Xyrem" paragraph 1, ROXGHB004250). How Does Xyrem Work? TalkAboutSleep: Originally Xyrem was expected to be a drug for the control of cataplexy for people who have Narcolepsy. We know from personal experiences that it can also help alleviate Excessive Daytime Sleepiness (EDS). Does Orphan Medical know exactly how Xyrem alleviates cataplexy? Is it a chemical effect or does it occur purely by improving sleep?" (*See* "An Interview with Orphan Medical about Xyrem" paragraph 16, ROXGHB004251). Moreover, "An Interview with Orphan Medical about Xyrem" indicates that sodium oxybate provides "improve[d] daytime functioning":

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	"Orphan Medical, William Houghton, MD, COO: The ultimate mechanism of action is not known. Many of the biochemical changes in the brain have been identified in terms of modulation of levels of important chemicals and neurotransmitter functions in the brain. As well, primary effects of improved sleep architecture occur that may contribute to why Xyrem reaches its optimal results after 8 to 12 weeks. It stands to reason that maintained changes in sleep contribute to ***improve daytime functioning***, but further research into the science of narcolepsy is required." (*See* "An Interview with Orphan Medical about Xyrem" paragraph 17; emphasis added, ROXGHB004251).
the drug is "sodium oxybate"	In the 10/18/06 OA and the Examiner's Answer the Examiner found "the drug is GHB" disclosed by "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause a) receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed sodium oxybate and from any and all medical doctors allowed to prescribe sodium oxybate, the prescriptions containing information relating to the patient, sodium oxybate, and various credentials of the medical doctor who is prescribing the sodium oxybate;	
"all" prescriptions are received and contain information relating to the "patient," the drug, and "various credentials" of the doctor	In the Examiner's Answer, the Examiner found that Moradi, Lilly and Ukens disclosed "receiving ***all*** prescription requests at the exclusive central pharmacy from a medical doctor containing ***information identifying a patient, the sensitive drug, and various credentials of the doctor.***" *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3,

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"all prescriptions" are "only" received, "all prescriptions" are "for any and all patients being prescribed" the drug, and "from any and all medical doctors allowed to prescribe" the drug, and the various credentials are of the medical doctor "who is prescribing" the drug	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving all prescription requests at the exclusive central pharmacy ***from*** a medical ***doctor*** containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Ukens describes "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)) and indicates that such specialty medications are "prescribed" (*see* Ukens p. 3, para. 1, ROXGHB004315). Thus, Ukens teaches receiving only at the one pharmacy all prescriptions for any and all patients being prescribed the specialty medication and from any and all doctors allowed to prescribe it. In the Examiner's Answer the Examiner found that Moradi disclosed various doctor credentials. *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303. Such various doctor credentials, in view of the one pharmacy of Ukens, correspond to the medical doctor who is prescribing the specialty medication.
receipt is into an "exclusive central computer system"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving all prescription requests at the ***exclusive central*** pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Further, Moradi paragraph [0022] states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). Further, Lilly paragraph [0051] states: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)). Either the Moradi or Lilly computer would, in the context of the exclusive central pharmacy of Ukens, constitute an ***exclusive central*** computer. One skilled in the art at the time would have been motivated to modify "An Interview with Orphan Medical about Xyrem" in view of Moradi or Lilly to include the exclusive central pharmacy of Ukens in light of Ukens' teaching to "limit access to dangerous drugs (page 3, paragraph 5 of Ukens)." *See* the 10/18/06 OA and Examiner's Answer.

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
(clause b) requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion, such that all prescriptions for sodium oxybate are processed for authorization only using the exclusive central computer system and the exclusive computer database;	
"requiring entering" of "the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion"	In the 6/19/06 OA, the 10/18/06 OA and the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations." *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). (*See* claim 1 clause b, *supra*). The previously discussed exclusive central computer system of Lilly (or Moradi) is associated with the exclusive central database of Lilly when viewed in the context of Ukens' exclusive central pharmacy. *See* clause a, *supra*.
"all" prescriptions for the drug are processed "only" using the "exclusive central computer system" and the "exclusive computer database"	Borsand discusses storing ***all*** pharmaceutical-related information -- including prescription information -- ***only once*** and in a ***single*** database 62 and, thus, discloses an ***exclusive computer database***. Database 62 is the only location where processing can access the all pharmaceutical-related information, thus, ***all prescriptions*** are processed ***only*** using the exclusive computer database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention,

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	all pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). Moreover, at least Fig. 3 at ROXGHB004112 of Borsand indicates the pharmaceutical-related information stored in single database 62 includes pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, patient information, and provider information. At least Fig. 3 at ROXGHB004112 and paragraph [0043] at ROXGHB004127 of Borsand disclose exclusive computer database 62 to be ***associated with single computer 26*** of Borsand. *See also* Borsand paragraph [0031] stating: "The computer 26 can be a ***single centralized*** computer or server, a single network, a series of interconnected networks, a series of devices capable of accessing the Internet or World Wide Web including an application server, or any other configuration which supports the ability of different entities to communicate with one another." (*See* Borsand paragraph [0031], ROXGHB004125-26 (emphasis added)).

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
processing is "for authorization"	Lilly discloses: "For instance, if a pharmacist is checking on a prescriptive medication ***prior to dispensing*** the prescriptive medication, a red flag as indicated at 140 may be issued if the prescription presents a problem, e.g., is a conflicting type of drug (contraindicated prescriptive medication) or perhaps a similar type of drug which in combination with a previous prescriptive medication might be harmful to the consumer. Red flags may be issued as a result of automatic or manual operation. ***System 100*** and/or the pharmacist and/or the doctor ***may require or suggest declining or approving the prescriptive medication***, and otherwise add notes, comments, and flags, as desired." (*See* Lilly paragraph [0070], ROXGHB004263 (emphasis added)). A person of ordinary skill in the art would be motivated to combine the single exclusive database of Borsand with one or more of Moradi and Lilly in view of Ukens and "An Interview with Orphan Medical about Xyrem" because these references relate to storing pharmaceutical related information using a computer. (See 6/19/06 OA, Examiner's Answer and Borsand paragraph [0043], ROXGHB004127).
(clause c) controlling the distribution of sodium oxybate using the exclusive central computer system that tracks all prescriptions of sodium oxybate and analyzes for the potential abuse, misuse, or diversion by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of sodium oxybate from periodic reports generated by the exclusive central computer system based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, sodium oxybate as the drug prescribed, and credentials of	

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
the doctor; and	
"controlling the distribution" of the drug	In the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed "***only mailing*** the drug to the patient ***if*** no potential abuse is found …" *See* Moradi, paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." Moreover, as noted above in connection with the preamble, *supra*, in the 10/18/06 OA and the Examiner's Answer the Examiner found "the drug is GHB" disclosed by "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"controlling the distribution" of the drug uses the "exclusive central computer system"	As noted above in connection with clause a, *supra*, a computer of Moradi or Lilly would, in the context of the exclusive central pharmacy of Ukens, constitute an exclusive central computer. Additionally, as discussed above, Borsand also discloses an exclusive central computer (*see* clause b, *supra*).
the exclusive central computer system "tracks all prescriptions" of the drug	As noted, Lilly or Moradi in the context of Ukens, or Borsand alone, provide an exclusive central computer. Lilly discloses at least via paragraphs [0009], [0050], and [0054] that such exclusive central computer tracks prescriptions: "The industry has widely recognized a need for better efficiencies, but without notable success in many areas, including prescription abuse. For instance, the Healthcare Information Portability and Accountability Act (HIPAA) mandates making the exchange of information more ubiquitous, secure, and efficient but does not provide a solution with respect to ***prescription tracking*** and abuse." (*See* Lilly paragraph [0009], ROXGHB004256 (emphasis added)). "In accord with the method of the present invention, a secure, private, independent, network-based, centralized method operable for ***tracking*** and managing ***prescriptive medication information*** in aggregate is provided which allows electronic querying and real-time notification of patients' prescriptive

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	medication history at the time of prescriptive medication creation." (*See* Lilly paragraph [0050], ROXGHB004260 (emphasis added)). "All of these entities can have immediate access to potential medication abuse by ***identification*** of needless ***prescription duplications***, potential drug interactions, and multi-source interstate prescriptive medication abuse." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)). As noted above in connection with the preamble, *supra*, in the 10/18/06 OA and the Examiner's Answer the Examiner found "the drug is GHB" disclosed by "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
the exclusive central computer system "analyzes for the potential abuse, misuse, or diversion" of the drug	As noted above in connection with clause b, *supra*, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer database associated with the ***exclusive central*** pharmacy for ***analysis of potential abuse*** situations." (Emphasis added). *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." Moreover, as noted above in connection with the preamble, *supra*, in the 10/18/06 OA and the Examiner's Answer the Examiner found "the drug is GHB" disclosed by "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). It would have been obvious to perform the potential abuse analysis in an exclusive central computer system in Ukens' exclusive central pharmacy in view of the teachings of Moradi, Lilly or Borsand.

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
determining of patterns of "potential prescription abuse, misuse, or diversion" of the drug from "periodic reports"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found that Lilly disclosed "generating ***periodic reports*** via the exclusive computer database to evaluate ***potential diversion*** patterns." *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263. The BPAI Decision affirmed the Examiner's finding that Lilly disclosed an "exclusive computer database" and held all other findings of the Examiner accepted as being undisputed" (see clause b, *supra*). Moreover, Lilly discloses abuse of the drug: "All of these entities can have immediate access to potential medication abuse by identification of needless prescription duplications, potential drug interactions, and multi-source interstate ***prescriptive medication abuse.***" (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)).
"the exclusive central computer system" generates the periodic reports	In the 6/19/06 OA and the Examiner's Answer, the Examiner found Lilly disclosed "generating periodic reports via the ***exclusive computer database*** to evaluate potential diversion patterns." *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263 (emphasis added). The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (*See* clause b, *supra*). As noted in connection with clause b, *supra*, the computer of Moradi or Lilly, in the context of the exclusive central pharmacy of Ukens, or the computer of Borsand alone, would correspond to an ***exclusive central*** computer system.
the determined potential diversion patterns are "current and anticipated" diversion patterns	Lilly teaches: "Pharmacies 26 may check to personally verify the drug usage of each

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	purchaser to ***immediately*** detect problems related to ***abuse, fraud, and misuse*** of medications … Pharmacists are constantly challenged to circumvent duplication, ***abuse, fraud, and misuse*** of these medications while providing a cost effective medication delivery system. In the present health system the wide availability of pharmaceuticals from different pharmacies raises the risks of negative drug interactions and its associated destructive medical outcome. ***Pharmaceutical information control organization 12 can flag these issues*** in real time, thereby ***completely preventing*** or at least minimizing their occurrences." (*See* Lilly paragraph [0057], ROXGHB004261 (emphasis added)). "FIG. 2 discloses a presently preferred pharmaceutical information flow diagram 100 for a method of operation of ***pharmaceutical information control organization 12*** in accord with the present invention. A plurality of entities, networks, organizations may be utilized in accord with the present invention including doctors 102. Pharmacies 104 include pharmacies that are affiliated with each other as well as pharmacies that are unaffiliated with each other. Other entities include hospitals 106, pharmaceutical companies 108, insurance companies 110 (which may include health or life insurance companies or any other type of insurance companies), government agencies 112, health care informatics companies 114, health researchers 116, managed care organizations 118, and other healthcare providers 120 … In a preferred embodiment, the present invention provides that ***data storage 122*** is able to access the ***databases*** of the above-listed entities and/or other member organizations as needed and/or store the corresponding pharmaceutical data in data storage 122 which is external to each entity's database(s) … Data storage 122 preferably has the ability to allow the software schemas to be changed without disruption of system 100." (See Lilly paragraph [0061], ROXGHB004262 (emphasis added)). *See also* Lilly, paragraph [0058], ROXGHB004261.

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
the periodic reports are generated based on prescription data from a medical doctor	Lilly teaches: "All of these entities can have immediate access to potential medication abuse by ***identification*** of needless ***prescription duplications***, potential drug interactions, and multi-source interstate prescriptive medication abuse." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)). "The display may be made by a patient identifier, patient name, date, drug name, ***doctor prescribing the medication***, pharmacy, geography (city, state, zip code), by phone number, and/or by aberrant use flag." (*See* Lilly paragraph [0069], ROXGHB004263 (emphasis added)).
the prescription data contain "information identifying" the "patient," "sodium oxybate as the drug prescribed," and "credentials of the doctor"	As noted in connection with clause a, *supra*, in the Examiner's Answer, the Examiner found that Moradi, Lilly and Ukens disclose "receiving all ***prescription*** requests at the exclusive central pharmacy from a medical doctor containing information identifying a ***patient***, the sensitive ***drug***, and various ***credentials of the doctor***." (Emphasis added). *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). Moreover, as noted above in connection with the preamble, *supra*, in the 10/18/06 OA and the Examiner's Answer the Examiner found "the drug is GHB" disclosed by "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause d) selecting multiple controls for distribution using said exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license,	

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe sodium oxybate by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash	

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
payments, and for inappropriate questions; "selecting" of "multiple controls," the controls "selected from the group consisting of … identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; … [and] obtaining patient information …"	Moradi discloses selecting the control of identifying the physician's name, license, and Drug Enforcement Agency registration information at least by indicating the control is required. Moradi discloses selecting the control of obtaining patient information at least by disclosing registering the patient where it is determined that the patient is not registered. "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by the automated prescription delivery system 100. The data includes the physician's ***name***, address, practice information, ***DEA number, license numbers***, e-mail, phone number and web site address." (*See* Moradi paragraph [0118], ROXGHB004304; emphasis added). "This module allows a physician to complete an online registration form for access to the automated prescription delivery system 100. This module is part of the Registration module 218. This module is used for entering ***required*** physician registration information and does not grant access to the system. Access is granted the system by another module controlled and used by authorized employees. Entries and editing of registration data is tracked via an automated audit trail." (*See* Moradi paragraph [0109], ROXGHB004303 (emphasis added)). "If the POC System 104 is in a physician's office, the processing begins instead with the physician completing, at step 302, the prescription form. The prescription can be a new prescription or a prescription for a refill. The processing next ***determines, at step 304, whether the patient is registered*** with the automated prescription delivery system 100. The exemplary embodiment of the present invention has the patient tell the physician's office staff whether or not he or she is registered with the system. If the patient is registered, the processing continues with the POCP operator's entering the patient's identification into the POC system 104. The patient's identification in the

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	exemplary embodiment of the present invention is the patient's name and social security number. Alternative embodiments utilize different patient identification techniques, including identification cards encoded with printed or magnetically readable identification numbers or data, biometric identification devices and other identification devices that provide a unique identification of the patient. ***If the patient is not registered***, the processing continues instead by ***registering the patient***, at step 308, by collecting patient information and entering it into the POC system 104 and relaying it to the CSS 102. The patient information can be entered either manually into the POC system 104 or by scanning a form that is completed by the patient, as is described below." (*See* Moradi paragraph [0035], ROXGHB004297-98 (emphasis added)). Further, in the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all prescription requests at the exclusive central pharmacy from a medical doctor containing ***information identifying a patient***, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). The Examiner's Answer found that Moradi, Lilly, and Ukens disclosed receipt of prescription requests containing patient information. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260.
the selected "controls" are "for distribution"	Moradi discloses the control of identifying the physician's name, license, and Drug Enforcement Agency registration information to be for distribution at least by indicating it to be for the automated prescription ***delivery*** system:

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	"This module allows a physician to complete an online registration form for access to the automated prescription ***delivery*** system 100. This module is part of the Registration module 218. This module is used for entering required physician registration information and does not grant access to the system. Access is granted the system by another module controlled and used by authorized employees. Entries and editing of registration data is tracked via an automated audit trail." (*See* Moradi paragraph [0109], ROXGHB004303 (emphasis added)). Moradi discloses the control of obtaining patient information to be for distribution at least by indicating the corresponding registration of steps 304, 306, and 308 to precede step 322 of "giv[ing] ordered medicine to delivery person for hand ***delivery.***" (*See* Moradi Fig. 3 at ROXGHB004285 (emphasis added)): "After the patient is either registered or has his or her identification entered into the system, the POCP operator then scans and submits, at step 310, the prescription for the patient. The prescription is scanned by an image scanner that is part of the POC system 104." (*See* Moradi paragraph [0036], ROXGHB004298). "The PMS system assigns the prescription a prescription number, and the pharmacist enters that prescription number and the number of refills into the PODP 216, which then communicates that data back to the CSS 102 with an identification of the prescription. The pharmacist then gives, at step 322, the ordered medicine and a copy of the prescription image to a prescription deliverer, which is a delivery person in the exemplary embodiments, for delivery to the patient." (*See* Moradi paragraph [0043], ROXGHB004299). Moreover, the 6/19/06 OA and the Examiner's Answer each found Moradi disclosed "a method of ***distributing a drug under exclusive control of an exclusive central pharmacy***." *See* Moradi, paragraphs [0003] at ROXGHB004295 and [0024] at ROXGHB004296. Also, the 10/18/06 OA and

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	the Examiner's Answer each found Ukens disclosed an exclusive central pharmacy at page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision held the Examiner's findings "accepted as being undisputed." The noted ***controls*** would, in the context of such distribution under ***control*** of such exclusive central pharmacy, be ***controls*** for distribution .
selecting control for the "distribution" uses the "exclusive central computer system"	As noted above in connection with clause b, *supra*, Moradi or Lilly in the context of Ukens, or Borsand alone, provides an exclusive central computer, and Moradi discloses that the exclusive central computer controls distribution of the drug (*see* clause c, *supra*).
(clause e) authorizing the filling, using the exclusive central computer system, of a prescription for sodium oxybate that has been subjected to said multiple controls and has been approved for shipment to the patient;	
"the exclusive central computer system" authorizes the filling of the prescription	As noted above in connection with clause b, *supra*, Lilly or Moradi in the context of Ukens, or Borsand alone, provides an exclusive central computer. Lilly discloses that such exclusive central computer authorizes the filling of a prescription for a prescriptive medication: "For instance, if a pharmacist is checking on a prescriptive medication ***prior to dispensing*** the prescriptive medication, a red flag as indicated at 140 may be issued if the prescription presents a problem, e.g., is a conflicting type of drug (contraindicated prescriptive medication) or perhaps a similar type of drug which in combination with a previous prescriptive medication might be harmful to the consumer. Red flags may be issued as a result of automatic or manual operation. ***System 100*** and/or the pharmacist and/or the doctor may require or suggest ***declining or approving*** the ***prescriptive medication***, and otherwise add notes, comments, and flags, as desired."

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	(*See* Lilly paragraph [0070], ROXGHB004263 (emphasis added)).
the drug has been subjected to said multiple controls	At least paragraphs [0118] and [0035] of Moradi teach subjecting the drug to the multiple controls of identifying the physician's name, license, and Drug Enforcement Agency registration information; and obtaining patient information: "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by the automated prescription delivery system 100. The data includes the physician's ***name***, address, practice information, ***DEA number, license numbers***, e-mail, phone number and web site address." (*See* Moradi paragraph [0118], ROXGHB004304 (emphasis added)). "If the POC System 104 is in a physician's office, the processing begins instead with the physician completing, at step 302, the prescription form. The prescription can be a new prescription or a prescription for a refill. The processing next determines, at step 304, whether the patient is registered with the automated prescription delivery system 100. The exemplary embodiment of the present invention has the patient tell the physician's office staff whether or not he or she is registered with the system. If the patient is registered, the processing continues with the POCP operator's entering the patient's identification into the POC system 104. The patient's identification in the exemplary embodiment of the present invention is the patient's name and social security number. Alternative embodiments utilize different patient identification techniques, including identification cards encoded with printed or magnetically readable identification numbers or data, biometric identification devices and other identification devices that provide a unique identification of the patient. If the patient is not registered, the processing continues instead by ***registering the patient***, at step 308, by collecting patient information and entering it into the POC system 104 and relaying it to the CSS 102. The patient information can be entered either manually into the POC system 104 or by scanning a form that is completed by the patient, as is described below."

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	(*See* Moradi paragraph [0035], ROXGHB004297-98 (emphasis added)).
the drug "has been approved for shipment to the patient"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed "only ***mailing*** the drug to the patient ***if no potential abuse is found*** …" *See* Moradi, paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause f) noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and	
noting that there is patient potential for "abuse, misuse, or diversion"	Borsand discloses checking, both before and after prescription 28 is filled, for evidence of fraud or misuse by provider 30 and ***evidence of fraud or misuse by patient 22***. Borsand further explains that prescription 28 is canceled where such fraud or misuse is detected: "The system 20 facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 even after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the cancellation or modification of a prescription 28. The modification of a prescription at 132 is an event triggered process. There must be an event that triggers the modification or cancellation of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a provider 30, pharmacist 40, or ***patient 22.***" (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)).
noting is "based on <u>one or</u> more of the analysis	As is discussed in connection with clause b, *supra*, in the 6/19/06 OA, the

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
of the potential abuse, misuse, or diversion" of the drug and the periodic reports	10/18/06 OA and the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy ***for analysis of potential abuse*** situations." (Emphasis added). *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. Further, the BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly, and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause g) delivering the sodium oxybate to the patient in order to treat the patient with the sodium oxybate. the drug is delivered to the patient "in order to treat the patient" with the drug	 As is discussed in connection with clause e, *supra*, in the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed the feature of "only ***mailing the drug to the patient*** if no potential abuse is found …" (Emphasis added). *See* Moradi paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Borsand teaches: "The process of creating a prescription 28, canceling a prescription 28, or accessing patient-related information is done in the context of a particular patient 22. Patient 22 attributes include the patient's medical ***condition to be remedied or mitigated with a pharmaceutical 32***; medical history such as allergies and medication history; eligibility and other coverage information relating to payor's 60 health plan; refill behavior; and any other characteristic or attribute that could affect the desirability of a pharmaceutical 32 or

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	prescription 28 with respect to a particular patient 22." (*See* Borsand paragraph [0053], at ROXGHB004128 (emphasis added)).
4. The method of claim 3, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.	
the "control" of "communicating prescriptions from a physician to the exclusive central computer system"	
that the "prescriptions" are communicated "from a physician"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all ***prescription requests*** at the exclusive central pharmacy ***from*** a ***medical doctor*** containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
communication is to the "exclusive central	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
computer system"	disclosed "receiving all prescription requests at the ***exclusive central*** pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Further, Moradi paragraph [0022] states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)).a *See also* Lilly paragraph [0051], ROXGHB004260. Either the Moradi or Lilly computer would, in the context of the exclusive central pharmacy of Ukens, constitute an ***exclusive central*** computer.
that the "control" of "communicating prescriptions from a physician to the exclusive central computer system" is selected	In the Examiner's Answer, the Examiner found Moradi, Lilly, and Ukens disclosed prescription request receipt. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260.
the "control" of "identifying the physician's name, license, and DEA (Drug Enforcement	Moradi discloses: "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
Agency) registration information"	the automated prescription delivery system 100. The data includes the physician's ***name, address, practice information, DEA number, license numbers***, e-mail, phone number and web site address." (*See* Moradi paragraph [0118] at ROXGHB004304; emphasis added).
selecting the "control" of "identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information"	Moradi describes: "This module allows a physician to complete an online registration form for access to the automated prescription delivery system 100. This module is part of the Registration module 218. This module is used for entering required physician registration information and does not grant access to the system." (*See* Moradi paragraph [0109] at ROXGHB004303).
the "control" of "verifying the prescription"	Moradi discloses: "Once the POD system 106 at the pharmacy has received the image of the prescription from the CSS 102, the data are decrypted and the processing continues by using a software based data authenticator to ***verify***, at step 316, ***the prescription*** at the POD system 106. This step includes operating a software based digital signature authenticator to ensure that a valid digital signature has been added to the prescription. This step also requires that if the prescription is not refillable, or if the prescription is refillable but the number of digital signatures added to the prescription image is equal to or greater than the number of refills, the operator is to check the order for cancellations of previous submissions to the POD 106." (*See* Moradi paragraph [0042] ROXGHB004299 (emphasis added)).
selecting the "control" of "verifying the prescription"	Moradi discloses verifying the prescription with a computer or processing device, which can correspond to PODP software 212 of that computer or processing device. (*See* Moradi paragraph [0028] at ROXGHB004297).
the "control" of "obtaining patient	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all prescription requests at the exclusive central pharmacy

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
information"	from a medical doctor containing ***information identifying a patient***, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." *See also* Moradi paragraph [0035] at ROXGHB004297-98.
selecting the "control" of "obtaining patient information"	In the Examiner's Answer, the Examiner found Moradi, Lilly, and Ukens disclosed prescription request receipt. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260. *See also* Moradi paragraph [0031] at ROXGHB004297.
the "control" of "verifying patient registry information"	Williams discloses a computer readable storage medium in which patients are registered, and where a patient's prescription for a drug is filled only after the medium has been consulted to assure that the patient is registered in the storage medium: "[a]s noted above, the drug delivery methods described herein also preferably involve the ***registration of the patient*** in a ***computer readable storage medium***. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein" (*See* Williams col. 5 ln. 61 - col. 6 ln. 3, ROXGHB004324 (emphasis added)). "[t]he present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	side effect known or suspected of being caused by the drug, of the type in which ***prescriptions for the drug are filled only after*** a computer readable storage medium has been ***consulted*** to ***assure*** that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the ***patient is registered*** in the medium and approved to receive the drug" (*See* Williams col. 2 ln. 49-60, ROXGHB004322 (emphasis added)). "[t]he ***registration*** into one or more computer readable storage media of the prescriber, pharmacy and ***patient***, according to the methods described herein, provide a means to ***monitor and authorize distribution of contraindicated drugs***, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, ***the drugs generally may not be prescribed and/or dispensed to patients who are not registered*** in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and ***registered*** in the computer readable media, the ***patient*** generally ***may not receive the prescription for the drug***. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted" (*See* Williams col. 13 ln. 19-41, ROXGHB004328 (emphasis added)). *See also* Moradi paragraph [0161] at ROXGHB004305.
selecting the control of "verifying patient registry information"	As noted above in connection with clauses a and b of claim 3, *supra*, Moradi, Borsand, and Lilly each disclose a computer processor. Additionally, as Williams discusses a "computer readable storage medium" (*see* Williams col. 2 ln. 50-60) a

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	computer processor is described or suggested. Williams discloses consulting a ***computer readable storage medium*** to assure that the patient is registered: "[t]he present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a ***computer readable storage medium*** has been ***consulted*** to ***assure*** that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the ***patient*** is ***registered in the medium*** and approved to receive the drug" (*see* Williams col. 2 ln. 49-60, ROXGHB004322 (emphasis added)). "[s]imilarly, the ***drugs*** generally ***may not be prescribed and/or dispensed to patients*** who are ***not registered in*** a ***computer readable storage medium***" (*see* Williams col. 13 ln. 31-33, ROXGHB004328 (emphasis added)). *See also* Moradi paragraphs [0031] at ROXGHB004297 and [0161] at ROXGHB004305. One skilled in the art would have been motivated to modify one or more of Lilly, "An Interview with Orphan Medical about Xyrem," Moradi, Ukens, and Borsand to have selected the control of verifying patient registry information as taught by Williams at least to ensure patient compliance with taking a drug (*see* Williams col. 3 ln. 56-59, ROXGHB004323).
the "control" of "providing comprehensive education information to the patient"	Williams discloses: "Preferably the patient is provided ***full*** disclosure of ***all*** the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such ***counsel*** may be provided verbally, as well as in ***written form***. In preferred embodiments, the prescriber provides the patient with ***literature materials*** on the drug for which a prescription is contemplated, such ***as product information, educational brochures, continuing education monographs, and the like***." (*See* Williams col. 8 ln. 57 - col. 9 ln. 2, ROXGHB004325 (emphasis added)). *See also* the 6/19/06 OA and the Examiner's Answer wherein the Examiner found that Califano disclosed "confirming with the patient that educational material has been read prior to shipping the drug." *See*, Califano, paragraph [0084] at ROXGHB004163. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "providing comprehensive education information to the patient"	As noted above in connection with clauses a and b of claim 3, *supra*, Moradi, Borsand, and Lilly each disclose a computer processor. As noted above in connection with the control of "verifying patient registry information," Williams discloses a computer processor. *See also* Califano's paragraph [0052] disclosure of a computer processor at ROXGHB004159. Williams discloses the control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, ***in order to become registered in the computer readable storage medium, the prescriber may be required*** to comply with various aspects of the methods described herein including, for example, ***providing patient education and counseling***, and the like, as described in detail below."

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	(*See* Williams col. 4 ln. 43-54, ROXGHB004323 (emphasis added)). *See also* Califano paragraphs [0052] at ROXGHB004159 and [0084] at ROXGHB004163. One skilled in the art at the time would have been motivated to modify one or more of Lilly, "An Interview with Orphan Medical about Xyrem," Moradi, Ukens, Borsand, and Williams to have selected with a computer processor the control of providing comprehensive education information to the patient as taught by Califano at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "ensure that the patient knows about the risks and dangers associated with the drug (para. 43 of Califano)."
the "control" of "verifying the patient has received and/or reviewed the educational materials"	Williams discloses: "In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the ***patient to fill out an informed consent form*** which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. ***Verification that the patient*** has given his/her informed consent may also be registered in the computer readable storage medium … By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. ***In the informed consent form***, the patient preferably ***agrees to*** comply with the risk avoidance measures provided, and to ***behave in a manner which is consistent with the prescriber's counsel***." (*See* Williams col. 10 ln. 23-46, ROXGHB004326 (emphasis added)). *See also* the 6/19/06 OA and the Examiner's Answer wherein the Examiner found paragraph [0084] of Califano disclosed "confirming with the patient that

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	educational material has been read prior to shipping the drug." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "verifying the patient has received and/or reviewed the educational materials"	Williams discloses: "In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. ***Verification*** that the patient has given his/her informed consent may also be registered ***in the computer readable storage medium.***" *(See* Williams col. 10 ln. 23-32, ROXGHB004326 (emphasis added)). *See also* Califano paragraphs [0084] and [0086] at ROXGHB004163-64.
the "control" of "requiring rewriting of the prescription periodically"	Williams discloses: "In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will ***not be permitted*** without a ***renewal prescription from the prescriber***, as discussed in detail below." (*See* Williams col. 12 ln. 3-8 at ROXGHB004327 (emphasis added)). *See also* Moradi paragraph [0098] at ROXGHB004302.
selecting the control of "requiring rewriting of the prescription periodically"	Williams discloses this control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, ***in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein*** including, for example, providing patient education and counseling, and the like, as described in detail below." (*See* Williams col. 4 ln. 43-54 at ROXGHB004323 (emphasis added)).

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
(preamble) 5. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a claim limitation, then it is disclosed in the prior art as follows:
a "therapeutic" method for "treating" a "patient" with a drug	Moradi discloses at least at paragraph [0008] delivering a drug to a patient: "Briefly, according to an aspect of the present invention, a method and system for delivering prescription medicine provides method of performing prescription medicine delivery that issues a prescription to a person and also accepts an identification of that person … The method then delivers the medicine that was prescribed by the prescription to the person." (*See* Moradi paragraph [0008], ROXGHB004295). Borsand also discloses that a drug is "effective for therapeutic purposes": "The process of creating a prescription 28, canceling a prescription 28, or accessing patient-related information is done in the context of a particular patient 22. ***Patient 22*** attributes include the patient's medical ***condition to be remedied or mitigated with a pharmaceutical*** 32;." (*See* Borsand paragraph [0053], ROXGHB004128 (emphasis added)).
the drug is a "prescription" drug	Moradi discloses at least in paragraph [0003]: "This invention generally relates to the field of ***prescription*** delivery systems, and more particularly to the field of automated prescription handling." (*See* Moradi paragraph [0003], ROXGHB004295 (emphasis added)).
the drug "has potential to be abused, misused, or diverted"	Moradi discloses at least in paragraph [0006]: "Delivery of prescription medication by mail is also possible … This technique is also open to ***fraud*** since the individual patient typically does not personally

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	present his or her prescription to the pharmacy. This technique can also lead to ***an improper person receiving the prescription***, such as when a child that is living with the recipient retrieves mail that contains the mailed prescription." (*See* Moradi paragraph [0006], ROXGHB004295 (emphasis added)).
(clause a) receiving, only into an exclusive computer database in a computer system, from any and all medical doctors allowed to prescribe the prescription drug and any and all patients being prescribed the prescription drug, all prescriptions for the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is prescribing the prescription drug;	
"all" prescriptions are received and contain information identifying the "patient," the "drug," and "various credentials" of the doctor	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving ***all*** prescription requests at the exclusive central pharmacy from a medical doctor ***containing information identifying a patient, the sensitive drug, and various credentials of the doctor.***" *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"all prescriptions" are "only" received, "all prescriptions" are from "any and all medical doctors allowed to prescribe" and "any and all patients being prescribed" the drug, and the various credentials are of the medical doctor	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving all prescription requests at the exclusive central pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
"who is prescribing" the drug	[0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Ukens describes "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)) and indicates that such specialty medications are "prescribed" (*see* Ukens p. 3, para. 1, ROXGHB004315). Thus, Ukens teaches receiving only at the one pharmacy all prescriptions from any and all doctors allowed to prescribe the specialty medication and from any and all patients being prescribed the specialty medication In the Examiner's Answer the Examiner found Moradi disclosed various doctor credentials. *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303. Such various doctor credentials, in view of the one pharmacy of Ukens, correspond to the medical doctor who is prescribing the specialty medication.
receipt of the prescriptions is into an "exclusive computer database"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all prescription requests ***at the exclusive central pharmacy*** from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	In the 6/19/06 OA, the 10/18/06 OA and the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into ***an exclusive computer database associated with the exclusive central pharmacy*** for analysis of potential abuse situations." *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Such an exclusive computer database associated with the exclusive central pharmacy would, in the context of such receipt at the exclusive central pharmacy, correspond to an exclusive computer database at which such receipt occurs. Moreover, Borsand discusses ***storing all*** pharmaceutical-related information -- including prescription information -- ***only once*** and in a ***single*** database 62 and, thus, discloses an ***exclusive computer database*** and that prescriptions are ***received at*** that exclusive computer database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
that the exclusive computer database is "in a computer system"	appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). At least Fig. 3 of Borsand at ROXGHB004112 indicates the pharmaceutical-related information stored in single database 62 includes pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, patient information, and provider information. Moradi discloses the employment of "one or more computers or processing devices": "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). Lilly discloses employment of a computer: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)). Borsand discuses the employment of "computer 26": "The ***computer 26*** can be a single centralized computer or server, a single network, a series of interconnected networks, a series of devices capable of accessing the Internet or World Wide Web including an application server, or any other configuration which supports the ability of different entities to communicate with one another."

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	(*See* Borsand paragraph [0031], ROXGHB004125-26 (emphasis added)). That an exclusive ***computer*** database be "in a computer system" is well-known. Moreover, at least Fig. 3 at ROXGHB004112 and paragraph [0043] at ROXGHB004127 of Borsand disclose exclusive computer database 62 to be ***associated with computer 26*** of Borsand. One skilled in the art at the time would have been motivated to modify Moradi or Lilly to include the exclusive central pharmacy of Ukens in light of Ukens' teaching to "limit access to dangerous drugs (page 3, paragraph 5 of Ukens)." *See* the 10/18/06 OA and Examiner's Answer.
(clause b) requiring entering of the information into the exclusive computer database for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only via the exclusive central computer system and the exclusive computer database; "requiring entering" of "the information into the exclusive computer database for analysis of potential <u>abuse</u>, misuse, <u>or</u> diversion"	In the 6/19/06 OA, the 10/18/06 OA and the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations." *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). (*See* claim 1 clause b, *supra*).

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
the "abuse" is "of" the drug	Lilly discloses: "All of these entities can have immediate access to potential medication abuse by identification of needless prescription duplications, potential drug interactions, and multi-source interstate ***prescriptive medication abuse.***" (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)).
"all" prescriptions for the drug are processed "only" via the "exclusive computer database"	Borsand discusses storing ***all*** pharmaceutical-related information -- including prescription information -- ***only once*** and in a ***single*** database 62 and, thus, discloses an ***exclusive computer database***. Database 62 is the only location where processing can access the all pharmaceutical-related information, thus, ***all prescriptions*** are processed ***only*** using the exclusive computer database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). Moreover, at least Fig. 3 of Borsand at ROXGHB004112 indicates the pharmaceutical-related information stored in single database 62 includes pharmacy benefit managers ("PBM") information, payor information,

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
processing is "for authorization"	***prescription*** information, patient information, and provider information. Lilly discloses: "For instance, if a pharmacist is checking on a prescriptive medication ***prior to dispensing*** the prescriptive medication, a red flag as indicated at 140 may be issued if the prescription presents a problem, e.g., is a conflicting type of drug (contraindicated prescriptive medication) or perhaps a similar type of drug which in combination with a previous prescriptive medication might be harmful to the consumer. Red flags may be issued as a result of automatic or manual operation. ***System 100*** and/or the pharmacist and/or the doctor ***may require or suggest declining or approving the prescriptive medication***, and otherwise add notes, comments, and flags, as desired." (*See* Lilly paragraph [0070], ROXGHB004263 (emphasis added)). A person of ordinary skill in the art would be motivated to combine the single exclusive database of Borsand with one or more of Moradi and Lilly in view of Ukens because these references relate to storing pharmaceutical related information using a computer. (*See* 6/19/06 OA, Examiner's Answer and Borsand paragraph [0043], ROXGHB004127).
(clause c) controlling the distribution of said prescription drug with the computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the computer system based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor;	

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
and	
"controlling the distribution" of the drug	In the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed "***only mailing*** the drug to the patient ***if*** no potential abuse is found …" *See* Moradi, paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"controlling the distribution" of the drug is with the computer system	At least paragraph [0022] of Moradi states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet" (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). *See also* Lilly paragraphs [0051], ROXGHB004260 and Borsand paragraph [0031], ROXGHB004125-26.
the computer system "tracks all prescriptions" of the drug	As noted, Lilly, Moradi, and Borsand each provide a computer system. Lilly discloses at least via paragraphs [0009], [0050], and [0054] that such computer tracks prescriptions: "The industry has widely recognized a need for better efficiencies, but without notable success in many areas, including prescription abuse. For instance, the Healthcare Information Portability and Accountability Act (HIPAA) mandates making the exchange of information more ubiquitous, secure, and efficient but does not provide a solution with respect to ***prescription tracking*** and abuse." (*See* Lilly paragraph [0009], ROXGHB004256 (emphasis added)). "In accord with the method of the present invention, a secure, private, independent, network-based, centralized method operable for ***tracking*** and

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	managing ***prescriptive medication information*** in aggregate is provided which allows electronic querying and real-time notification of patients' prescriptive medication history at the time of prescriptive medication creation." (*See* Lilly paragraph [0050], ROXGHB004260 (emphasis added)). "All of these entities can have immediate access to potential medication abuse by ***identification*** of needless ***prescription duplications***, potential drug interactions, and multi-source interstate prescriptive medication abuse." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)).
the computer system "analyzes for the potential abuse, misuse, or diversion" of the drug	In the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for ***analysis of potential abuse*** situations." (Emphasis added). *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). (*See* claim 1 clause b, *supra*). It would have been obvious to perform the potential abuse analysis in a computer system in Ukens' exclusive central pharmacy in view of the teachings of Moradi, Lilly or Borsand.
determining of patterns of "potential prescription abuse, misuse, or diversion" of the drug from "periodic reports"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found Lilly disclosed "generating ***periodic reports*** via the exclusive computer database to evaluate ***potential diversion*** patterns." *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263.

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	The BPAI Decision affirmed the Examiner's finding that Lilly disclosed an "exclusive computer database" and held all other findings of the Examiner to be "accepted as being undisputed" (BPAI Decision, p. 6, ROXGHB004756) (see claim 1 clause a, *supra*). Moreover, as additionally noted in connection with clause b, *supra*, Lilly discloses abuse of the drug.
"the computer system" generates the periodic reports	In the 6/19/06 OA and the Examiner's Answer, the Examiner found Lilly disclosed "generating periodic reports via the exclusive computer database to evaluate potential diversion patterns." *See* Lilly, paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263. The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). (*See* claim 1 clause b, *supra*). As noted above in connection with clause a, *supra*, that an exclusive computer database be in a computer is well-known. Also, as noted above in connection with claim 1, clause b, *supra*, at least Fig. 3 at ROXGHB004112 and paragraph [0043] at ROXGHB004127 of Borsand disclose exclusive computer database 62 to be associated with computer 26 of Borsand.
the determined potential diversion patterns are "current and anticipated" diversion patterns	Lilly teaches: "Pharmacies 26 may check to personally verify the drug usage of each purchaser to ***immediately*** detect problems related to ***abuse, fraud, and misuse*** of medications … Pharmacists are constantly challenged to circumvent duplication, ***abuse, fraud, and misuse*** of these medications while providing a cost effective medication delivery system. In the present health system the wide availability of pharmaceuticals from different pharmacies raises the risks of negative drug interactions and its associated destructive medical outcome. ***Pharmaceutical information control organization 12 can flag these issues*** in real time, thereby ***completely preventing*** or at least minimizing their

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	occurrences." (*See* Lilly paragraph [0057], ROXGHB004261 (emphasis added)). "FIG. 2 discloses a presently preferred pharmaceutical information flow diagram 100 for a method of operation of ***pharmaceutical information control organization 12*** in accord with the present invention. A plurality of entities, networks, organizations may be utilized in accord with the present invention including doctors 102. Pharmacies 104 include pharmacies that are affiliated with each other as well as pharmacies that are unaffiliated with each other. Other entities include hospitals 106, pharmaceutical companies 108, insurance companies 110 (which may include health or life insurance companies or any other type of insurance companies), government agencies 112, health care informatics companies 114, health researchers 116, managed care organizations 118, and other healthcare providers 120 … In a preferred embodiment, the present invention provides that ***data storage 122*** is able to access the ***databases*** of the above-listed entities and/or other member organizations as needed and/or store the corresponding pharmaceutical data in data storage 122 which is external to each entity's database(s) … Data storage 122 preferably has the ability to allow the software schemas to be changed without disruption of system 100." (See Lilly paragraph [0061], ROXGHB004262 (emphasis added)). *See also* Lilly, paragraph [0058], ROXGHB004261.
the periodic reports are generated based on prescription data from a medical doctor	Lilly teaches: "All of these entities can have immediate access to potential medication abuse by ***identification*** of needless ***prescription duplications***, potential drug interactions, and multi-source interstate prescriptive medication abuse." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)). "The display may be made by a patient identifier, patient name, date, drug name, ***doctor prescribing the medication***, pharmacy, geography (city, state,

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
the prescription data contain "information identifying the patient, the drug prescribed, and credentials of the doctor"	zip code), by phone number, and/or by aberrant use flag." (*See* Lilly paragraph [0069], ROXGHB004263 (emphasis added)). As noted in connection with clause a, *supra*, in the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving all ***prescription*** requests at the exclusive central pharmacy from a medical doctor containing information identifying a ***patient***, the sensitive ***drug***, and various ***credentials of the doctor***." (Emphasis added). *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added).
(clause d) selecting multiple controls for distribution of the prescription drug, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive computer database; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or	

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing the release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;	
"selecting" of "multiple controls," the controls "selected from the group consisting of … identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; … [and] obtaining patient information …"	Moradi discloses selecting the control of identifying the physician's name, license, and Drug Enforcement Agency registration information at least by indicating the control is required. Moradi discloses selecting the control of obtaining patient information at least by disclosing registering the patient where it is determined that the patient is not registered. "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by the automated prescription delivery system 100. The data includes the physician's ***name***, address, practice information, ***DEA number, license numbers***, e-mail, phone number and web site address."

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	(*See* Moradi paragraph [0118], ROXGHB004304; emphasis added). "This module allows a physician to complete an online registration form for access to the automated prescription delivery system 100. This module is part of the Registration module 218. This module is used for entering ***required*** physician registration information and does not grant access to the system. Access is granted the system by another module controlled and used by authorized employees. Entries and editing of registration data is tracked via an automated audit trail." (*See* Moradi paragraph [0109], ROXGHB004303 (emphasis added)). "If the POC System 104 is in a physician's office, the processing begins instead with the physician completing, at step 302, the prescription form. The prescription can be a new prescription or a prescription for a refill. The processing next ***determines, at step 304, whether the patient is registered*** with the automated prescription delivery system 100. The exemplary embodiment of the present invention has the patient tell the physician's office staff whether or not he or she is registered with the system. If the patient is registered, the processing continues with the POCP operator's entering the patient's identification into the POC system 104. The patient's identification in the exemplary embodiment of the present invention is the patient's name and social security number. Alternative embodiments utilize different patient identification techniques, including identification cards encoded with printed or magnetically readable identification numbers or data, biometric identification devices and other identification devices that provide a unique identification of the patient. ***If the patient is not registered***, the processing continues instead by ***registering the patient***, at step 308, by collecting patient information and entering it into the POC system 104 and relaying it to the CSS 102. The patient information can be entered either manually into the POC system 104 or by scanning a form that is completed by the patient, as is described below." (*See* Moradi paragraph [0035], ROXGHB004297-98 (emphasis added)).

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	Further, in the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all prescription requests at the exclusive central pharmacy from a medical doctor containing ***information identifying a patient***, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). The Examiner's Answer found that Moradi, Lilly, and Ukens disclosed receipt of prescription requests containing patient information. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260.
the selected "controls" are "for distribution" of the drug	Moradi discloses the control of identifying the physician's name, license, and Drug Enforcement Agency registration information to be for distribution of the drug at least by indicating it to be for the automated ***prescription delivery*** system: "This module allows a physician to complete an online registration form for access to the automated prescription ***delivery*** system 100. This module is part of the Registration module 218. This module is used for entering required physician registration information and does not grant access to the system. Access is granted the system by another module controlled and used by authorized employees. Entries and editing of registration data is tracked via an automated audit trail." (*See* Moradi paragraph [0109], ROXGHB004303 (emphasis added)). Moradi discloses the control of obtaining patient information to be for distribution of the drug at least by indicating the corresponding registration of steps 304, 306, and 308 to precede step 322 of "giv[ing] ordered ***medicine*** to delivery person for

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	hand ***delivery.***" (*See* Moradi Fig. 3 at ROXGHB004285 (emphasis added)): "After the patient is either registered or has his or her identification entered into the system, the POCP operator then scans and submits, at step 310, the prescription for the patient. The prescription is scanned by an image scanner that is part of the POC system 104." (*See* Moradi paragraph [0036], ROXGHB004298). "The PMS system assigns the prescription a prescription number, and the pharmacist enters that prescription number and the number of refills into the PODP 216, which then communicates that data back to the CSS 102 with an identification of the prescription. The pharmacist then gives, at step 322, the ordered medicine and a copy of the prescription image to a prescription deliverer, which is a delivery person in the exemplary embodiments, for delivery to the patient." (*See* Moradi paragraph [0043], ROXGHB004299). Moreover, the 6/19/06 OA and the Examiner's Answer each found Moradi disclosed "a method of ***distributing a drug under exclusive control of an exclusive central pharmacy***." *See* Moradi, paragraphs [0003] at ROXGHB004295 and [0024] at ROXGHB004296. Also, the 10/18/06 OA and the Examiner's Answer each found Ukens disclosed an exclusive central pharmacy at page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). The noted ***controls*** would, in the context of such distribution under ***control*** of such exclusive central pharmacy, be ***controls*** for distribution .
(clause e) authorizing the filling, using the exclusive computer database, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for	

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
shipment to the patient;	
"the exclusive computer database" authorizes the filling of the prescription	The BPAI Decision affirmed the Examiner's finding that Lilly disclosed an "exclusive computer database." (*See* claim 1 clause b, *supra*). Lilly discloses employing such exclusive computer database in the filling of a prescription for a prescriptive medication: "For instance, if a pharmacist is checking on a prescriptive medication ***prior to dispensing*** the prescriptive medication, a red flag as indicated at 140 may be issued if the prescription presents a problem, e.g., is a conflicting type of drug (contraindicated prescriptive medication) or perhaps a similar type of drug which in combination with a previous prescriptive medication might be harmful to the consumer. Red flags may be issued as a result of automatic or manual operation. ***System 100*** and/or the pharmacist and/or the doctor may require or suggest ***declining or approving*** the ***prescriptive medication***, and otherwise add notes, comments, and flags, as desired." (*See* Lilly paragraph [0070], ROXGHB004263 (emphasis added)).
the drug has been subjected to said multiple controls	At least paragraphs [0118] and [0035] of Moradi teach subjecting the drug to the multiple controls of identifying the physician's name, license, and Drug Enforcement Agency registration information; and obtaining patient information: "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by the automated prescription delivery system 100. The data includes the physician's ***name***, address, practice information, ***DEA number, license numbers***, e-mail, phone number and web site address." (*See* Moradi paragraph [0118], ROXGHB004304 (emphasis added)). "If the POC System 104 is in a physician's office, the processing begins instead with the physician completing, at step 302, the prescription form. The prescription can be a new prescription or a prescription for a refill. The processing next determines, at step 304, whether the patient is registered with

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	the automated prescription delivery system 100. The exemplary embodiment of the present invention has the patient tell the physician's office staff whether or not he or she is registered with the system. If the patient is registered, the processing continues with the POCP operator's entering the patient's identification into the POC system 104. The patient's identification in the exemplary embodiment of the present invention is the patient's name and social security number. Alternative embodiments utilize different patient identification techniques, including identification cards encoded with printed or magnetically readable identification numbers or data, biometric identification devices and other identification devices that provide a unique identification of the patient. If the patient is not registered, the processing continues instead by ***registering the patient***, at step 308, by collecting patient information and entering it into the POC system 104 and relaying it to the CSS 102. The patient information can be entered either manually into the POC system 104 or by scanning a form that is completed by the patient, as is described below." (*See* Moradi paragraph [0035], ROXGHB004297-98 (emphasis added)).
the drug "has been approved for shipment to the patient"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed "only ***mailing*** the drug to the patient ***if no potential abuse is found*** …" *See* Moradi, paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause f) noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and	
noting that there is patient potential for "abuse,	Borsand discloses checking, both before and after prescription 28 is filled, for

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
misuse, or diversion"	evidence of fraud or misuse by provider 30 and ***evidence of fraud or misuse by patient 22***. Borsand further explains that prescription 28 is canceled where such fraud or misuse is detected: "The system 20 facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 even after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the cancellation or modification of a prescription 28. The modification of a prescription at 132 is an event triggered process. There must be an event that triggers the modification or cancellation of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a provider 30, pharmacist 40, or ***patient 22.***" (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)).
noting is "based on <u>one or</u> more of the analysis of the potential abuse, misuse, or diversion" of the drug and the periodic reports	As is discussed in connection with clause a, *supra*, in the 6/19/06 OA, the 10/18/06 OA and the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy ***for analysis of potential abuse*** situations." (Emphasis added). *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. Further, the BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly, and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). (*See* claim 1 clause b, *supra*).
(clause g) delivering the prescription drug to the patient in order to treat the patient with the prescription drug.	

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
the drug is delivered to the patient "in order to treat the patient" with the drug	In the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed the feature of "only ***mailing the drug to the patient*** if no potential abuse is found …" (Emphasis added). *See* Moradi paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Borsand teaches: "The process of creating a prescription 28, canceling a prescription 28, or accessing patient-related information is done in the context of a particular patient 22. Patient 22 attributes include the patient's medical ***condition to be remedied or mitigated with a pharmaceutical 32***; medical history such as allergies and medication history; eligibility and other coverage information relating to payor's 60 health plan; refill behavior; and any other characteristic or attribute that could affect the desirability of a pharmaceutical 32 or prescription 28 with respect to a particular patient 22." (*See* Borsand paragraph [0053], at ROXGHB004128 (emphasis added)).
6. The method of claim 5, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive computer database; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.	

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
the "control" of "communicating prescriptions from a physician to the exclusive computer database"	
that the "prescriptions" are communicated "from a physician"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all ***prescription requests*** at the exclusive central pharmacy ***from*** a ***medical doctor*** containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
communication is to the "exclusive computer database"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclose "***receiving*** all prescription requests ***at the exclusive central pharmacy*** from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). (*See* claim 1 clause a, *supra*). In the 6/19/06 OA, the 10/18/06 OA dated and the Examiner's Answer, the Examiner found that "requiring entering of the information into ***an exclusive computer database associated with the exclusive central pharmacy*** for analysis of potential abuse situations" is disclosed among paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61,

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	[0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263 of Lilly and page 3, paragraphs 3-5 at ROXGHB004315 of Ukens (emphasis added). The BPAI Decision affirmed the Examiner's finding of an "exclusive computer database" in Lilly, and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). (*See* claim 1 clause b, *supra*). Such an exclusive computer database associated with the exclusive central pharmacy would, in the context of such communication to that exclusive central pharmacy, correspond to an exclusive computer database to which such communication is directed. Moreover, Borsand discusses ***storing all*** pharmaceutical-related information -- including prescription information -- ***only once*** and in a ***single*** database 62 and thus discloses an exclusive computer database and that prescriptions are ***communicated to*** that exclusive computer database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties."

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	(*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). At least Fig. 3 of Borsand at ROXGHB004112 indicates the pharmaceutical-related information stored in single database 62 includes pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, ***patient*** information, and ***provider*** information. Borsand further indicates that such a provider can be a ***physician***: "A ***health care provider 30*** includes any person capable of issuing a pharmaceutical 32 prescription 28 such as a ***physician***, physician's assistant, or veterinarian." (*See* Borsand paragraph [0030], ROXGHB004125 (emphasis added)).
that the "control" of "communicating prescriptions from a physician to the exclusive computer database" is selected	In the Examiner's Answer, the Examiner found Moradi, Lilly, and Ukens disclosed prescription request receipt. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. (*See* Moradi paragraph [0022], ROXGHB004296 and Lilly paragraph [0051], ROXGHB004260). Moreover, Borsand discloses the communication to the exclusive computer database of Borsand to be performed via computer 26 of Borsand. (*See* Borsand paragraph [0031], ROXGHB004125-26).
the "control" of "identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information"	Moradi discloses: "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by the automated prescription delivery system 100. The data includes the physician's ***name, address, practice information, DEA number, license numbers***, e-mail, phone number and web site address." (*See* Moradi paragraph [0118], ROXGHB004304; emphasis added).
selecting the "control" of "identifying the physician's name, license, and DEA (Drug	Moradi describes:

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
Enforcement Agency) registration information"	"This module allows a physician to complete an online registration form for access to the automated prescription delivery system 100. This module is part of the Registration module 218. This module is used for entering required physician registration information and does not grant access to the system." (*See* Moradi paragraph [0109], ROXGHB004303 (emphasis added)).
the "control" of "verifying the prescription"	Moradi discloses: "Once the POD system 106 at the pharmacy has received the image of the prescription from the CSS 102, the data are decrypted and the processing continues by using a software based data authenticator to ***verify***, at step 316, ***the prescription*** at the POD system 106. This step includes operating a software based digital signature authenticator to ensure that a valid digital signature has been added to the prescription. This step also requires that if the prescription is not refillable, or if the prescription is refillable but the number of digital signatures added to the prescription image is equal to or greater than the number of refills, the operator is to check the order for cancellations of previous submissions to the POD 106." (*See* Moradi paragraph [0042] ROXGHB004299 (emphasis added)).
selecting the "control" of "verifying the prescription"	Moradi discloses verifying the prescription with a computer or processing device, which can correspond to PODP software 212 of that computer or processing device. (*See* Moradi paragraph [0028] at ROXGHB004297).
the "control" of "obtaining patient information"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all prescription requests at the exclusive central pharmacy from a medical doctor containing ***information identifying a patient***, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). *See also* Moradi paragraph [0035] at ROXGHB004297-98.
selecting the "control" of "obtaining patient information"	In the Examiner's Answer, the Examiner found Moradi, Lilly, and Ukens disclosed prescription request receipt. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260. *See also* Moradi paragraph [0031] at ROXGHB004297.
the "control" of "verifying patient registry information"	Moradi discloses server-side validation of patient registration data: "If the 'Continue' button was pressed, the processing continues by determining, at step 814, if there is successful client-side validation. If there is not successful client side validation, the processing displays, at step 816, an error message that indicates which field is in error. If there is successful client side validation, the ***patient registration data*** is securely sent, at step 812, to the CSS 102. The exemplary embodiment uses an HTTPS communications link to securely communicate all data. Once the CSS 102 receives the data, the ***processing determines***, at step 818, ***if there is successful server-side validation***. If there is not successful server-side validation, the processing displays, at step 820, an error message indicating which data field is in error." (*See* Moradi paragraph [0161] at ROXGHB004305 (emphasis added)).
selecting the control of "verifying patient registry information"	Moradi discloses effecting server-side validation with a computer or processing device that can correspond to registration software component 218 of such computer or processing device. (*See* Moradi paragraphs [0031] at ROXGHB004297 and [0161] at ROXGHB004305).
the "control" of "providing comprehensive education information to the patient"	Williams discloses: "Preferably the patient is provided ***full*** disclosure of ***all*** the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such ***counsel*** may be provided verbally, as well as in ***written form***. In preferred embodiments, the prescriber provides the patient with ***literature materials*** on the drug for which a prescription is contemplated, such ***as product information, educational brochures, continuing education monographs, and the like***." (*See* Williams col. 8 ln. 57 - col. 9 ln. 2, ROXGHB004325 (emphasis added)) *See also* the 6/19/06 OA and the Examiner's Answer wherein the Examiner found Califano disclosed "confirming with the patient that educational material has been read prior to shipping the drug." *See*, Califano, paragraph [0084] at ROXGHB004163. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "providing comprehensive education information to the patient"	As noted above in connection with clause a of claim 5, *supra*, Moradi, Borsand, and Lilly each disclose a computer processor. Additionally, Williams' discussion of a "computer readable storage medium" (*see* Williams col. 2 ln. 50-60 at ROXGHB004322) describes or suggests a computer processor. *See also* Califano's paragraph [0052] disclosure of a computer processor at ROXGHB004159. Williams discloses the control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, ***in order to become registered in the computer readable storage medium, the prescriber may be required*** to comply with various aspects of the methods described herein including, for example, ***providing***

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	patient education and counseling, and the like, as described in detail below." (*See* Williams col. 4 ln. 43-54, ROXGHB004323 (emphasis added)). *See also* Califano paragraphs [0052] at ROXGHB004159 and [0084] at ROXGHB004163. One skilled in the art at the time would have been motivated to modify one or more of Lilly, Moradi, Ukens, and Borsand to have selected with a computer processor the control of providing comprehensive education information to the patient as taught by Williams at least to ensure patient compliance with taking a drug. (*See* Williams col. 3 ln. 56-59, ROXGHB004323). One skilled in the art at the time would have been motivated to modify one or more of Lilly, Moradi, Ukens, Borsand, and Williams to have selected with a computer processor the control of providing comprehensive education information to the patient as taught by Califano at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "ensure that the patient knows about the risks and dangers associated with the drug (para. 43 of Califano)."
the "control" of "verifying the patient has received and/or reviewed the educational materials"	Williams discloses: "In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the ***patient to fill out an informed consent form*** which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. ***Verification that the patient*** has given his/her informed consent may also be registered in the computer readable storage medium … By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. ***In the***

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	informed consent form, the patient preferably ***agrees to*** comply with the risk avoidance measures provided, and to ***behave in a manner which is consistent with the prescriber's counsel***." (*See* Williams col. 10 ln. 23-46, ROXGHB004326 (emphasis added)). *See also* the 6/19/06 OA and the Examiner's Answer wherein the Examiner found that paragraph [0084] of Califano disclosed "confirming with the patient that educational material has been read prior to shipping the drug." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "verifying the patient has received and/or reviewed the educational materials"	Williams discloses: "In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. ***Verification*** that the patient has given his/her informed consent may also be registered ***in the computer readable storage medium.***" *(See* Williams col. 10 ln. 23-32, ROXGHB004326 (emphasis added)). *See also* Califano paragraphs [0084] and [0086] at ROXGHB004163-64.
the "control" of "requiring rewriting of the prescription periodically"	Williams discloses: "In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will ***not be permitted*** without a ***renewal prescription from the prescriber***, as discussed in detail below." (*See* Williams col. 12 ln. 3-8 at ROXGHB004327 (emphasis added)).

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
selecting the control of "requiring rewriting of the prescription periodically"	*See also* Moradi paragraph [0098] at ROXGHB004302. Williams discloses this control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, ***in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein*** including, for example, providing patient education and counseling, and the like, as described in detail below." (*See* Williams col. 4 ln. 43-54 at ROXGHB004323 (emphasis added)).

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
(preamble) 7. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a claim limitation, then it is disclosed in the prior art as follows:
a "therapeutic" method for "treating" a "patient" with a drug	Moradi discloses at least at paragraph [0008] delivering a drug to a patient: "Briefly, according to an aspect of the present invention, a method and system for delivering prescription medicine provides method of performing prescription medicine delivery that issues a prescription to a person and also accepts an identification of that person … The method then delivers the medicine that was prescribed by the prescription to the person." (*See* Moradi paragraph [0008], ROXGHB004295). Borsand also discloses that a drug is "effective for therapeutic purposes": "The process of creating a prescription 28, canceling a prescription 28, or accessing patient-related information is done in the context of a particular patient 22. ***Patient 22*** attributes include the patient's medical ***condition to be remedied or mitigated with a pharmaceutical*** 32;." (*See* Borsand paragraph [0053], ROXGHB004128 (emphasis added)).
the drug is a "prescription" drug	Moradi discloses at least in paragraph [0003]: "This invention generally relates to the field of ***prescription*** delivery systems, and more particularly to the field of automated prescription handling." (*See* Moradi paragraph [0003], ROXGHB004295 (emphasis added)).
the drug "has potential to be abused, misused, or diverted"	Moradi discloses at least in paragraph [0006]: "Delivery of prescription medication by mail is also possible … This technique is also open to ***fraud*** since the individual patient typically does not personally

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	present his or her prescription to the pharmacy. This technique can also lead to ***an improper person receiving the prescription***, such as when a child that is living with the recipient retrieves mail that contains the mailed prescription." (*See* Moradi paragraph [0006], ROXGHB004295 (emphasis added)).
(clause a) receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and any and all medical doctors allowed to prescribed the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is writing the prescription;	
"all" prescriptions are received and contain information identifying the "patient," the "drug," and "various credentials" of the doctor	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving ***all*** prescription requests at the exclusive central pharmacy from a medical doctor ***containing information identifying a patient, the sensitive drug, and various credentials of the doctor.***" *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"all prescriptions" are "only" received, "all prescriptions" are for "any and all patients being prescribed" the drug, and "any and all medical doctors allowed to prescribe" the drug, and the various credentials are of the medical doctor "who is writing the prescription"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving all prescription requests at the exclusive central pharmacy ***from*** a medical ***doctor*** containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
receipt is into an "exclusive central computer system"	ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Ukens describes "restricting distribution of a specialty medication to only ***one*** pharmacy" (*see* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)) and indicates that such specialty medications are "prescribed" (*see* Ukens p. 3, para. 1, ROXGHB004315). Thus, Ukens teaches receiving only at the one pharmacy all prescriptions for any and all patients being prescribed the specialty medication and from any and all doctors allowed to prescribe it. In the Examiner's Answer the Examiner found Moradi disclosed various doctor credentials. *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303. Such various doctor credentials, in view of the one pharmacy of Ukens, correspond to the medical doctor who is prescribing the specialty medication. In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving all prescription requests at the ***exclusive central*** pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Further, Moradi paragraph [0022] states: "The system 100 includes several processing components that are located at

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). Further, Lilly paragraph [0051] states: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)). Either the Moradi or Lilly computer would, in the context of the exclusive central pharmacy of Ukens, constitute an ***exclusive central*** computer. One skilled in the art at the time would have been motivated to modify Moradi or Lilly to include the exclusive central pharmacy of Ukens in light of Ukens' teaching to "limit access to dangerous drugs (page 3, paragraph 5 of Ukens)." *See* the 10/18/06 OA and Examiner's Answer.
(clause b) requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database; "requiring entering" of "the information into an exclusive computer database associated with	In the 6/19/06 OA, the 10/18/06 OA and the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
the exclusive central computer system for analysis of potential abuse, misuse, or diversion"	exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations." *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (*See* claim 1 clause b, *supra*). The previously discussed exclusive central computer system of Lilly (or Moradi) is associated with the exclusive central database of Lilly when viewed in the context of Ukens' exclusive central pharmacy. *See* clause a, *supra*.
the "abuse" is "of" the drug	Lilly discloses: "All of these entities can have immediate access to potential medication abuse by identification of needless prescription duplications, potential drug interactions, and multi-source interstate ***prescriptive medication abuse.***" (*See* Lilly paragraph [0054], ROXGHB004260-61; emphasis added).
"all" prescriptions for the drug are processed "only" using the "exclusive central computer system" and the "exclusive computer database"	Borsand discusses storing ***all*** pharmaceutical-related information -- including prescription information -- ***only once*** and in a ***single*** database 62 and, thus, discloses an ***exclusive computer database***. Database 62 is the only location where processing can access the all pharmaceutical-related information, thus, ***all prescriptions*** are processed ***only*** using the exclusive computer database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)).

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	"As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). Moreover, at least Fig. 3 of Borsand at ROXGHB004112 indicates the pharmaceutical-related information stored in single database 62 includes pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, patient information, and provider information. At least Fig. 3 at ROXGHB004112 and paragraph [0043] at ROXGHB004127 of Borsand disclose exclusive computer database 62 to be ***associated with single computer 26*** of Borsand. *See also* Borsand paragraph [0031] stating: "The computer 26 can be a ***single centralized*** computer or server, a single network, a series of interconnected networks, a series of devices capable of accessing the Internet or World Wide Web including an application server, or any other configuration which supports the ability of different entities to communicate with one another." (*See* Borsand paragraph [0031], ROXGHB004125-26 (emphasis added)).
processing is "for authorization"	Lilly discloses: "For instance, if a pharmacist is checking on a prescriptive medication ***prior to dispensing*** the prescriptive medication, a red flag as indicated at 140 may be issued if the prescription presents a problem, e.g., is a conflicting type of drug

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	(contraindicated prescriptive medication) or perhaps a similar type of drug which in combination with a previous prescriptive medication might be harmful to the consumer. Red flags may be issued as a result of automatic or manual operation. ***System 100*** and/or the pharmacist and/or the doctor ***may require or suggest declining or approving the prescriptive medication***, and otherwise add notes, comments, and flags, as desired." (*See* Lilly paragraph [0070], ROXGHB004263 (emphasis added)). A person of ordinary skill in the art would be motivated to combine the single exclusive database of Borsand with one or more of Moradi and Lilly in view of Ukens because these references relate to storing pharmaceutical related information using a computer. (*See* 6/19/06 OA, Examiner's Answer and Borsand paragraph [0043], ROXGHB004127).
(clause c) controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and "<u>controlling</u> the <u>distribution</u>" of the drug	In the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed "***only mailing*** the drug to the patient ***if*** no potential abuse is found …" *See* Moradi, paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285 (emphasis

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"controlling the distribution" of the drug uses the "exclusive central computer system"	As noted above in connection with clause a, *supra*, a computer of Moradi or Lilly would, in the context of the exclusive central pharmacy of Ukens, constitute an exclusive central computer. Additionally, as discussed above, Borsand also discloses an exclusive central computer (*see* clause b, *supra*).
the exclusive central computer system "tracks all prescriptions" of the drug	As noted, Lilly or Moradi in the context of Ukens, or Borsand alone, provide an exclusive central computer. Lilly discloses at least via paragraphs [0009], [0050], and [0054] that such exclusive central computer tracks prescriptions: "The industry has widely recognized a need for better efficiencies, but without notable success in many areas, including prescription abuse. For instance, the Healthcare Information Portability and Accountability Act (HIPAA) mandates making the exchange of information more ubiquitous, secure, and efficient but does not provide a solution with respect to ***prescription tracking*** and abuse." (*See* Lilly paragraph [0009], ROXGHB004256 (emphasis added)). "In accord with the method of the present invention, a secure, private, independent, network-based, centralized method operable for ***tracking*** and managing ***prescriptive medication information*** in aggregate is provided which allows electronic querying and real-time notification of patients' prescriptive medication history at the time of prescriptive medication creation." (*See* Lilly paragraph [0050], ROXGHB004260 (emphasis added)). "All of these entities can have immediate access to potential medication abuse by ***identification*** of needless ***prescription duplications***, potential drug interactions, and multi-source interstate prescriptive medication abuse." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)).
the exclusive central computer system "analyzes for the potential abuse, misuse, or	As noted above in connection with clause b, *supra*, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
diversion" of the drug	database associated with the ***exclusive central*** pharmacy for ***analysis of potential abuse*** situations." (Emphasis added). *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). It would have been obvious to perform the potential abuse analysis in an exclusive central computer system in Ukens' exclusive central pharmacy in view of the teachings of Moradi, Lilly or Borsand.
determining of patterns of "potential prescription abuse, misuse, or diversion" of the drug from "periodic reports"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found Lilly disclosed "generating ***periodic reports*** via the exclusive computer database to evaluate ***potential diversion*** patterns." *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263 (emphasis added). The BPAI Decision affirmed the Examiner's finding that Lilly disclosed an "exclusive computer database" and held all other findings of the Examiner to be "accepted as being undisputed" (BPAI Decision, p. 6, ROXGHB004756) (see clause b, *supra*). Moreover, as additionally noted in connection with clause b, *supra*, Lilly discloses abuse of the drug.
the "exclusive computer database" generates the periodic reports	In the 6/19/06 OA and the Examiner's Answer, the Examiner found Lilly disclosed "generating periodic reports via the ***exclusive computer database*** to evaluate potential diversion patterns." *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263 (emphasis added). The BPAI Decision affirmed the Examiner's

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). (*See* clause b, *supra*).
"the exclusive central computer system" generates the periodic reports	As noted in connection with clause b, *supra*, the computer of Moradi or Lilly, in the context of the exclusive central pharmacy of Ukens, or the computer of Borsand alone, would correspond to an ***exclusive central*** computer system.
the determined potential diversion patterns are "current and anticipated" diversion patterns	Lilly teaches: "Pharmacies 26 may check to personally verify the drug usage of each purchaser to ***immediately*** detect problems related to ***abuse, fraud, and misuse*** of medications … Pharmacists are constantly challenged to circumvent duplication, ***abuse, fraud, and misuse*** of these medications while providing a cost effective medication delivery system. In the present health system the wide availability of pharmaceuticals from different pharmacies raises the risks of negative drug interactions and its associated destructive medical outcome. ***Pharmaceutical information control organization 12 can flag these issues*** in real time, thereby ***completely preventing*** or at least minimizing their occurrences." (*See* Lilly paragraph [0057], ROXGHB004261 (emphasis added)). "FIG. 2 discloses a presently preferred pharmaceutical information flow diagram 100 for a method of operation of ***pharmaceutical information control organization 12*** in accord with the present invention. A plurality of entities, networks, organizations may be utilized in accord with the present invention including doctors 102. Pharmacies 104 include pharmacies that are affiliated with each other as well as pharmacies that are unaffiliated with each other. Other entities include hospitals 106, pharmaceutical companies 108, insurance companies 110 (which may include health or life insurance companies or any other type of insurance companies), government agencies 112, health care informatics companies 114, health researchers 116, managed care organizations 118, and other healthcare providers 120 … In a preferred

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	embodiment, the present invention provides that ***data storage 122*** is able to access the ***databases*** of the above-listed entities and/or other member organizations as needed and/or store the corresponding pharmaceutical data in data storage 122 which is external to each entity's database(s) … Data storage 122 preferably has the ability to allow the software schemas to be changed without disruption of system 100." (See Lilly paragraph [0061], ROXGHB004262 (emphasis added)). *See also* Lilly, paragraph [0058], ROXGHB004261.
the periodic reports are generated based on prescription data from a medical doctor	Lilly teaches: "All of these entities can have immediate access to potential medication abuse by ***identification*** of needless ***prescription duplications***, potential drug interactions, and multi-source interstate prescriptive medication abuse." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)). "The display may be made by a patient identifier, patient name, date, drug name, ***doctor prescribing the medication***, pharmacy, geography (city, state, zip code), by phone number, and/or by aberrant use flag." (*See* Lilly paragraph [0069], ROXGHB004263 (emphasis added)).
the prescription data contain "information identifying the patient, the drug prescribed, and credentials of the doctor"	As noted in connection with clause a, *supra*, in the Examiner's Answer, the Examiner found that Moradi, Lilly and Ukens disclose "receiving all ***prescription*** requests at the exclusive central pharmacy from a medical doctor containing information identifying a ***patient***, the sensitive ***drug***, and various ***credentials of the doctor***." (Emphasis added). *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added).

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
(clause d) selecting multiple controls for distribution using the exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances	

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;	
"selecting" of "multiple controls," the controls "selected from the group consisting of … identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; … [and] obtaining patient information …"	Moradi discloses selecting the control of identifying the physician's name, license, and Drug Enforcement Agency registration information at least by indicating the control is required. Moradi discloses selecting the control of obtaining patient information at least by disclosing registering the patient where it is determined that the patient is not registered. "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by the automated prescription delivery system 100. The data includes the physician's ***name***, address, practice information, ***DEA number, license numbers***, e-mail, phone number and web site address." (*See* Moradi paragraph [0118], ROXGHB004304; emphasis added). "This module allows a physician to complete an online registration form for access to the automated prescription delivery system 100. This module is part of the Registration module 218. This module is used for entering ***required*** physician registration information and does not grant access to the system. Access is granted the system by another module controlled and used by authorized employees. Entries and editing of registration data is tracked via an automated audit trail." (*See* Moradi paragraph [0109], ROXGHB004303 (emphasis added)). "If the POC System 104 is in a physician's office, the processing begins instead with the physician completing, at step 302, the prescription form. The prescription can be a new prescription or a prescription for a refill. The

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	processing next ***determines, at step 304, whether the patient is registered*** with the automated prescription delivery system 100. The exemplary embodiment of the present invention has the patient tell the physician's office staff whether or not he or she is registered with the system. If the patient is registered, the processing continues with the POCP operator's entering the patient's identification into the POC system 104. The patient's identification in the exemplary embodiment of the present invention is the patient's name and social security number. Alternative embodiments utilize different patient identification techniques, including identification cards encoded with printed or magnetically readable identification numbers or data, biometric identification devices and other identification devices that provide a unique identification of the patient. ***If the patient is not registered***, the processing continues instead by ***registering the patient***, at step 308, by collecting patient information and entering it into the POC system 104 and relaying it to the CSS 102. The patient information can be entered either manually into the POC system 104 or by scanning a form that is completed by the patient, as is described below." (*See* Moradi paragraph [0035], ROXGHB004297-98 (emphasis added)). Further, in the Examiner's Answer, the Examiner found that Moradi, Lilly and Ukens disclosed "***receiving*** all prescription requests at the exclusive central pharmacy from a medical doctor containing ***information identifying a patient***, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). The Examiner's Answer found that Moradi, Lilly, and Ukens disclosed receipt of prescription requests containing patient information. Such prescription request receipt is in view of Moradi and Lilly performed with a

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260.
the selected "controls" are "for distribution"	Moradi discloses the control of identifying the physician's name, license, and Drug Enforcement Agency registration information to be for distribution at least by indicating it to be for the automated prescription ***delivery*** system: "This module allows a physician to complete an online registration form for access to the automated prescription ***delivery*** system 100. This module is part of the Registration module 218. This module is used for entering required physician registration information and does not grant access to the system. Access is granted the system by another module controlled and used by authorized employees. Entries and editing of registration data is tracked via an automated audit trail." (*See* Moradi paragraph [0109], ROXGHB004303 (emphasis added)). Moradi discloses the control of obtaining patient information to be for distribution at least by indicating the corresponding registration of steps 304, 306, and 308 to precede step 322 of "giv[ing] ordered medicine to delivery person for hand ***delivery.***" (*See* Moradi Fig. 3 at ROXGHB004285 (emphasis added)): "After the patient is either registered or has his or her identification entered into the system, the POCP operator then scans and submits, at step 310, the prescription for the patient. The prescription is scanned by an image scanner that is part of the POC system 104." (*See* Moradi paragraph [0036], ROXGHB004298). "The PMS system assigns the prescription a prescription number, and the pharmacist enters that prescription number and the number of refills into the PODP 216, which then communicates that data back to the CSS 102 with an identification of the prescription. The pharmacist then gives, at step 322, the ordered medicine and a copy of the prescription image to a prescription deliverer, which is a delivery person in the exemplary embodiments, for

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	delivery to the patient." (*See* Moradi paragraph [0043], ROXGHB004299). Moreover, the 6/19/06 OA and the Examiner's Answer each found Moradi disclosed "a method of ***distributing a drug under exclusive control of an exclusive central pharmacy***." *See* Moradi, paragraphs [0003] at ROXGHB004295 and [0024] at ROXGHB004296. Also, the 10/18/06 OA and the Examiner's Answer each found Ukens disclosed an exclusive central pharmacy at page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). The noted ***controls*** would, in the context of such distribution under ***control*** of such exclusive central pharmacy, be ***controls*** for distribution .
selecting control for the "distribution" uses the "exclusive central computer system"	As noted above in connection with clause b, *supra*, Moradi or Lilly in the context of Ukens, or Borsand alone, provides an exclusive central computer, and Moradi discloses that the exclusive central computer controls distribution of the drug (*see* clause c, *supra*).
(clause e) authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;	
"the exclusive central computer system" authorizes the filling of the prescription	As noted above in connection with clause b, *supra*, Lilly or Moradi in the context of Ukens, or Borsand alone, provides an exclusive central computer. Lilly discloses that such exclusive central computer authorizes the filling of a prescription for a prescriptive medication: "For instance, if a pharmacist is checking on a prescriptive medication ***prior to dispensing*** the prescriptive medication, a red flag as indicated at 140 may be

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	issued if the prescription presents a problem, e.g., is a conflicting type of drug (contraindicated prescriptive medication) or perhaps a similar type of drug which in combination with a previous prescriptive medication might be harmful to the consumer. Red flags may be issued as a result of automatic or manual operation. ***System 100*** and/or the pharmacist and/or the doctor may require or suggest ***declining or approving*** the ***prescriptive medication***, and otherwise add notes, comments, and flags, as desired." (*See* Lilly paragraph [0070], ROXGHB004263 (emphasis added)).
the drug has been subjected to said multiple controls	At least paragraphs [0118] and [0035] of Moradi teach subjecting the drug to the multiple controls of identifying the physician's name, license, and Drug Enforcement Agency registration information; and obtaining patient information: "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by the automated prescription delivery system 100. The data includes the physician's ***name***, address, practice information, ***DEA number, license numbers***, e-mail, phone number and web site address." (*See* Moradi paragraph [0118], ROXGHB004304 (emphasis added)). "If the POC System 104 is in a physician's office, the processing begins instead with the physician completing, at step 302, the prescription form. The prescription can be a new prescription or a prescription for a refill. The processing next determines, at step 304, whether the patient is registered with the automated prescription delivery system 100. The exemplary embodiment of the present invention has the patient tell the physician's office staff whether or not he or she is registered with the system. If the patient is registered, the processing continues with the POCP operator's entering the patient's identification into the POC system 104. The patient's identification in the exemplary embodiment of the present invention is the patient's name and social security number. Alternative embodiments utilize different patient identification techniques, including identification cards encoded with printed or magnetically readable identification numbers or data, biometric

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	identification devices and other identification devices that provide a unique identification of the patient. If the patient is not registered, the processing continues instead by ***registering the patient***, at step 308, by collecting patient information and entering it into the POC system 104 and relaying it to the CSS 102. The patient information can be entered either manually into the POC system 104 or by scanning a form that is completed by the patient, as is described below." (*See* Moradi paragraph [0035], ROXGHB004297-98 (emphasis added)).
the drug "has been approved for shipment to the patient"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed "only ***mailing*** the drug to the patient ***if no potential abuse is found*** …" *See* Moradi, paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause f) noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and	
noting that there is patient potential for "abuse, misuse, or diversion"	Borsand discloses checking, both before and after prescription 28 is filled, for evidence of fraud or misuse by provider 30 and ***evidence of fraud or misuse by patient 22***. Borsand further explains that prescription 28 is canceled where such fraud or misuse is detected: "The system 20 facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 even after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the cancellation or modification of a prescription 28. The modification of a prescription at 132 is an event triggered process. There must be an event that triggers the modification or cancellation

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	of a prescription 28. The triggering event could be a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse***, or redundancy on the part of a provider 30, pharmacist 40, or ***patient 22.***" (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)).
noting is "based on <u>one or</u> more of the analysis of the potential abuse, misuse, or diversion" of the drug and the periodic reports	As is discussed in connection with clause b, *supra*, in the 6/19/06 OA, the 10/18/06 OA and the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy ***for analysis of potential abuse*** situations." (Emphasis added). *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. Further, the BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly, and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
(clause g) delivering the prescription drug to the patient in order to treat the patient with the prescription drug. the drug is delivered to the patient "in order to treat the patient" with the drug	 As is discussed in connection with clause e, *supra*, in the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed the feature of "only ***mailing the drug to the patient*** if no potential abuse is found …" (Emphasis added). *See* Moradi paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285. The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Borsand teaches:

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	"The process of creating a prescription 28, canceling a prescription 28, or accessing patient-related information is done in the context of a particular patient 22. Patient 22 attributes include the patient's medical ***condition to be remedied or mitigated with a pharmaceutical 32***; medical history such as allergies and medication history; eligibility and other coverage information relating to payor's 60 health plan; refill behavior; and any other characteristic or attribute that could affect the desirability of a pharmaceutical 32 or prescription 28 with respect to a particular patient 22." (*See* Borsand paragraph [0053], at ROXGHB004128 (emphasis added)).
8. The method of claim 7, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically. the "control" of "communicating prescriptions from a physician to the exclusive central computer system" the "prescriptions" are communicated "from a physician"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all ***prescription requests*** at the exclusive central pharmacy ***from*** a ***medical doctor*** containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
communication is to the "exclusive central computer system"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving all prescription requests at the ***exclusive central*** pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Further, Moradi paragraph [0022] states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). *See also* Lilly paragraph [0051], ROXGHB004260. Either the Moradi or Lilly computer would, in the context of the exclusive central pharmacy of Ukens, constitute an ***exclusive central*** computer.
the "control" of "communicating prescriptions from a physician to the	In the Examiner's Answer, the Examiner found Moradi, Lilly, and Ukens disclosed prescription request receipt. Such prescription request receipt is in view

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
exclusive central computer system" is selected	of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260.
the "control" of "identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information"	Moradi discloses: "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by the automated prescription delivery system 100. The data includes the physician's ***name, address, practice information, DEA number, license numbers***, e-mail, phone number and web site address." (*See* Moradi paragraph [0118] at ROXGHB004304; emphasis added).
selecting the "control" of "identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information"	Moradi describes: "This module allows a physician to complete an online registration form for access to the automated prescription delivery system 100. This module is part of the Registration module 218. This module is used for entering required physician registration information and does not grant access to the system." (*See* Moradi paragraph [0109] at ROXGHB004303).
the "control" of "verifying the prescription"	Moradi discloses: "Once the POD system 106 at the pharmacy has received the image of the prescription from the CSS 102, the data are decrypted and the processing continues by using a software based data authenticator to ***verify***, at step 316, ***the prescription*** at the POD system 106. This step includes operating a software based digital signature authenticator to ensure that a valid digital signature has been added to the prescription. This step also requires that if the prescription is not refillable, or if the prescription is refillable but the number of digital signatures added to the prescription image is equal to or greater than the number of refills, the operator is to check the order for cancellations of previous submissions to the POD 106."

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	(*See* Moradi paragraph [0042] ROXGHB004299 (emphasis added)).
selecting the "control" of "verifying the prescription"	Moradi discloses verifying the prescription with a computer or processing device, which can correspond to PODP software 212 of that computer or processing device. (*See* Moradi paragraph [0028] at ROXGHB004297).
the "control" of "obtaining patient information"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all prescription requests at the exclusive central pharmacy from a medical doctor containing ***information identifying a patient***, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). *See also* Moradi paragraph [0035] at ROXGHB004297-98.
selecting the "control" of "obtaining patient information"	In the Examiner's Answer, the Examiner found Moradi, Lilly, and Ukens disclosed prescription request receipt. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260. *See also* Moradi paragraph [0031] at ROXGHB004297.
the "control" of "verifying patient registry information"	Moradi discloses server-side validation of patient registration data: "If the 'Continue' button was pressed, the processing continues by determining, at step 814, if there is successful client-side validation. If there is not successful client side validation, the processing displays, at step 816, an error message that indicates which field is in error. If there is successful client side validation, the ***patient registration data*** is securely sent, at step 812, to the CSS 102. The exemplary embodiment uses an HTTPS communications link to securely communicate all data. Once the CSS 102 receives the data, the

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	processing determines, at step 818, ***if there is successful server-side validation***. If there is not successful server-side validation, the processing displays, at step 820, an error message indicating which data field is in error." (*See* Moradi paragraph [0161] at ROXGHB004305 (emphasis added)).
selecting the control of "verifying patient registry information"	Moradi discloses effecting server-side validation with a computer or processing device that can correspond to registration software component 218 of such computer or processing device. (*See* Moradi paragraphs [0031] at ROXGHB004297 and [0161] at ROXGHB004305).
the "control" of "providing comprehensive education information to the patient"	Williams discloses: "Preferably the patient is provided ***full*** disclosure of ***all*** the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such ***counsel*** may be provided verbally, as well as in ***written form***. In preferred embodiments, the prescriber provides the patient with ***literature materials*** on the drug for which a prescription is contemplated, such ***as product information, educational brochures, continuing education monographs, and the like***." (*See* Williams col. 8 ln. 57 - col. 9 ln. 2, ROXGHB004325 (emphasis added)). *See also* the 6/19/06 OA and the Examiner's Answer wherein the Examiner found that Califano disclosed "confirming with the patient that educational material has been read prior to shipping the drug." *See*, Califano, paragraph [0084] at ROXGHB004163. The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). As noted above in connection with clauses a and b of claim 7, *supra*, Moradi, Borsand, and Lilly each disclose a computer processor. Additionally, Williams' discussion of a "computer readable storage medium" (*see* Williams col. 2 ln. 50-

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	60 at ROXGHB004322) describes or suggests a computer processor. *See also* Califano's paragraph [0052] disclosure of a computer processor at ROXGHB004159.
selecting the control of "providing comprehensive education information to the patient"	Williams discloses the control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, ***in order to become registered in the computer readable storage medium, the prescriber may be required*** to comply with various aspects of the methods described herein including, for example, ***providing patient education and counseling***, and the like, as described in detail below." (*See* Williams col. 4 ln. 43-54, ROXGHB004323 (emphasis added)). *See also* Califano paragraphs [0052] at ROXGHB004159 and [0084] at ROXGHB004163. One skilled in the art at the time would have been motivated to modify one or more of Lilly, Moradi, Ukens, and Borsand to have selected with a computer processor the control of providing comprehensive education information to the patient as taught by Williams at least to ensure patient compliance with taking a drug. (*See* Williams col. 3 ln. 56-59, ROXGHB004323). One skilled in the art at the time would have been motivated to modify one or more of Lilly, Moradi, Ukens, Borsand, and Williams to have selected with a computer processor the control of providing comprehensive education information to the patient as taught by Califano at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "ensure that the patient knows about the risks and dangers associated with the drug (para.

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	43 of Califano)."
the "control" of "verifying the patient has received and/or reviewed the educational materials"	Williams discloses: "In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the ***patient to fill out an informed consent form*** which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. ***Verification that the patient*** has given his/her informed consent may also be registered in the computer readable storage medium … By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. ***In the informed consent form***, the patient preferably ***agrees to*** comply with the risk avoidance measures provided, and to ***behave in a manner which is consistent with the prescriber's counsel***." (*See* Williams col. 10 ln. 23-46, ROXGHB004326 (emphasis added)). *See also* the 6/19/06 OA and the Examiner's Answer wherein the Examiner found that paragraph [0084] of Califano disclosed "confirming with the patient that educational material has been read prior to shipping the drug." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "verifying the patient has received and/or reviewed the educational materials"	Williams discloses: "In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the

Claims of U.S. Patent No. 7,765,106	Description in Prior Art:
	informed consent form for his/her records. ***Verification*** that the patient has given his/her informed consent may also be registered ***in the computer readable storage medium.***" *(See* Williams col. 10 ln. 23-32, ROXGHB004326 (emphasis added)). *See also* Califano paragraphs [0084] and [0086] at ROXGHB004163-64.
the "control" of "requiring rewriting of the prescription periodically"	Williams discloses: "In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will ***not be permitted*** without a ***renewal prescription from the prescriber***, as discussed in detail below." (*See* Williams col. 12 ln. 3-8 at ROXGHB004327 (emphasis added)). *See also* Moradi paragraph [0098] at ROXGHB004302.
selecting the control of "requiring rewriting of the prescription periodically"	Williams discloses this control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, ***in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein*** including, for example, providing patient education and counseling, and the like, as described in detail below." (*See* Williams col. 4 ln. 43-54 at ROXGHB004323; emphasis added).

G. The claims of United States Patent No. 7,765,107 are invalid:

1. The method claims of the '107 patent are invalid on the ground that the claimed subject matter is not encompassed by 35 U.S.C. § 101. The patent claims are invalid because the patentee admittedly seeks to patent an algorithm or an abstract idea, *see Bilski v. Kappos*, 130 S.Ct. 3218, 3229-30 (2010), and the claims do not satisfy the machine-or-transformation test, *see In re Bilski*, 545 F.3d 943, 962-63 (Fed. Cir. 2008).

2. First, the claims of the distribution patents are directed to functions or algorithms that are implemented in computer software or a combination of software and human implemented procedures. (*See*, *e.g.*, '107 patent at col. 3, lines 5-19.) The Supreme Court has repeatedly rejected patents that claim a formula or an algorithm. *See*, *e.g.*, *Gottschalk v. Benson*, 409 U.S. 63, 71 (1972); *Parker v. Flook*, 437 U.S. 584, 594 (1978); *In re Grams*, 888 F.2d 835, 837, n.1 (Fed. Cir. 1989) ("It is of no moment that the algorithm is not expressed in terms of a mathematical formula. Words used in a claim operating on data to solve a problem can serve the same purpose as a formula."); *Bilski v. Kappos*, 130 S.Ct. at 3231. The claims are also directed to a patent ineligible, abstract idea, *i.e.*, the concept of checking for potential abuse of a prescription drug by a patient or the prescribing doctor and applying that concept to a specific drug, GHB.

3. Second, the method claims of the distribution patents are not patent-eligible because the claimed methods do not transform an article into a different state or thing. The patents merely claim a method of distributing sensitive drugs that does not transform or make the drugs any less sensitive. And while the methods arguably include a "data-gathering step," wherein the pharmacy technician, specialist or pharmacist must "confirm[] with a patient that educational material has been read" or "confirm[] receipt by the patient of the prescription drug,"

the Federal Circuit has noted that "gathering data would not constitute a transformation of any article." *Bilski*, 545 F.3d at 963. And while the claimed methods refer to periodic reports that are generated "to evaluate potential diversion patterns" or "potential for abuse, misuse, or diversion," this is merely an addition of "non-essential post-solution activity" that will not save the claims from invalidity. *See Bilski*, 545 F.3d at 962-63. Generating a report containing data to be analyzed later is not the main purpose of the claimed process—distributing sensitive drugs in a manner to minimize risk and protect against abuse. (*See*, *e.g.*, '107 patent at col. 1, lines 13-14.)

4. Third, the claims of the distribution patents are not tied to a particular machine. While many of the steps require uses of so-called "exclusive computer system under the control of an exclusive central pharmacy," "exclusive central computer system," "computer processor" or "exclusive central pharmacy that maintains a central database," the specification does not require any specific type of computer system—the software can be executed "on a digital signal processor, ASIC, microprocessor, or other type of possessor operating on a computer system, such as a personal computer, server or other computer system." (*See*, *e.g.*, '107 patent at col. 3, lines 16-19.) The Supreme Court in *Gottschalk* rejected a claimed process that utilized any general-purpose digital computer of any type. *See Gottschalk*, 409 U.S. at 71-72. The Board of Patent Appeals and Interferences has followed the Gottschalk approach and has rejected applications that are not tied to a specific computer system. *See*, *e.g.*, *Ex Parte Kuno, et al.*, Appeal No. 2009-006896 (B.P.A.I. Dec. 13, 2010); *Ex Parte Monk, et al.*, Appeal No. 2009-013250 (B.P.A.I. Dec. 30, 2010).

5. Finally, no patent can be obtained for a method an essential component of which consists of human mental participation. If a method necessarily involves human judgment and

choice, then the method will not meet the standard of definiteness required for patent protection. *See, e.g., Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1356 (Fed. Cir. 2005) ("The scope of claim language cannot depend solely on the unrestrained, subjective opinion of a particular individual purportedly practicing the invention. *See Application of Musgrave*, 57 C.C.P.A. 1352, 431 F.2d 882, 893 (1970)."). The claims of the distribution patents are invalid for indefiniteness because they require someone, for example, a pharmacy specialist, technician or pharmacist, to make certain subjective judgment calls as to whether the patient indeed received and read the program materials or whether there is potential for abuse of the prescription drug by the patient. The applicants repeatedly argued to the PTO that the claimed methods of distribution or distribution models "analyse[] (sic) for and determine[] potential abuse situations and current and anticipated patterns of potential adverse reactions." (*See*, *e.g.*, '730 PH, 9/30/04 Petition to Make Special at ROXGHB004395.) Neither the claims nor the specifications of the distribution patents, however, provide objective steps or criteria for evaluating the potential for abuse or on how to verify whether the patient has indeed truthfully reviewed the program materials—the technician could accept what the patient says or could exercise his or her own judgment to determine whether the patient is being truthful or not. Because the claimed methods seek to address the problems associated with the abuse and illegal distribution of sensitive prescription drugs like GHB, pharmacy specialists, technicians and pharmacists must be given authority to act on their "gut" feeling as to whether a certain patient is being deceitful or untrustworthy. Patent claims that require such human mental participation are indefinite and not proper patent-eligible subject matter.

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	Borsand (U.S. Patent Application Publication No. 2003/0074225), ROXGHB004109-36, ("Borsand"), **Califano (U.S. Patent Application Publication No. 2003/0033168), ROXGHB004137-70, ("Califano"),** **"Making good in your own mail-order business." Changing Times October 1980 vol. 34 no. 10, pp. 66-68, ROXGHB004171-74 ("Changing Times"),** **"The Credentialing Handbook," S. Deutsch, 1999, ROXGHB004175-4221 ("Deutsch"),** **Fletcher (U.S. Patent Application Publication No. 2001/0042050), ROXGHB004222-40 ("Fletcher"),** **Gibson ("Drugs of Abuse," C. Gibson, 1997), ROXGHB004241-49 ("Gibson"),** **"An Interview with Orphan Medical about Xyrem" ("An Interview with Orphan Medical about Xyrem," Feb. 12, 2001, http://www.talkaboutsleep.com/sleepdisorders/archives/Narcolepsy_xyrem_interview.htm), ROXGHB004250-52 ("An Interview with Orphan Medical about Xyrem"),** **Lilly (U.S. Patent Application Publication No. 2004/0176985), ROXGHB004253-64 ("Lilly"),** **Moradi (U.S. Patent Application Publication No. 2004/0019794), ROXGHB004282-312 ("Moradi"),** **Ukens ("Specialty Pharmacy," Jun. 5, 2000, Drug Topics, v. 144, p. 40), ROXGHB004313-20 ("Ukens"), and** **Williams (U.S. Patent No. 6,315,720), ROXGHB004321-31 ("Williams").**
(preamble) 1. A computerized method to control abuse of a prescription drug comprising: "control abuse" of a "prescription drug"	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a limitation, then it is disclosed in the prior art as follows: Lilly discloses: "In accord with the method of the present invention, a secure, private, independent, network-based, centralized ***method*** operable for ***tracking and managing prescriptive medication*** information in aggregate is provided which

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
a "computerized" method	allows electronic querying and real-time notification of patients' prescriptive medication history at the time of prescriptive medication creation. According to the method of the invention, this information is accessible within a controlled and appropriate context for use by healthcare professionals involved in the delivery of care to that patient." (*See* Lilly paragraph [0050], ROXGHB004260 (emphasis added)). "Government oversight entities 14, such as the DEA, FBI, CDC, and so forth, may be able to utilize data as required to reach the organization goals and within the limitations required therefore. For instance, the DEA may review data to determine areas where ***violations*** may be occurring … All of these entities can have immediate access to potential medication ***abuse*** by identification of needless prescription duplications, potential drug interactions, and multi-source interstate ***prescriptive medication abuse***." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)). Lilly teaches: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)).
(clause a) controlling with a computer processor the distribution of said prescription drug via an exclusive central pharmacy that maintains a central database that tracks all prescriptions of said prescription drug and analyzes for potential abuse situations;	

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
"controlling the distribution" of the drug	U.S. Patent No. 7,765,107 is a divisional application of U.S. Patent No. 7,668,730 ("the '730 patent"). In the October 18, 2006 Office Action, ROXGHB004586-ROXGHB004600 ("the 10/18/06 OA") and the October 3, 2007 Examiner's Answer, ROXGHB004708-ROXGHB004725 ("the Examiner's Answer"), the Examiner found that Moradi disclosed "***only mailing*** the drug to the patient ***if*** no potential abuse is found …" *See* Moradi, paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285 (emphasis added). The August 31, 2009 Decision on Appeal, ROXGHB004750-ROXGHB004763 ("BPAI Decision") stated that: "But for the Examiner's finding, that Moradi and Lilly disclose 'exclusive' computer databases, the Examiner's remaining findings characterizing the scope and content of the cited references as well as the differences between the claimed subject matter and the prior art have not been rebutted. Accordingly, as to these findings, they are accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
a computer processor controls "the distribution" of the drug	Moradi states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)).
the distribution is "via" an "exclusive central pharmacy"	The June 19, 2006 Office Action, ROXGHB004525-ROXGHB004545 ("the 6/19/06 OA") and the Examiner's Answer each found Moradi disclosed "a method of ***distributing a drug under*** exclusive ***control of*** an ***exclusive central pharmacy.***" *See* Moradi, paragraphs [0003] at ROXGHB004295 and [0024] at ROXGHB004296. Also, the 10/18/06 OA and the Examiner's Answer each found that Ukens, at page 3, paragraphs 3-5 at ROXGHB004315, disclosed an exclusive

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	central pharmacy. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
the "exclusive central pharmacy" "maintains" a "database"	In the 6/19/06 OA, the 10/18/06 OA and the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer ***database associated with the exclusive central pharmacy*** for analysis of potential abuse situations." *See*, Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly stating: "To one of ordinary skill in the art reading Lilly, Lilly's data storage is 'exclusive' in that it is the sole data storage that 'contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information.'" (BPAI Decision, p. 10, ROXGHB004760). The BPAI Decision held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
the database is a "central database"	In the context of Ukens' exclusive ***central*** pharmacy, the Lilly database constitutes an exclusive ***central*** database.
the central database "tracks" "prescriptions" of the drug and "analyzes for potential abuse situations"	Lilly discloses that the central database (1) tracks prescriptions: "The industry has widely recognized a need for better efficiencies, but without notable success in many areas, including prescription abuse. For instance, the Healthcare Information Portability and Accountability Act (HIPAA) mandates making the exchange of information more ubiquitous, secure, and efficient but does not provide a solution with respect to ***prescription tracking*** and abuse."

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	(*See* Lilly paragraph [0009], ROXGHB004256 (emphasis added)). "In accord with the method of the present invention, a secure, private, independent, network-based, centralized method operable for ***tracking*** and managing ***prescriptive medication information*** in aggregate is provided which allows electronic querying and real-time notification of patients' prescriptive medication history at the time of prescriptive medication creation." (*See* Lilly paragraph [0050], ROXGHB004260 (emphasis added)). "All of these entities can have immediate access to potential medication abuse by ***identification*** of needless ***prescription duplications***, potential drug interactions, and multi-source interstate prescriptive medication abuse." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)). and (2) analyzes for potential abuse situations. In the 6/19/06 OA, the 10/18/06 OA, and the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer ***database*** associated with the exclusive central pharmacy for ***analysis of potential abuse situations.***" *See*, Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"all" prescriptions are tracked	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving ***all*** prescription requests at the exclusive central pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). As the exclusive central pharmacy of Ukens receives all prescriptions, the tracking performed by the central database of Lilly in the context of Ukens would be of such all prescriptions. One skilled in the art at the time would have been motivated to modify Lilly to control distribution of the drug as taught by Moradi at least to "securely provid[e] prescription medication to patients." (*See* Moradi, abstract, ROXGHB004282). One skilled in the art at the time would have been further motivated to modify Lilly and Moradi to include the exclusive central pharmacy of Ukens, to, as noted by the Examiner in connection with the 10/18/06 OA and the Examiner's Answer, "limit access to dangerous drugs (page 3, paragraph 5 of Ukens)."
(clause b) receiving in the computer processor all prescription requests, for any and all patients being prescribed the prescription drug, only at the exclusive central pharmacy, from any and all medical doctors allowed to prescribe the prescription drug; receiving all prescription requests "in the computer processor"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving all prescription requests at the exclusive central pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Moradi states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). (*See* also Lilly paragraph [0051], ROXGHB004260 (emphasis added)).
"… <u>for any and all patients being prescribed the prescription drug, only</u> at the exclusive central pharmacy from <u>any and all</u> medical doctors <u>allowed to prescribe the prescription drug</u> …"	Ukens discloses "restricting distribution of a specialty medication to only ***one*** pharmacy." (*See* Ukens p. 3, para. 3, ROXGHB004315 (emphasis added)). Ukens also teaches that the specialty medications are "prescribed." (*See* Ukens p. 3, para. 1 at ROXGHB004315).
(clause c) processing with the computer processor all prescriptions for the prescription drug only by the exclusive central pharmacy using only the central database;	
processing all prescriptions "only by the exclusive central pharmacy"	Ukens teaches "restricting distribution of a [prescribed] specialty medication to only one pharmacy." (*See* Ukens p. 3, paragraphs 1 and 3, ROXGHB004315 (emphasis added)).
processing all prescriptions "using only the central database"	Borsand describes storing ***all*** pharmaceutical-related information ***only once*** and in a ***single*** database 62: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
exclusive central pharmacy processes "with the computer processor"	the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). *See also* Fig. 3 of Borsand at ROXGHB004112, which describes the pharmaceutical-related information stored in single database 62 as including pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, ***patient*** information, and *provider* information. Borsand further discloses at paragraph [0030] at ROXGHB004125 that such a provider can be a ***physician***. As noted above in connection with clause a, *supra*, Moradi discloses a computer processor. Further, Borsand states: "The ***computer 26*** can be a single centralized computer or server, a single network, a series of interconnected networks, a series of devices capable of accessing the Internet or World Wide Web including an application server, or any other configuration which supports the ability of different entities to communicate with one another." (*See* Borsand paragraph [0031] at ROXGHB004125 (emphasis added)). One skilled in the art at the time would have been motivated to modify Moradi, Ukens and Lilly to process prescriptions using ***only*** a central database as taught by Borsand at least to allow all pharmaceutical-related information to be stored on a single database that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines. (*See* Borsand paragraph [0043], ROXGHB004127).
(clause d) determining with the computer processor current and anticipated patterns of potential prescription abuse of said prescription	

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
drug from periodic reports generated only by the central database based on prescription request data from a particular medical doctor and further based on filling of prescriptions by a particular patient, wherein said request data contain information identifying the patient, the drug prescribed, and credentials of the medical doctor; and	
determining patterns of "potential prescription abuse" of the drug from "periodic reports"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found Lilly discloses "generating ***periodic reports*** via the exclusive computer database to evaluate ***potential diversion*** patterns." *See*, Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263 (emphasis added). The BPAI Decision affirmed the Examiner's finding of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
determining the patterns "with the computer processor"	As noted above in connection with clause a, *supra*, Moradi discloses a computer processor. As noted above in connection with clause c, *supra*, Borsand also discloses a computer processor. Further, Lilly teaches: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)).
the "central database" generates the periodic reports	As noted above in clause a, the "central database" is disclosed at least in Lilly in view of Ukens. In the 6/19/06 OA and the Examiner's Answer, the Examiner found Lilly disclosed "***generating periodic reports*** via the exclusive computer ***database*** to evaluate potential diversion patterns." *See* Lilly paragraphs [0011] at

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263 (emphasis added). The Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly was affirmed in the BPAI Decision holding all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
the patterns which are determined are "current and anticipated" patterns	Lilly teaches: "Pharmacies 26 may check to personally verify the drug usage of each purchaser to ***immediately*** detect problems related to ***abuse, fraud, and misuse*** of medications … Pharmacists are constantly challenged to circumvent duplication, ***abuse, fraud, and misuse*** of these medications while providing a cost effective medication delivery system. In the present health system the wide availability of pharmaceuticals from different pharmacies raises the risks of negative drug interactions and its associated destructive medical outcome. ***Pharmaceutical information control organization 12 can flag these issues*** in real time, thereby ***completely preventing*** or at least minimizing their occurrences." (*See* Lilly paragraph [0057] at ROXGHB004261 (emphasis added)). "FIG. 2 discloses a presently preferred pharmaceutical information flow diagram 100 for a method of operation of ***pharmaceutical information control organization 12*** in accord with the present invention. A plurality of entities, networks, organizations may be utilized in accord with the present invention including doctors 102. Pharmacies 104 include pharmacies that are affiliated with each other as well as pharmacies that are unaffiliated with each other. Other entities include hospitals 106, pharmaceutical companies 108, insurance companies 110 (which may include health or life insurance companies or any other type of insurance companies), government agencies 112, health care informatics companies 114, health researchers 116, managed care organizations 118, and other healthcare providers 120 … In a preferred embodiment, the present invention provides that ***data storage 122*** is able to

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	access the ***databases*** of the above-listed entities and/or other member organizations as needed and/or store the corresponding pharmaceutical data in data storage 122 which is external to each entity's database(s) … Data storage 122 preferably has the ability to allow the software schemas to be changed without disruption of system 100." (See Lilly paragraph [0061], ROXGHB004262 (emphasis added)). *See also* Lilly, paragraph [0058] at ROXGHB004261.
generating periodic reports based on prescription request data from a particular medical doctor and further based on filling of prescriptions by a particular patient	Lilly teaches: "The method may further comprise providing that the pharmaceutical computer data for each of the prescriptive medication purchases comprises a name of ***a*** respective ***prescriptive medication purchaser***, an address of the respective prescriptive medication purchaser, *a drug prescribed,* the respective prescriptive medication purchaser, a quantity of the drug, a dosage of the drug, a pharmacist name, and *a doctor* name." (See Lilly paragraph [0041], ROXGHB004259 (emphasis added)). "Presently, legal regulations may require that each time a prescriptive medication is ***filled*** that a paper copy of the transaction is forwarded to the DEA … All of these entities can have immediate access to potential medication abuse by ***identification*** of needless *prescription duplications*, potential drug interactions, and multi-source interstate prescriptive medication abuse." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)). "Various types of data may be stored and/or obtained such as ***the doctor name, the doctor DEA number, patient name, patient ID*** (e.g. SS#, passport #, driver's license, etc.), ***patient address, city, state, zip, patient phone number***, drugs prescribed, dosage, frequency, start/end date, duration, quantity, number refills, whether substitution is allowed, generic allowed, notes, aberrant use flag, date *prescription filled*, place ***prescription filled***, pharmacist name,

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	pharmacist phone number, pharmacist DEA number, and application programming interfaces utilized." (*See* Lilly paragraph [0068], ROXGHB004263 (emphasis added)). "The display may be made by ***a patient identifier, patient name,*** date, drug name, ***doctor prescribing the medication***, pharmacy, geography (city, state, zip code), by phone number, and/or by aberrant use flag." (*See* Lilly paragraph [0069], ROXGHB004263 (emphasis added)).
generating the periodic reports based on the prescription request data and based on the filling of prescriptions "only" by the central database	Borsand describes storing ***all*** pharmaceutical-related information -- including prescription information -- ***only once*** and in a ***single*** database 62 and, thus, periodic reports would be generated ***only*** by the central database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)).
the request data contain "information identifying the patient, the drug prescribed, and	In the Examiner's Answer, the Examiner found "receiving all ***prescription requests*** at the exclusive central pharmacy from a medical doctor containing information identifying a ***patient***, the sensitive ***drug***, and various ***credentials of***

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
credentials of the medical doctor"	***the doctor***" disclosed in Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added).
(clause e) selecting with the computer processor multiple controls for distribution by said exclusive central pharmacy, the controls comprising communicating prescriptions from a physician to the central pharmacy; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient returning the drug to the	

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; releasing inventory in a controlled manner to the central pharmacy; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse patterns in the data, for cash payments, and for inappropriate questions.	
"selecting" with the computer processor of "multiple controls," the controls comprising …"	
the "control" of "communicating prescriptions from a physician to the central pharmacy"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving all prescription requests at the exclusive central pharmacy from a medical doctor*** containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See*, Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the "control" of "communicating prescriptions from a physician to the central pharmacy"	As noted, in the Examiner's Answer, the Examiner found Moradi, Lilly, and Ukens disclosed prescription request receipt. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
"with the computer processor"	paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260. It would have been obvious to a person of ordinary skill in the art to have a computer processor select this prescription drug distribution control (or any of the other listed controls) in order to control abuse of a prescription drug.
the "control" of "identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information"	Moradi discloses: "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by the automated prescription delivery system 100. The data includes the physician's ***name, address, practice information, DEA number, license numbers***, e-mail, phone number and web site address." (*See* Moradi paragraph [0118], ROXGHB004304 (emphasis added)).
selecting the "control" of "identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information" "with the computer processor"	Moradi describes: "This module allows a physician to complete an online registration form for access to the automated prescription delivery system 100. This module is part of the Registration module 218. This module is used for entering required physician registration information and does not grant access to the system." (*See* Moradi paragraph [0109] at ROXGHB004303).
the "control" of "verifying the prescription"	Moradi discloses: "Once the POD system 106 at the pharmacy has received the image of the prescription from the CSS 102, the data are decrypted and the processing continues by using a software based data authenticator to ***verify***, at step 316, ***the prescription*** at the POD system 106. This step includes operating a software based digital signature authenticator to ensure that a valid digital signature has been added to the prescription. This step also requires that if the prescription is not refillable, or if the prescription is refillable but the number

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	of digital signatures added to the prescription image is equal to or greater than the number of refills, the operator is to check the order for cancellations of previous submissions to the POD 106." (*See* Moradi paragraph [0042] ROXGHB004299 (emphasis added)).
selecting the "control" of "verifying the prescription" "with the computer processor"	Moradi discloses verifying the prescription with a computer or processing device, which can correspond to PODP software 212 of that computer or processing device. (*See* Moradi paragraph [0028] at ROXGHB004297).
the "control" of "obtaining patient information"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all prescription requests at the exclusive central pharmacy from a medical doctor containing ***information identifying a patient***, the sensitive drug, and various credentials of the doctor." *See*, Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the "control" of "obtaining patient information" "with the computer processor"	As noted, in the Examiner's Answer the Examiner found that Moradi, Lilly, and Ukens disclosed receipt of prescription requests containing patient information. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260. *See also* Moradi paragraph [0031] at ROXGHB004297.
the "control" of "verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether	Moradi discloses validation of physician data that involves: "The CSS program 202 ***performs the following validations*** and if there are any validation errors, an error message is displayed to the user identifying the

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
the physician has an active DEA number and to check on whether any actions are pending against the physician"	field or fields in error: Physician License Number: The Physician License number consists of an alphabetical prefix (used as license type) followed by a number assigned to licensed physician. It is used to identify physician to various payers. ***Existing*** Internet data resources are used by the exemplary embodiment to verify the physician license number … ***DEA Number Validation***: The DEA is an alphanumeric string that is currently a number beginning with an A or B that is followed by another letter. The exemplary embodiment of the present invention is configured to accommodate any alphanumeric string so as to allow for DEA numbers that begin with other values. The DEA number in the exemplary embodiment is able to begin with any two alphanumeric characters." (*See* Moradi paragraphs [0113] - [0116], ROXGHB004303 (emphasis added)). The National Technical Information Service is a well known data resource for physician data including DEA number. *See, e.g.,* Deutsch pp. 253-254 at ROXGHB004197-98 and 269-272 at ROXGHB004213-16. Moreover, it is well known to employ a data resource in performing a disciplinary action check with respect to a physician. *See, e.g.,* Deutsch pp. 252-253 at ROXGHB004196-97 and 269-272 at ROXGHB004213-16. Borsand discloses checking, both before and after prescription 28 is filled, for ***evidence of fraud or misuse by provider 30***. (*See* Borsand paragraph [0120] at ROXGHB004134). Such checking would obviously include checking whether any actions are pending using, as for example taught by paragraph [0114] of Moradi at ROXGHB004303, a data resource for physician data. Accordingly, it would have been obvious to verify the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
selecting the "control" of "verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician" "with the computer processor"	check on whether any actions are pending against the physician. Moradi discloses the validation of physician data to be performed with a computer processor: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). (*See* Moradi paragraph [0109], ROXGHB004303 (emphasis added)). Borsand discloses: "The ***system 20*** facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 even after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the cancellation or modification of a prescription 28. The modification of a prescription at 132 is an event triggered process. There must be an ***event that triggers the modification or cancellation of a prescription 28***. The ***triggering event could be*** a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse, or redundancy on the part of a provider 30***, pharmacist 40, or patient 22" (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)). One skilled in the art at the time would have been motivated to modify one or more of Lilly, Moradi, Ukens, and Borsand to have selected the control of verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician as is obvious in view of one or more of Deutsch, Moradi, and Borsand at least to make use of resources that are helpful with verification

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	and information gathering. (*See* Deutsch p. 269 at ROXGHB004213).
the "control" of "providing comprehensive printed materials to the physician"	Borsand describes allowing provider 30 to view via computer "detailed information for a particular pharmaceutical 32." (*See* Borsand paragraphs [0050] and [0054] at ROXGHB004128). That information viewed via computer can be provided in printed form is well-known.
selecting the "control" of "providing comprehensive printed materials to the physician" "with the computer processor"	Borsand discloses use of "java script" execution in connection with provider home page 30.02 of computer 26 in viewing detailed information on a particular pharmaceutical. (*See* Borsand paragraphs [0031] at ROXGHB004125-26, [0050], and [0054] at ROXGHB004128).
the control of "contacting the patient's insurance company if any"	Borsand describes contacting a patient's payor (health insurance company), including pre-authorization contact: "The present invention relates to a computer based system for tracking information related to pharmaceutical prescriptions, and communicating the information to all entities appropriately involved in that particular prescription. The invention supports direct, proactive, and timely ***communication between a payor***, pharmacy benefit managers ('PBMs'), pharmacies, and providers. Such communication facilitates cost savings and eliminates unnecessary processes and 're-work.'" (*See* Borsand paragraph [0010], ROXGHB004125 (emphasis added)). "In a preferred embodiment of the invention, ***an e-mail (or similar communication such as a facsimile)*** containing the relevant pre-authorization information ***is sent*** directly ***to a payor*** or PBM when the provider confirms that the prescription 28 is to include the pre-authorized pharmaceutical 32." (*See* Borsand paragraph [0062] at ROXGHB004129 (emphasis added)). *See also* Borsand paragraph [0037] at ROXGHB004126 and [0053] at ROXGHB004128.

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
selecting the control of "contacting the patient's insurance company if any" "with the computer processor"	Borsand describes: "The present invention relates to a ***computer*** based system for tracking information related to pharmaceutical prescriptions, and communicating the information to all entities appropriately involved in that particular prescription. The invention supports direct, proactive, and timely communication between a payor, pharmacy benefit managers ('PBMs'), pharmacies, and providers. Such communication facilitates cost savings and eliminates unnecessary processes and 're-work.'" (*See* Borsand paragraph [0010], ROXGHB004125 (emphasis added)).
the "control" of "verifying patient registry information"	Moradi discloses server-side validation of patient registration data: "If the 'Continue' button was pressed, the processing continues by determining, at step 814, if there is successful client-side validation. If there is not successful client side validation, the processing displays, at step 816, an error message that indicates which field is in error. If there is successful client side validation, the ***patient registration data*** is securely sent, at step 812, to the CSS 102. The exemplary embodiment uses an HTTPS communications link to securely communicate all data. Once the CSS 102 receives the data, the ***processing determines***, at step 818, ***if there is successful server-side validation***. If there is not successful server-side validation, the processing displays, at step 820, an error message indicating which data field is in error." (*See* Moradi paragraph [0161] at ROXGHB004305 (emphasis added)).
selecting the control of "verifying patient registry information" "with the computer processor"	Moradi discloses effecting server-side validation with a computer or processing device that can correspond to registration software component 218 of such computer or processing device. (*See* Moradi paragraphs [0031] at ROXGHB004297 and [0161] at ROXGHB004305).
the "control" of "providing comprehensive education information to the patient"	Williams discloses: "Preferably the patient is provided ***full*** disclosure of ***all*** the known and

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such ***counsel*** may be provided verbally, as well as in ***written form***. In preferred embodiments, the prescriber provides the patient with ***literature materials*** on the drug for which a prescription is contemplated, such ***as product information, educational brochures, continuing education monographs, and the like***." (*See* Williams col. 8 ln. 57 - col. 9 ln. 2, ROXGHB004325-26 (emphasis added)). *See also* the 6/19/06 OA and the Examiner's Answer wherein the Examiner found Califano disclosed "confirming with the patient that educational material has been read prior to shipping the drug." *See*, Califano, paragraph [0084] at ROXGHB004163. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "providing comprehensive education information to the patient" "with the computer processor"	As noted above in connection, respectively, with clauses a, c, and d, *supra*, Moradi, Borsand, and Lilly each disclose a computer processor. Additionally, Williams' discussion of a "computer readable storage medium" (*see* Williams col. 2 ln. 50-60 at ROXGHB004322) describes or suggests a computer processor. *See also* Califano's paragraph [0052] at ROXGHB004159 for disclosure of a computer processor. Williams discloses the control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug.

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	Generally speaking, ***in order to become registered in the computer readable storage medium, the prescriber may be required*** to comply with various aspects of the methods described herein including, for example, ***providing patient education and counseling***, and the like, as described in detail below." (*See* Williams col. 4 ln. 43-54, ROXGHB004323 (emphasis added)). *See also* Califano paragraphs [0052] at ROXGHB004159 and [0084] at ROXGHB004163. One skilled in the art at the time would have been motivated to modify one or more of Lilly, Moradi, Ukens, Borsand, and Deutsch to have selected with a computer processor the control of providing comprehensive education information to the patient as taught by Williams at least to ensure patient compliance with taking a drug. (*See* Williams col. 3 ln. 56-59, ROXGHB004323). Also, one skilled in the art at the time would have been motivated to modify one or more of Lilly, Moradi, Ukens, Borsand, Deutsch, and Williams to have selected with a computer processor the control of providing comprehensive education information to the patient as taught by Califano at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "ensure that the patient knows about the risks and dangers associated with the drug (para. 43 of Califano)."
the "control" of "verifying the patient has reviewed the educational materials"	Williams discloses: "In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the ***patient to fill out an informed consent form*** which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. ***Verification that the patient*** has given his/her informed consent may also be registered in the computer

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	readable storage medium … By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. ***In the informed consent form***, the patient preferably ***agrees to*** comply with the risk avoidance measures provided, and to ***behave in a manner which is consistent with the prescriber's counsel***." (*See* Williams col. 10 ln. 23-46, ROXGHB004326 (emphasis added)). *See also* the 6/19/06 OA and the Examiner's Answer wherein the Examiner found that paragraph [0084] of Califano disclosed "confirming with the patient that educational material has been read prior to shipping the drug." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "verifying the patient has reviewed the educational materials" "with the computer processor"	Williams discloses: "In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. ***Verification*** that the patient has given his/her informed consent may also be registered ***in the computer readable storage medium.***" *(See* Williams col. 10 ln. 23-32, ROXGHB004326 (emphasis added)). *See also* Califano paragraphs [0084] and [0086] at ROXGHB004163-64.
the "control" of "verifying the home address of the patient"	Moradi discloses server-side validation of patient registration data, including postal code validation. *See, e.g.,* Moradi paragraphs [0136] at ROXGHB004304, [0139], [0140], [0141] and [0161] at ROXGHB004305.

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
selecting the control of "verifying the home address of the patient" "with the computer processor"	Moradi describes that the server-side validation takes place via a computer or processing device and can correspond to registration software component 218 of the computer or processing device. (*See* Moradi paragraphs [0031] at ROXGHB004297 and [0161] at ROXGHB004305).
the "control" of "shipping via US postal service or a commercial shipping service"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi discloses "only ***mailing*** the drug to the patient if no potential abuse is found …." *See* Moradi, paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "shipping via US postal service or a commercial shipping service" is selected "with the computer processor"	Paragraph [0022] of Moradi states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." ROXGHB004296 (Emphasis added). Accordingly, Moradi teaches implementing the "mailing the drug to the patient" noted by the Examiner to be disclosed by Moradi with a computer or processing device.
the "control" of "receiving the name of an at least 18 year old designee to receive the drug"	
receipt of the name of a designee to receive the drug	Moradi discloses: "The exemplary embodiment further includes providing the delivery person with a 'Route Slip' that has printed directions to the patient's address along with the scanned prescription image. The delivery person hand-delivers the

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	medicine to the recipient if and only if the recipient is holding the original copy of the prescription that is identical to the image provided to the delivery person. This ensures that the proper patient gets the medicine and that the medicine is delivered only once." (*See* Moradi paragraph [0043] at ROXGHB004299).
the individual receiving the drug is at least 18 years old	Moradi teaches the impropriety of a child retrieving a mailed prescription: "Delivery of prescription medication by mail is also possible … This technique is also open to fraud since the individual patient typically does not personally present his or her prescription to the pharmacy. This technique can also lead to an improper person receiving the prescription, such as when a child that is living with the recipient retrieves mail that contains the mailed prescription." (*See* Moradi paragraph [0006] at ROXGHB004295).
selecting the control of "receiving the name of an at least 18 year old designee to receive the drug" "with the computer processor"	Paragraph [0022] of Moradi states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." ROXGHB004296 (Emphasis added).
the "control" of "confirming receipt of an initial shipment of the drug to the patient returning the drug to the pharmacy after two attempts to deliver"	Paragraph [0006] of Moradi at ROXGHB004295 discloses delivery by mail of the "initial fulfillment" of a prescription medication. Moreover, paragraph [0043] of Moradi at ROXGHB004299 discloses a delivery person communicating to Central Service Station (CSS) 102 of system 100 via Point of Delivery (POD) system 106 of system 100 status designations of "delivered, no one at the address, prescription mismatch or one of a number of other potential reasons for non-delivery." Further, in the 6/19/06 OA and the Examiner's Answer, the Examiner found the

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	abstract of Moradi disclosed "confirming receipt by the patient of the drug." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). To require returning to the sender, especially in the case where the item to be delivered is a restricted drug, after two attempts to deliver are unsuccessful would have been obvious.
selecting the control of "confirming receipt of an initial shipment of the drug to the patient returning the drug to the pharmacy after two attempts to deliver" "with the computer processor"	Moradi discloses the communication of the status designations to be implemented via POD system 106 and CSS 102 of system 100. (*See* Moradi paragraph [0043] at ROXGHB004299).
the "control" of "launching an investigation when a shipment is lost"	Fletcher describes denying further orders "pending a satisfactory resolution" of a corresponding investigation of a lost shipment: "The invention relates to electronic commerce (e-commerce) and a system and method for the secure electronic procurement of goods or services particularly narcotics, ***controlled drugs*** and substances or other goods generally subject to a 'chain of custody' for ordering and ***delivering***." (*See* Fletcher paragraph [0002] at ROXGHB004231 (emphasis added)). "In accordance with a further aspect of the invention the procurement transaction processor comprises means for performing business rules analysis using the order, notification or confirmation of receipt; and means for ***alarming potential instances of diversion or loss of goods/services***. The means for performing business rules analysis and means for alarming are preferably configured to: upon receiving a notification of provision of goods/services at the secure procurement system, initiate a timer for a predetermined period of time within which to receive the confirmation of receipt corresponding to the notification; if the timer expires, ***alarm a potential instance of diversion or loss of goods/services*** and prevent further

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	orders from the user." (*See* Fletcher paragraph [0054] at ROXGHB004233 (emphasis added)). "According to business rules implemented by SPS 38, if a 856 message is not properly confirmed by the qualified person to whom the product was shipped with a digitally signed and certified 861 message, further orders for narcotics or other controlled substances will be denied ***pending a satisfactory resolution***. The 861 message must be received by SPS 38 within a predefined period of time. Currently the defined period is five days under the Canadian regulatory framework. Additional rules ensure that variances between quantity shipped and quantity confirmed received are promptly noted to VAS or a regulatory authority (eg. DEA)." (*See* Fletcher paragraph [0087] at ROXGHB004235 (emphasis added)).
selecting the control of "launching an investigation when a shipment is lost" "with the computer processor"	As noted above in connection, respectively, with clauses a, c, and d, *supra*, Moradi, Borsand, and Lilly each disclose a computer processor. As noted above in the instant clause in connection with the control of "providing comprehensive education information to the patient," Williams and Califano also each disclose a computer processor. Additionally, Fletcher states: "Further illustrated in FIG. 2 is a preferred ***SPS 38***. In the preferred embodiment, SPS 38 comprises ***web server hardware and software*** such as a Compaq. Proliant 5000 Pentium Pro server running Microsoft. Windows NT operating system (not shown) and Netscape. Suitespot integrated software for the network enterprise (not shown)." (*See* Fletcher paragraph [0073] at ROXGHB004234 (emphasis added)). Fletcher indicates the control to be a business rule "implemented" by web server hardware and software SPS 38: "According to business rules ***implemented by SPS 38***, if a 856 message is not

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	properly confirmed by the qualified person to whom the product was shipped with a digitally signed and certified 861 message, further orders for narcotics or other controlled substances will be denied pending a satisfactory resolution." (*See* Fletcher paragraph [0087] at ROXGHB004235 (emphasis added)). One skilled in the art at the time would have been motivated to modify one or more of Lilly, Moradi, Ukens, Borsand, Deutsch, Williams, and Califano, to have selected with a computer processor the control of launching an investigation when a shipment is lost as taught by Fletcher at least to prevent diversion and loss in connection with the delivery of a controlled drug. (*See* Fletcher paragraph [0024] at ROXGHB004231-32).
the "control" of "shipping to another pharmacy for delivery"	Ukens' just-in-time inventory system wherein drugs are provided from specialty pharmacy TheraCom to an independent pharmacy in response to an order from that independent pharmacy discloses shipping to "another" pharmacy: "Declaration of independents Not content to just sit on the sidelines and watch patients and business shunted to their old nemesis, mail-service pharmacies, the National Community Pharmacists Association is attempting to build a national network of ***independent pharmacies*** willing to stock specialty products and care for the patients who need them. Teaming up with the *specialty pharmacy TheraCom*, NCPA launched the Specialty Drugs Network in January. So far, about 4,000 independents have agreed to be part of a primary distribution channel for specialty pharmaceutical manufacturers and payer programs. The free network is designed to give independents access to new products, increased revenue streams, and strategic alliances with manufacturers, insurers, and PBMs. 'Our conception of the Specialty Drugs Network was to gain access to products primarily not available through retail today,' said Todd Dankmyer, NCPA executive v.p. communications. 'There's a wide range of these

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	products, primarily injectables, that are extremely expensive and usually for very limited patient populations where reimbursement and insurance coverage are the major challenges.' Independent members of the specialty Drugs Network can pick and choose which drugs they want to stock and provide patient support for. There's also a ***just-in-time inventory system. 'The members don't have to order anything until they know they have a patient coming in who needs this medication***,' said Dankmyer. 'Second, all major medical claims are handled by TheraCom, so the members don't get into any battling to get the reimbursement, and they don't obligate themselves to accept certain levels of reimbursement.'" (*See* Ukens p. 4 at ROXGHB004316 (emphasis added)). Moradi also discloses shipping to such an independent pharmacy "for" delivery: "The pharmacy router 210 of the exemplary embodiment determines a ***pharmacy*** or other type of POD 106 *that is to deliver the prescription* by determining a POD 106 that is registered with the automated prescription delivery system 100 and that was selected by the patient or that is closest to the patient's registered address." (*See* Moradi paragraph [0040] at ROXGHB004298 (emphasis added)).
selecting the control of "shipping to another pharmacy for delivery" "with the computer processor"	Moradi discloses CSS 102 of system 100 to implement the dispatch of a medicine where the recipient of that dispatch acts to deliver the medicine to a patient by explaining that CSS 102 tracks such dispatch in CSS database 204: "The PMS system assigns the prescription a prescription number, and the pharmacist enters that prescription number and the number of refills into the PODP 216, which then communicates that data back to the CSS 102 with an identification of the prescription. The pharmacist then ***gives***, at step 322, ***the ordered medicine*** and a copy of the prescription image to a prescription deliverer, which is a delivery person in the exemplary embodiments, ***for***

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	delivery to the patient. The ***CSS 102*** is notified that the delivery person is in the process of delivering the medication and the ***status of the prescription is changed to 'delivery' within the CSS database 204***." (*See* Moradi paragraph [0043] at ROXGHB004299 (emphasis added)). CSS 102 would also, in the context of the Specialty Drugs Network of Ukens, correspond to a computer or processing device that implements the shipment of a drug to an independent pharmacy of Ukens from specialty pharmacy TheraCom of Ukens.
the "control" of "requiring manufacture at a single location"	Gibson discloses at pages 5 and 6, ROXGHB004247-48, that control of Schedule I drugs can be made at the manufacturer tier, distributor tier or supplier tier, and dispenser tier. Ukens teaches that "restricting distribution of a specialty medication to only one pharmacy," "product going to only one distributor," "going with one pharmacy provider," and "let[ting] only one pharmacy have access" (*see* Ukens, p. 3 at ROXGHB004315) provides control of drug distribution by limiting distribution and dispensing to a sole entity. In view of such teaching by Ukens, it would have been obvious to similarly limit to a sole entity the manufacture tier, and additionally to manufacture at a single location, to further control distribution. *See also*, Borsand's teaching regarding the problems that arise "[a]s a result of the numerous entities involved in a pharmaceutical transaction." (*See* Borsand paragraph [0003], ROXGHB004124).
selecting the control of "requiring manufacture at a single location" "with the computer processor"	As noted, Moradi discloses a computer processor that controls ***distribution*** of the drug. Ukens teaches "restricting ***distribution*** of a specialty medication to only one pharmacy" (*see* Ukens p. 3 at ROXGHB004315 (emphasis added)). Extending the computer processor to require manufacture at a single location would be obvious.

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	One skilled in the art at the time would have been motivated to modify one or more of Lilly, Moradi, Ukens, Borsand, Deutsch, Williams, Califano, and Fletcher to have selected the control of requiring manufacture at a single location as taught by Gibson in view of one or more of Ukens, Borsand, and Moradi to make certain that only authorized individuals may obtain a drug. (*See* Gibson p. 5 at ROXGHB004247).
the "control" of "releasing inventory in a controlled manner to the central pharmacy"	Ukens' disclosure of "product going to ***only***" the exclusive central pharmacy describes releasing inventory in a controlled manner to the exclusive central pharmacy: "She pointed out that by restricting distribution of a specialty medication ***to only one pharmacy***, a manufacturer exposes patients to the risk of not receiving their medications in a timely manner if there's a disruption in the delivery system. In addition, shunting one part of therapy away from a patient's regular pharmacist can create the potential for undiscovered drug interactions. 'If you have ***a product going to only one distributor***, you have no safety net for the patient,' said Winckler. 'It creates problems if there are any issues of drug interactions or coordinating therapy. Using an 800 number for patient care may work for some patients, but if they don't want that, what's their alternative? They have to use whatever the system provides.'" (*See* Ukens p. 3 at ROXGHB004315 (emphasis added)).
selecting the control of releasing inventory in a controlled manner to the central pharmacy "with the computer processor"	Ukens discloses the implementation of inventory release in a controlled manner. Borsand's disclosure of computerized system 20 "track[ing]" pharmaceutical 28 involves pharmacy 40: "The ***pharmacy 40*** can confirm the lack of drug interactions, allergic reactions, protocol compliance, and otherwise confirm that the issued prescription 28 is pre-certified 38 and in compliance with the appropriate rules

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	and policies 34. The ***system 20*** provides functionality for ***tracking pharmaceutical 28***, prescription 32, and related information. The system 20 can temporarily or permanently link together the prescription 32 with the diagnosis resulting in the provider's 30 pharmaceutical 28 decision. Such linkage can allow the system 20 to track diagnosis information at potentially any time that prescription 32 information is also being tracked." (*See* Borsand paragraphs [0033] and [0034] at ROXGHB004126 (emphasis added)).
the "control" of "questioning early refills"	Borsand discloses: "The ***system 20*** can ***track*** whether or not a patient 22 has ***attempted to refill a prescription 32 before*** the pharmaceutical 28 in ***the initial prescription 32 was to have run out*** in accordance with the prescribed use of the pharmaceutical 28." (*See* Borsand paragraph [0034] at ROXGHB004126 (emphasis added)).
selecting the control of "questioning early refills" "with the computer processor"	Borsand describes use of computer 26 to perform the tracking for system 20. (*See* Borsand paragraphs [0033] and [0034] at ROXGHB004126).
the "control" of "flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions"	Lilly, in paragraphs [0068] and [0070] at ROXGHB004263, discloses aberrant use flags and the issuance of a flag if a "prescription presents a problem," and that system 100 "may require or suggest declining or approving the prescriptive medication." Additionally, the flagging of repeat instances of an individual reporting that an order has not been received is well-known. For instance, Changing Times p. 68 at ROXGHB004174, describing that "a ***second*** shipment [is sent] without question when a customer complains that he didn't receive his order," teaches that a record is kept pertaining to the quantity of such complaints that a customer makes.

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	Moreover, by discussing at paragraph [0011] at ROXGHB004256 fraud with the aim of obtaining "drugs for resale on the street," Lilly teaches flagging an attempt to obtain excess of a drug, such as by claims of lost, stolen, destroyed or spilled prescriptions.
selecting the control of "flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions" "with the computer processor"	Lilly discloses issuing a flag and declining to fill the prescription via system 100: "For instance, if a pharmacist is checking on a prescriptive medication prior to dispensing the prescriptive medication, ***a red flag as indicated at 140 may be issued if the prescription presents a problem***, e.g., is a conflicting type of drug (contraindicated prescriptive medication) or perhaps a similar type of drug which in combination with a previous prescriptive medication might be harmful to the consumer. *Red flags may be issued* as a result of *automatic* or manual operation. *System 100* and/or the pharmacist and/or the doctor *may require or suggest declining or approving the prescriptive medication*, and otherwise add notes, comments, and flags, as desired." (*See* Lilly paragraph [0070] at ROXGHB004263 (emphasis added)). One skilled in the art at the time would have been motivated to modify one or more of Lilly, Moradi, Ukens, Borsand, Deutsch, Williams, Califano, Fletcher, and Gibson to have selected the control of flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions as is obvious in view of one or more of Lilly and Changing Times at least to employ a major element for success in mail order. (*See* Changing Times p. 67-68 at ROXGHB004173-74).
the "control" of "limiting the prescription to a one month supply"	Williams discloses: "In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably ***no more than about 28 days***. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below." (*See* Williams col. 12 ln. 3-8 at ROXGHB004327 (emphasis added)).

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
selecting the control of "limiting the prescription to a one month supply" "with the computer processor"	Williams discloses the control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, ***in order to become registered in the computer readable storage medium***, the ***prescriber may be required to comply with various aspects of the methods described herein*** including, for example, providing patient education and counseling, and the like, as described in detail below." (*See* Williams col. 4 ln. 43-54 at ROXGHB004323 (emphasis added)).
the "control" of "requiring rewriting of the prescription periodically"	Williams discloses: "In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will ***not be permitted*** without a ***renewal prescription from the prescriber***, as discussed in detail below." (*See* Williams col. 12 ln. 3-8 at ROXGHB004327 (emphasis added)). *See also* Moradi paragraph [0098] at ROXGHB004302.
selecting the control of "requiring rewriting of the prescription periodically" "with the computer processor"	Williams discloses this control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, ***in order to become registered in the computer readable***

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below." (*See* Williams col. 4 ln. 43-54 at ROXGHB004323 (emphasis added)).
the "control" of "making the database available to the DEA for checking for abuse patterns in the data, for cash payments, and for inappropriate questions"	Lilly discloses making available to the DEA from the central database data required to reach the DEA's goals such as "determin[ing] where violations may be occurring." The data would be available to the DEA "for" checking for abuse patterns, for cash payments, and for inappropriate actions: "Many different types of entities/organizations may be electronically interconnected in accord with the present invention with respect to pharmaceutical information control organization 12. The ***types of data available to each organization*** maybe filtered depending on the type of organization/entity and the ***need thereof*** for the various types of pharmaceutical information available from pharmaceutical information control organization 12." (*See* Lilly paragraph [0052] at ROXGHB004260 (emphasis added)). "Government oversight entities 14, such as the ***DEA***, FBI, CDC, and so forth, may be able to ***utilize data as required to reach the organization goals*** and within the limitations required therefore. For instance, the DEA may review data to determine areas where violations may be occurring." (*See* Lilly paragraph [0054] at ROXGHB004260-61 (emphasis added)).
selecting the control of "making the database available to the DEA for checking for abuse patterns in the data, for cash payments, and for inappropriate questions" "with the computer processor"	Lilly discloses making, via computer interconnection arrangement 10, the needed data available to the DEA: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention."

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	(*See* Lilly paragraph [0051] at ROXGHB004260 (emphasis added)). "Many different types of entities/organizations may be electronically interconnected in accord with the present invention with respect to pharmaceutical information control organization 12. The ***types of data available to each organization*** maybe filtered depending on the type of organization/entity and the ***need thereof*** for the various types of pharmaceutical information available from pharmaceutical information control organization 12" (S*ee* Lilly paragraph [0052] at ROXGHB004260 (emphasis added)).
the selected "controls" are "for distribution by said exclusive central pharmacy"	The 6/19/06 OA and the Examiner's Answer each found Moradi disclosed "a method of ***distributing a drug under exclusive control of an exclusive central pharmacy***." *See*, Moradi, paragraphs [0003] at ROXGHB004295 and [0024] at ROXGHB004296. Also, the 10/18/06 OA and the Examiner's Answer each found Ukens disclosed an exclusive central pharmacy at page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). The noted ***controls*** would, in the context of such distribution under ***control*** of such exclusive central pharmacy, be ***controls*** for distribution by that exclusive central pharmacy.
2. The method of claim 1 wherein initially selected controls comprise communicating prescriptions from a physician to the central pharmacy; identifying the physician's name, license, and DEA registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check	

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
on whether any actions are pending against the physician; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has reviewed the educational materials; verifying the home address of the patient; shipping via US postal service; confirming receipt of an initial shipment of the drug to the patient; releasing inventory in a controlled manner to the central pharmacy; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; and making the database available to the DEA for checking for abuse patterns in the data.	
the "control" of "communicating prescriptions from a physician to the central pharmacy"	As noted above in connection with clause e of claim 1, *supra*, in the Examiner's Answer the Examiner found Moradi, Lilly and Ukens disclosed "***receiving all prescription requests at the exclusive central pharmacy from a medical doctor*** containing information identifying a patient, the sensitive drug, and various credentials of the doctor" (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the "control" of "communicating prescriptions from a physician to the central pharmacy"	As noted, in the Examiner's Answer the Examiner found that Moradi, Lilly, and Ukens disclosed prescription request receipt. As noted above in connection with clause e of claim 1, *supra*, such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260.
the selection is initial	Performance of prescription submission step 310 of Moradi, relating to the portions of Moradi cited by the Examiner's Answer in connection with recognizing the disclosure of prescription request receipt, is indicated by Fig. 3 of Moradi at ROXGHB004285 to be initial as performance of step 310 is depicted

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	by Fig. 3 as occurring prior to performance of subsequent steps.
the "control" of "identifying the physician's name, license, and DEA registration information"	As noted above in connection with clause e of claim 1, *supra*, Moradi discloses this control in relation to physician registration (*see* Moradi paragraph [0118] at ROXGHB004304).
selecting the "control" of "identifying the physician's name, license, and DEA registration information"	As noted above in connection with clause e of claim 1, *supra*, Moradi discloses this control selection (*see* Moradi paragraph [0109], ROXGHB004303).
the selection is initial	Fig. 7 of Moradi at ROXGHB004290 depicts physician registration as occurring prior to further actions (e.g., prior to "Display Successful Registration to user" step 730 and "Notify Admin of new Registration form" step 732).
the "control" of "verifying the prescription"	As noted above in connection with clause e of claim 1, *supra*, Moradi discloses this control in relation to step 316 of verifying the prescription (*see* Moradi paragraph [0042] at ROXGHB004299).
selecting the "control" of "verifying the prescription"	As noted above in connection with clause e of claim 1, *supra*, Moradi discloses the control selection (*see* Moradi paragraph [0028] at ROXGHB004297).
the selection is initial	Fig. 3 of Moradi at ROXGHB004285 depicts the processing of prescription verification step 316 as occurring prior to the processing of subsequent steps.
the "control" of "obtaining patient information"	As noted above in connection with clause e of claim 1, *supra*, in the Examiner's Answer the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all prescription requests at the exclusive central pharmacy from a medical doctor containing ***information identifying a patient***, the sensitive drug, and various credentials of the doctor" (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." As further noted in connection with clause e of claim 1, *supra*, *see also* Moradi paragraph [0035] at ROXGHB004297-98.

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
selecting the "control" of "obtaining patient information"	As noted, in the Examiner's Answer, the Examiner found Moradi, Lilly, and Ukens disclosed receipt of prescription requests containing patient information. As noted above in connection with clause e of claim 1, *supra*, such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260. As further noted above in connection with clause e of claim 1, *supra*, *see also* Moradi paragraph [0031] at ROXGHB004297.
the selection is initial	Performance of prescription submission step 310 of Moradi, relating to the portions of Moradi cited by the Examiner's Answer in connection with recognizing the disclosure of the receipt of prescription requests containing patient information, is indicated by Fig. 3 of Moradi at ROXGHB004285 to be initial as performance of step 310 is depicted by Fig. 3 as occurring prior to performance of subsequent steps. *See also* Fig. 3 of Moradi at ROXGHB004285 depicting patient registration as occurring prior to further actions.
the "control" of "verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician"	As noted above in connection with clause e of claim 1, *supra*, this control selection is obvious in view of one or more of Deutsch, Moradi, and Borsand (*see* Moradi paragraphs [0113] – [0116] at ROXGHB004303, Deutsch pp. 252-254 at ROXGHB004196-98 and 269-272 at ROXGHB004213-16, and Borsand paragraph [0120] at ROXGHB004134).
selecting the "control" of "verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician"	As noted above in connection with clause e of claim 1, *supra*, Moradi discloses the performance of validation of physician data (*see* Moradi paragraph [0022] at ROXGHB004296). *See also* Moradi paragraph [0109] at ROXGHB004303 and Borsand paragraph [0120] at ROXGHB004134.

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
the selection is initial	Moradi indicates such validation to be initial by indicating such validation to correspond to physician registration and by Fig. 7 of Moradi at ROXGHB004290 indicating such physician registration as occurring prior to further actions (e.g., prior to "Display successful Registration to user" step 730 and "Notify Admin of new Registration form" step 732). Borsand indicates such checking to be initial as paragraph [0120] of Borsand at ROXGHB004134 explains the checking to occur prior to, as is found to be appropriate, either performing or not performing prescription modification or cancellation.
the "control" of "verifying patient registry information"	As noted above in connection with clause e of claim 1, *supra*, this is disclosed by Moradi in relation to server-side validation of patient registration data (*see* Moradi paragraph [0161] at ROXGHB004305).
selecting the control of "verifying patient registry information"	As noted above in connection with clause e of claim 1, *supra*, Moradi discloses this control selection (*see* Moradi paragraphs [0031] at ROXGHB004297 and [0161] at ROXGHB004305).
the selection is initial	Moradi indicates such validation to be initial by indicating such validation to correspond to patient registration and by Fig. 3 of Moradi at ROXGHB004285 depicting such patient registration as occurring prior to further actions (e.g., prior to prescription submission step 310).
the "control" of "providing comprehensive education information to the patient"	As noted above in connection with clause e of claim 1, *supra*, this is disclosed by Williams in relation to patient counseling (*see* Williams col. 8 ln. 57 - col. 9 ln. 2 at ROXGHB004325-26). As also noted above in connection with clause e of claim 1, *supra*, in the in the 6/19/06 OA and the Examiner's Answer the Examiner found "confirming with the patient that educational material has been read prior to shipping the drug" is disclosed by Califano. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
selecting that the control of "providing comprehensive education information to the patient"	As noted above in connection with clause e of claim 1, *supra*, Williams discloses this control selection (*see* Williams col. 4 ln. 43-54 at ROXGHB004323). As further noted above in connection with clause e of claim 1, *supra*, *see also* Califano paragraphs [0052] at ROXGHB004159 and [0084] at ROXGHB004163.
the selection is initial	Col. 8 ln. 45-59 of Williams at ROXGHB004325 discuss the patient counseling as occurring "[p]rior to prescribing the drug." *See also* paragraph [0084] of Califano at ROXGHB004163 which discusses occurrence "before participation in a study begins."
the "control" of "verifying the patient has reviewed the educational materials"	As noted above in connection with clause e of claim 1, *supra*, this is disclosed by Williams in relation to informed consent verification (*see* Williams col. 10 ln. 23-46 at ROXGHB004326). As also noted above in connection with clause e of claim 1, *supra*, in the 6/19/06 OA and the Examiner's Answer the Examiner found "confirming with the patient that educational material has been read prior to shipping the drug" is disclosed by Califano. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "verifying the patient has reviewed the educational materials"	As noted above in connection with clause e of claim 1, *supra*, Williams discloses this control selection (see Williams col. 10 ln. 23-32 at ROXGHB004326). As further noted above in connection with clause e of claim 1, *supra*, *see also* Califano paragraphs [0084] and [0086] at ROXGHB004163-64.
the selection is initial	Col. 10 ln. 23-32 of Williams at ROXGHB004326 discuss the informed consent verification as occurring "[p]rior to receiving a prescription for the drug." *See also* paragraph [0084] of Califano at ROXGHB004163 which discusses occurrence "before participation in a study begins."
the "control" of "verifying the home address of the patient"	As noted above in connection with clause e of claim 1, *supra*, Moradi discloses this control in relation to server-side validation of patient registration data (*see, e.g.,* Moradi paragraphs [0136] at ROXGHB004304, [0139], [0140], [0141] and

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	[0161] at ROXGHB004305).
selecting the control of "verifying the home address of the patient"	As noted above in connection with clause e of claim 1, *supra*, Moradi discloses this control selection (*see* Moradi paragraphs [0031] at ROXGHB004297 and [0161] at ROXGHB004305).
the selection is initial	Moradi indicates such validation to be initial by indicating such validation to correspond to patient registration and by Fig. 3 of Moradi at ROXGHB004285 depicting such patient registration as occurring prior to further actions (e.g., prior to prescription submission step 310).
the "control" of "shipping via US postal service"	As noted above in connection with clause e of claim 1, *supra*, in the 10/28/06 OA and the Examiner's Answer the Examiner found "only ***mailing*** the drug to the patient if no potential abuse is found …" to be disclosed by Moradi (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "shipping via US postal service"	As noted above in connection with clause e of claim 1, *supra*, Moradi teaches implementing the "mailing the drug to the patient" noted by the Examiner to be disclosed by Moradi with a computer or processing device (*see* Moradi paragraph [0022] at ROXGHB004296).
the selection is initial	Moradi indicates such shipping to be initial as Fig. 3 of Moradi at ROXGHB004285 depicts items 318 and 322 of Moradi cited by the 10/28/06 OA and the Examiner's Answer in connection with recognizing the disclosure of "only mailing the drug to the patient if no potential abuse is found …" as corresponding to steps occurring prior to further actions (e.g., prior to "Route to Admin Office for Further Action" step 320 and "Delivery Person Returns with Patient's Signature, Stamps Prescription Signifying Delivery, Update POD System" step 324).
the "control" of "confirming receipt of an	As noted above in connection with clause e of claim 1, *supra*, Moradi discloses delivery by mail of the "initial fulfillment" of a prescription medication and a

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
initial shipment of the drug to the patient"	delivery person communicating to Central Service Station (CSS) 102 of system 100 via Point of Delivery (POD) system 106 of system 100 status designations of "delivered, no one at the address, prescription mismatch or one of a number of other potential reasons for non-delivery" (*see* Moradi paragraphs [0006] at ROXGHB004295 and [0043] at ROXGHB004299). As also noted above in connection with clause e of claim 1, *supra*, in the 6/19/06 OA and the Examiner's Answer, the Examiner found that "confirming receipt by the patient of the drug" is disclosed by Moradi. The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "confirming receipt of an initial shipment of the drug to the patient"	As noted above in connection with clause e of claim 1, *supra*, Moradi discloses the communication of the status designations to be implemented via POD system 106 and CSS 102 of system 100 (*see* Moradi paragraph [0043] at ROXGHB004299).
the selection is initial	Paragraph [0006] of Moradi at ROXGHB004295, discussing the "initial fulfillment" of a prescription medication and "refills" for that prescription medication, explains that the communication of the status designations for the "initial fulfillment" is initial by indicating it to occur prior to those "refills."
the "control" of "releasing inventory in a controlled manner to the central pharmacy"	As noted above in connection with clause e of claim 1, *supra*, Ukens' disclosure of "product going to ***only***" the exclusive central pharmacy describes releasing inventory in a controlled manner to the exclusive central pharmacy (*see* Ukens p. 3 at ROXGHB004315).
selecting the control of "releasing inventory in a controlled manner to the central pharmacy"	As noted above in connection with clause e of claim 1, *supra*, Ukens discloses the implementation of inventory release in a controlled manner. As also noted above in connection with clause e of claim 1, *supra,* Borsand's disclosure of computerized system 20 "track[ing]" pharmaceutical 28 involves pharmacy 40.

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
the selection is initial	Ukens indicates inventory release in a controlled manner to the exclusive central pharmacy of Ukens to be initial as Ukens, by discussing patients being exposed "to the risk of not receiving their medications in a timely manner" in connection with "product going to only" the exclusive central pharmacy, indicates that inventory being released in a controlled manner to the exclusive central pharmacy of Ukens occurs prior to medication receipt by patients.
the "control" of "flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions"	As noted above in connection with clause e of claim 1, *supra*, this control selection is obvious in view of one or more of Lilly and Changing Times (*see* Lilly paragraphs [0011] at ROXGHB004256, [0068] and [0070] at ROXGHB004263 and Changing Times p. 68 at ROXGHB004174).
selecting the control of "flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions"	As noted above in connection with clause e of claim 1, *supra*, Lilly discloses issuing a flag and declining to fill the prescription via system 100 (*see* Lilly paragraph [0070] at ROXGHB004263).
the selection is initial	Lilly indicates the flagging to be initial by indicating such flagging to relate to step 140 of Fig. 2 of Lilly at ROXGHB004255 and by Fig. 2 of Lilly depicting step 140 as occurring prior to further actions.
the "control" of "making the database available to the DEA for checking for abuse patterns in the data"	As noted above in connection with clause e of claim 1, *supra*, Lilly discloses making available to the DEA from the central database data required to reach the DEA's goals such as "determin[ing] where violations may be occurring." The data would be available to the DEA "for" checking for abuse patterns (*see* Lilly paragraphs [0052] and [0054] at ROXGHB004260-61).
selecting the control of "making the database available to the DEA for checking for abuse patterns in the data"	As noted above in connection with clause e of claim 1, *supra*, Lilly discloses making, via computer interconnection arrangement 10, the needed data available to the DEA (*see* Lilly paragraphs [0051] and [0052] at ROXGHB004260).
the selection is initial	Lilly indicates making the needed data available to the DEA to be initial by explaining making the needed data available to the DEA to occur prior to the DEA "review[ing] data to determine areas where violations may be occurring"

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	(*see* Lilly paragraphs [0052] and [0054] at ROXGHB004260-61).
3. The method of claim 1 which further comprises consulting a separate database to verify that the medical doctor is eligible to prescribe the drug.	Moradi discloses validation of physician data: "The CSS program 202 performs the following validations and if there are any validation errors, an error message is displayed to the user identifying the field or fields in error: Physician License Number: The Physician License number consists of an alphabetical prefix (used as license type) followed by a number assigned to licensed physician. It is used to identify physician to various payers. ***Existing*** Internet data resources are used by the exemplary embodiment to verify the physician license number" (*See* Moradi paragraphs [0113] - [0114] at ROXGHB004303 (emphasis added)). Moradi indicates the data resources employed in the validation to be separate from CSS database 204 of Moradi by characterizing the data resources as "[e]xisting." That a data resource can be a database is well-known.

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
(preamble) 4. A computerized method to control abuse of gamma hydroxy butyrate (GHB) comprising:	The preamble is not a limitation of the claim. However, if the Court were to construe the preamble as a limitation, then it is disclosed in the prior art as follows:
"control abuse" of a drug	Lilly discloses: "In accord with the method of the present invention, a secure, private, independent, network-based, centralized ***method*** operable for ***tracking and managing prescriptive medication*** information in aggregate is provided which allows electronic querying and real-time notification of patients' prescriptive medication history at the time of prescriptive medication creation. According to the method of the invention, this information is accessible within a controlled and appropriate context for use by healthcare professionals involved in the delivery of care to that patient." (*See* Lilly paragraph [0050], ROXGHB004260 (emphasis added)). "Government oversight entities 14, such as the DEA, FBI, CDC, and so forth, may be able to utilize data as required to reach the organization goals and within the limitations required therefore. For instance, the DEA may review data to determine areas where ***violations*** may be occurring … All of these entities can have immediate access to potential medication ***abuse*** by identification of needless prescription duplications, potential drug interactions, and multi-source interstate ***prescriptive medication abuse***." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)).
the drug is "gamma hydroxy butyrate"	In the 10/18/06 OA and the Examiner's Answer , the Examiner found the drug GHB" disclosed by "An Interview with Orphan Medical about Xyrem." The BPAI Decision held the Examiner's findings "accepted as being undisputed" (BPAI Decision, p. 6, ROXGHB004756) (*see* claim 1 clause a, *supra*).
a "computerized" method	Lilly teaches: "Referring now to the drawings and, more particularly to FIG. 1, there is shown

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)). One skilled in the art would have been motivated to modify Lilly to implement the "An Interview with Orphan Medical about Xyrem" teaching of the drug being gamma hydroxy butyrate to, as noted by the Examiner in connection with the 10/18/06 OA and the Examiner's Answer history, "provide this medicine to patients that need it in a responsible manner (see 'An Interview with Orphan Medical about Xyrem,' talkaboutsleep.com)."
(clause a) controlling with a computer processor the distribution of GHB via an exclusive central pharmacy that maintains a central database that tracks all prescriptions of GHB and analyzes for potential abuse situations; "controlling the distribution" of the drug a computer processor controls "the distribution" of the drug	In the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi disclosed "***only mailing*** the drug to the patient ***if*** no potential abuse is found …" *See* Moradi, paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Moradi states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)).

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
the distribution is "via" an "exclusive central pharmacy"	The 6/19/06 OA and the Examiner's Answer each found Moradi disclosed "a method of ***distributing a drug under*** exclusive ***control of*** an ***exclusive central pharmacy.***" *See* Moradi, paragraphs [0003] at ROXGHB004295 and [0024] at ROXGHB004296. Also, the 10/18/06 OA and the Examiner's Answer each found that Ukens, at page 3, paragraphs 3-5 at ROXGHB004315, disclosed an exclusive central pharmacy. The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
the "exclusive central pharmacy" "maintains" a "database"	In the 6/19/06 OA, the 10/18/06 OA and the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer ***database associated with the exclusive central pharmacy*** for analysis of potential abuse situations." *See*, Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). (*See* claim 1 clause a, *supra*).
the database is a "central database"	In the context of Ukens' exclusive ***central*** pharmacy, the Lilly database constitutes an exclusive ***central*** database.
the central database "tracks" "prescriptions" of the drug and "analyzes for potential abuse situations"	Lilly discloses that the central database (1) tracks prescriptions: "The industry has widely recognized a need for better efficiencies, but without notable success in many areas, including prescription abuse. For instance, the Healthcare Information Portability and Accountability Act (HIPAA) mandates making the exchange of information more ubiquitous, secure, and efficient but does not provide a solution with respect to ***prescription tracking*** and abuse." (*See* Lilly paragraph [0009], ROXGHB004256 (emphasis added)). "In accord with the method of the present invention, a secure, private,

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	independent, network-based, centralized method operable for ***tracking*** and managing ***prescriptive medication information*** in aggregate is provided which allows electronic querying and real-time notification of patients' prescriptive medication history at the time of prescriptive medication creation." (*See* Lilly paragraph [0050], ROXGHB004260 (emphasis added)). "All of these entities can have immediate access to potential medication abuse by ***identification*** of needless ***prescription duplications***, potential drug interactions, and multi-source interstate prescriptive medication abuse." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)). and (2) analyzes for potential abuse situations. In the 6/19/06 OA, the 10/18/06 OA, and the Examiner's Answer, the Examiner found Lilly and Ukens disclosed "requiring entering of the information into an exclusive computer ***database*** associated with the exclusive central pharmacy for ***analysis of potential abuse situations.***" *See*, Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision affirmed the Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
"all" prescriptions are tracked	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving ***all*** prescription requests at the exclusive central pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3,

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	paragraphs 3-5, ROXGHB004315 (emphasis added). As the exclusive central pharmacy of Ukens receives all prescriptions, the tracking performed by the central database of Lilly in the context of Ukens would be of such all prescriptions. One skilled in the art at the time would have been motivated to modify Lilly and "An Interview with Orphan Medical about Xyrem" to control distribution of the drug as taught by Moradi at least to "securely provid[e] prescription medication to patients." (*See* Moradi, abstract, ROXGHB004282). One skilled in the art at the time would have been further motivated to modify Lilly, "An Interview with Orphan Medical about Xyrem," and Moradi to include the exclusive central pharmacy of Ukens, to, as noted by the Examiner in connection with the 10/18/06 OA and the Examiner's Answer, "limit access to dangerous drugs (page 3, paragraph 5 of Ukens)."
(clause b) receiving in the computer processor all prescription requests, for any and all patients being prescribed GHB, only at the exclusive central pharmacy, from any and all medical doctors allowed to prescribe GHB; receiving all prescription requests "in the computer processor"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "receiving all prescription requests at the exclusive central pharmacy from a medical doctor containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See* Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). Moradi states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). (*See* also Lilly paragraph [0051], ROXGHB004260 (emphasis added)).
"for any and all patients being prescribed" the drug, "only at the exclusive central pharmacy from any and all medical doctors allowed to prescribe" the drug	Ukens discloses "restricting distribution of a specialty medication to only ***one*** pharmacy." (*See* Ukens p. 3, para. 3; emphasis added). Ukens also teaches that the specialty medications are "prescribed." (*See* Ukens p. 3, para. 1 at ROXGHB004315).
(clause c) processing with the computer processor all prescriptions for GHB only by the exclusive central pharmacy using only the central database;	
processing all prescriptions "only by the exclusive central pharmacy"	Ukens teaches "restricting distribution of a [prescribed] specialty medication to only one pharmacy." (*See* Ukens p. 3, paragraphs 1 and 3, ROXGHB004315 (emphasis added)).
processing all prescriptions "using only the central database"	Borsand describes storing ***all*** pharmaceutical-related information ***only once*** and in a ***single*** database 62: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
exclusive central pharmacy processes "with the computer processor"	to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)). *See also* Fig. 3 of Borsand at ROXGHB004112, which describes the pharmaceutical-related information stored in single database 62 as including pharmacy benefit managers ("PBM") information, payor information, ***prescription*** information, ***patient*** information, and *provider* information. Borsand further discloses at paragraph [0030] at ROXGHB004125 that such a provider can be a ***physician***. As noted above in connection with clause a, *supra*, Moradi discloses a computer processor. Further, Borsand states: "The ***computer 26*** can be a single centralized computer or server, a single network, a series of interconnected networks, a series of devices capable of accessing the Internet or World Wide Web including an application server, or any other configuration which supports the ability of different entities to communicate with one another." (*See* Borsand paragraph [0031] at ROXGHB004125 (emphasis added)). One skilled in the art at the time would have been motivated to modify Lilly, "An Interview with Orphan Medical about Xyrem," Moradi, and Ukens to process prescriptions using ***only*** a central database as taught by Borsand at least to allow all pharmaceutical-related information to be stored on a single database that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines. (*See* Borsand paragraph [0043], ROXGHB004127).
(clause d) determining with the computer processor current and anticipated patterns of potential prescription abuse of GHB from periodic reports generated only by the central database based on prescription request data from a	

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
particular medical doctor and further based on filling of prescriptions by a particular patient, wherein said request data contain information identifying the patient, the drug prescribed, and credentials of the medical doctor; and	
determining patterns of "potential prescription abuse" of the drug from "periodic reports"	In the 6/19/06 OA and the Examiner's Answer, the Examiner found Lilly discloses "generating ***periodic reports*** via the exclusive computer database to evaluate ***potential diversion*** patterns." *See*, Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263 (emphasis added). The BPAI Decision affirmed the Examiner's finding of an "exclusive computer database" in Lilly and held all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
determining the patterns "with the computer processor"	As noted above in connection with clause a, *supra*, Moradi discloses a computer processor. As noted above in connection with clause c, *supra*, Borsand also discloses a computer processor. Further, Lilly teaches: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051], ROXGHB004260 (emphasis added)).
the "central database" generates the periodic reports	As noted above in clause a, the "central database" is disclosed at least in Lilly in view of Ukens. In the 6/19/06 OA and the Examiner's Answer, the Examiner found Lilly disclosed "***generating periodic reports*** via the exclusive computer ***database*** to evaluate potential diversion patterns." *See* Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61,

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	[0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263 (emphasis added). The Examiner's finding regarding the disclosure of an "exclusive computer database" in Lilly was affirmed in the BPAI Decision holding all other findings of the Examiner "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
the patterns which are determined are "current and anticipated" patterns	Lilly teaches: "Pharmacies 26 may check to personally verify the drug usage of each purchaser to ***immediately*** detect problems related to ***abuse, fraud, and misuse*** of medications … Pharmacists are constantly challenged to circumvent duplication, ***abuse, fraud, and misuse*** of these medications while providing a cost effective medication delivery system. In the present health system the wide availability of pharmaceuticals from different pharmacies raises the risks of negative drug interactions and its associated destructive medical outcome. ***Pharmaceutical information control organization 12 can flag these issues*** in real time, thereby ***completely preventing*** or at least minimizing their occurrences." (*See* Lilly paragraph [0057] at ROXGHB004261 (emphasis added)). "FIG. 2 discloses a presently preferred pharmaceutical information flow diagram 100 for a method of operation of ***pharmaceutical information control organization 12*** in accord with the present invention. A plurality of entities, networks, organizations may be utilized in accord with the present invention including doctors 102. Pharmacies 104 include pharmacies that are affiliated with each other as well as pharmacies that are unaffiliated with each other. Other entities include hospitals 106, pharmaceutical companies 108, insurance companies 110 (which may include health or life insurance companies or any other type of insurance companies), government agencies 112, health care informatics companies 114, health researchers 116, managed care organizations 118, and other healthcare providers 120 … In a preferred embodiment, the present invention provides that ***data storage 122*** is able to access the ***databases*** of the above-listed entities and/or other member

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	organizations as needed and/or store the corresponding pharmaceutical data in data storage 122 which is external to each entity's database(s) … Data storage 122 preferably has the ability to allow the software schemas to be changed without disruption of system 100." (See Lilly paragraph [0061], ROXGHB004262 (emphasis added)). *See also* Lilly, paragraph [0058] at ROXGHB004261
generating periodic reports based on prescription request data from a particular medical doctor and further based on filling of prescriptions by a particular patient	Lilly teaches: "The method may further comprise providing that the pharmaceutical computer data for each of the prescriptive medication purchases comprises a name of ***a*** respective ***prescriptive medication purchaser***, an address of the respective prescriptive medication purchaser, *a drug prescribed,* the respective prescriptive medication purchaser, a quantity of the drug, a dosage of the drug, a pharmacist name, and *a doctor* name." (See Lilly paragraph [0041], ROXGHB004259 (emphasis added)). "Presently, legal regulations may require that each time a prescriptive medication is ***filled*** that a paper copy of the transaction is forwarded to the DEA … All of these entities can have immediate access to potential medication abuse by ***identification*** of needless *prescription duplications*, potential drug interactions, and multi-source interstate prescriptive medication abuse." (*See* Lilly paragraph [0054], ROXGHB004260-61 (emphasis added)). "Various types of data may be stored and/or obtained such as ***the doctor name, the doctor DEA number, patient name, patient ID*** (e.g. SS#, passport #, driver's license, etc.), ***patient address, city, state, zip, patient phone number***, drugs prescribed, dosage, frequency, start/end date, duration, quantity, number refills, whether substitution is allowed, generic allowed, notes, aberrant use flag, date *prescription filled*, place ***prescription filled***, pharmacist name, pharmacist phone number, pharmacist DEA number, and

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	application programming interfaces utilized." (*See* Lilly paragraph [0068], ROXGHB004263 (emphasis added)). "The display may be made by ***a patient identifier, patient name,*** date, drug name, ***doctor prescribing the medication***, pharmacy, geography (city, state, zip code), by phone number, and/or by aberrant use flag." (*See* Lilly paragraph [0069], ROXGHB004263 (emphasis added)).
generating the periodic reports based on the prescription request data and based on the filling of prescriptions "only" by the central database	Borsand describes storing ***all*** pharmaceutical-related information -- including prescription information -- ***only once*** and in a ***single*** database 62 and, thus, periodic reports would be generated ***only*** by the central database: "FIG. 3 discloses some of the underlying technical architecture that could be utilized to support the system 20. In ***a preferred embodiment*** of the invention, ***all pharmaceutical-related information is stored on a single database 62*** that is accessible to any party subject to the appropriate privacy regulations, policies, and guidelines." (*See* Borsand paragraph [0043], ROXGHB004127 (emphasis added)). "As a result of the numerous entities involved in a pharmaceutical transaction, prior art systems and methods do not manage and utilize information in an efficient manner. Linear and reactive communications result in a lack of centralized data access, duplicative efforts, and redundant information while at the same time such systems fail to provide access to important information to the appropriate entities. It would be desirable for pharmaceutical information to be stored ***only once*** and in a centralized location accessible by the appropriate parties." (*See* Borsand paragraph [0003], ROXGHB004124 (emphasis added)).
the request data contain "information identifying the patient, the drug prescribed, and credentials of the medical doctor"	In the Examiner's Answer, the Examiner found that "receiving all ***prescription requests*** at the exclusive central pharmacy from a medical doctor containing information identifying a ***patient***, the sensitive ***drug***, and various ***credentials of the doctor***" disclosed in Moradi paragraphs [0035] at ROXGHB004297-98,

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	[0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added).
(clause e) selecting with the computer processor multiple controls for distribution by said exclusive central pharmacy, the controls comprising communicating prescriptions from a physician to the central pharmacy; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the GHB by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient returning the drug to the pharmacy after two attempts to deliver; launching an investigation	

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; releasing inventory in a controlled manner to the central pharmacy; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse patterns in the data, for cash payments, and for inappropriate questions.	
"selecting" with the computer processor of "multiple controls," the controls comprising …"	
the "control" of "communicating prescriptions from a physician to the central pharmacy"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving all prescription requests at the exclusive central pharmacy from a medical doctor*** containing information identifying a patient, the sensitive drug, and various credentials of the doctor." *See*, Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the "control" of "communicating prescriptions from a physician to the central pharmacy" "with the computer processor"	As noted, in the Examiner's Answer, the Examiner found that Moradi, Lilly, and Ukens disclosed prescription request receipt. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	ROXGHB004260. It would have been obvious to a person of ordinary skill in the art to have a computer processor select this prescription drug distribution control (or any of the other listed controls) in order to control abuse of a prescription drug.
the "control" of "identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information"	Moradi discloses: "The physician registration module starts by displaying an online registration page that is a single display page that allows a physician to enter data used by the automated prescription delivery system 100. The data includes the physician's ***name, address, practice information, DEA number, license numbers***, e-mail, phone number and web site address." (*See* Moradi paragraph [0118], ROXGHB004304 (emphasis added)).
selecting the "control" of "identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information" "with the computer processor"	Moradi describes: "This module allows a physician to complete an online registration form for access to the automated prescription delivery system 100. This module is part of the Registration module 218. This module is used for entering required physician registration information and does not grant access to the system." (*See* Moradi paragraph [0109] at ROXGHB004303).
the "control" of "verifying the prescription"	Moradi discloses: "Once the POD system 106 at the pharmacy has received the image of the prescription from the CSS 102, the data are decrypted and the processing continues by using a software based data authenticator to ***verify***, at step 316, ***the prescription*** at the POD system 106. This step includes operating a software based digital signature authenticator to ensure that a valid digital signature has been added to the prescription. This step also requires that if the prescription is not refillable, or if the prescription is refillable but the number of digital signatures added to the prescription image is equal to or greater than

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	the number of refills, the operator is to check the order for cancellations of previous submissions to the POD 106." (*See* Moradi paragraph [0042] ROXGHB004299 (emphasis added)).
selecting the "control" of "verifying the prescription" "with the computer processor"	Moradi discloses verifying the prescription with a computer or processing device, which can correspond to PODP software 212 of that computer or processing device. (*See* Moradi paragraph [0028] at ROXGHB004297).
the "control" of "obtaining patient information"	In the Examiner's Answer, the Examiner found Moradi, Lilly and Ukens disclosed "***receiving*** all prescription requests at the exclusive central pharmacy from a medical doctor containing ***information identifying a patient***, the sensitive drug, and various credentials of the doctor." *See*, Moradi paragraphs [0035] at ROXGHB004297-98, [0116], and [0117] at ROXGHB004303; Lilly paragraphs [0011] at ROXGHB004256, [0033] at ROXGHB004259, [0054] at ROXGHB004260-61, [0057], [0058] at ROXGHB004261, [0061] at ROXGHB004262, and [0069] at ROXGHB004263, and Ukens, page 3, paragraphs 3-5, ROXGHB004315 (emphasis added). The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the "control" of "obtaining patient information" "with the computer processor"	As noted, in the Examiner's Answer the Examiner found Moradi, Lilly, and Ukens disclosed receipt of prescription requests containing patient information. Such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260. *See also* Moradi paragraph [0031] at ROXGHB004297.
the "control" of "verifying the physician is eligible to prescribe" the drug "by consulting the National Technical Information Services to determine whether the physician has an active DEA number	Moradi discloses validation of physician data that involves: "The CSS program 202 ***performs the following validations*** and if there are any validation errors, an error message is displayed to the user identifying the field or fields in error:

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
and to check on whether any actions are pending against the physician"	Physician License Number: The Physician License number consists of an alphabetical prefix (used as license type) followed by a number assigned to licensed physician. It is used to identify physician to various payers. ***Existing*** Internet data resources are used by the exemplary embodiment to verify the physician license number … ***DEA Number Validation***: The DEA is an alphanumeric string that is currently a number beginning with an A or B that is followed by another letter. The exemplary embodiment of the present invention is configured to accommodate any alphanumeric string so as to allow for DEA numbers that begin with other values. The DEA number in the exemplary embodiment is able to begin with any two alphanumeric characters." (*See* Moradi paragraphs [0113] - [0116], ROXGHB004303 (emphasis added)). The National Technical Information Service is a well known data resource for physician data including DEA number. *See, e.g.,* Deutsch pp. 253-254 at ROXGHB004197-98 and 269-272 at ROXGHB004213-16. Moreover, it is well known to employ a data resource in performing a disciplinary action check with respect to a physician. *See, e.g.,* Deutsch pp. 252-253 at ROXGHB004196-97 and 269-272 at ROXGHB004213-16. Borsand discloses checking, both before and after prescription 28 is filled, for ***evidence of fraud or misuse by provider 30***. (*See* Borsand paragraph [0120] at ROXGHB004134). Such checking would obviously include checking whether any actions are pending using, as for example taught by paragraph [0114] of Moradi at ROXGHB004303, a data resource for physician data. Accordingly, it would have been obvious to verify the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
selecting the "control" of "verifying the physician is eligible to prescribe" the drug "by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician" "with the computer processor"	check on whether any actions are pending against the physician. Moradi discloses the validation of physician data to be performed with a computer processor: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." (*See* Moradi paragraph [0022], ROXGHB004296 (emphasis added)). (*See* Moradi paragraph [0109], ROXGHB004303 (emphasis added)). Borsand discloses: "The ***system 20*** facilitates communication between a payor 60, a PBM 50, a pharmacist 40, and a provider 30 even after a prescription 32 is generated and filled. FIG. 11 is a flow chart illustrating the cancellation or modification of a prescription 28. The modification of a prescription at 132 is an event triggered process. There must be an ***event that triggers the modification or cancellation of a prescription 28***. The ***triggering event could be*** a change in the condition of a patient 22, a change in the reimbursement rules 34 of a payor 60 or PBM 50, or ***evidence of fraud, misuse, or redundancy on the part of a provider 30***, pharmacist 40, or patient 22" (*See* Borsand paragraph [0120], ROXGHB004134 (emphasis added)). One skilled in the art at the time would have been motivated to modify one or more of Lilly, "An Interview with Orphan Medical about Xyrem," Moradi, Ukens, and Borsand to have selected the control of verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician as is obvious in view of one or more of Deutsch, Moradi, and Borsand at least to

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	make use of resources that are helpful with verification and information gathering. (*See* Deutsch p. 269 at ROXGHB004213).
the "control" of "providing comprehensive printed materials to the physician"	Borsand describes allowing provider 30 to view via computer "detailed information for a particular pharmaceutical 32." (*See* Borsand paragraphs [0050] and [0054] at ROXGHB004128). That information viewed via computer can be provided in printed form is well-known.
selecting the "control" of "providing comprehensive printed materials to the physician" "with the computer processor"	Borsand discloses use of "java script" execution in connection with provider home page 30.02 of computer 26 in viewing detailed information on a particular pharmaceutical. (*See* Borsand paragraphs [0031] at ROXGHB004125-26, [0050], and [0054] at ROXGHB004128).
the control of "contacting the patient's insurance company if any"	Borsand describes contacting a patient's payor (health insurance company), including pre-authorization contact: "The present invention relates to a computer based system for tracking information related to pharmaceutical prescriptions, and communicating the information to all entities appropriately involved in that particular prescription. The invention supports direct, proactive, and timely ***communication between a payor***, pharmacy benefit managers ('PBMs'), pharmacies, and providers. Such communication facilitates cost savings and eliminates unnecessary processes and 're-work.'" (*See* Borsand paragraph [0010], ROXGHB004125 (emphasis added)). "In a preferred embodiment of the invention, ***an e-mail (or similar communication such as a facsimile)*** containing the relevant pre-authorization information ***is sent*** directly ***to a payor*** or PBM when the provider confirms that the prescription 28 is to include the pre-authorized pharmaceutical 32." (*See* Borsand paragraph [0062] at ROXGHB004129 (emphasis added)). *See also* Borsand paragraph [0037] at ROXGHB004126 and [0053] at

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	ROXGHB004128.
selecting the control of "contacting the patient's insurance company if any" "with the computer processor"	Borsand describes: "The present invention relates to a ***computer*** based system for tracking information related to pharmaceutical prescriptions, and communicating the information to all entities appropriately involved in that particular prescription. The invention supports direct, proactive, and timely communication between a payor, pharmacy benefit managers ('PBMs'), pharmacies, and providers. Such communication facilitates cost savings and eliminates unnecessary processes and 're-work.'" (*See* Borsand paragraph [0010], ROXGHB004125 (emphasis added)).
the "control" of "verifying patient registry information"	Williams discloses a computer readable storage medium in which patients are registered. where a patient's prescription for a drug is filled only after the medium has been consulted to assure that the patient is registered in the storage medium: "[a]s noted above, the drug delivery methods described herein also preferably involve the ***registration of the patient*** in a ***computer readable storage medium***. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein" (*See* Williams col. 5 ln. 61 - col. 6 ln. 3 at ROXGHB004324 (emphasis added)). "[t]he present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which ***prescriptions for the drug are filled only after*** a computer readable

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	storage medium has been ***consulted*** to ***assure*** that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the ***patient is registered*** in the medium and approved to receive the drug" (*See* Williams col. 2 ln. 49-60 at ROXGHB004322 (emphasis added)). "[t]he ***registration*** into one or more computer readable storage media of the prescriber, pharmacy and ***patient***, according to the methods described herein, provide a means to ***monitor and authorize distribution of contraindicated drugs***, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacys who are not registered generally may not dispense the drug. Similarly, ***the drugs generally may not be prescribed and/or dispensed to patients who are not registered*** in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and ***registered*** in the computer readable media, the ***patient*** generally ***may not receive the prescription for the drug***. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted" (*See* Williams col. 13 ln. 19-41 at ROXGHB004328 (emphasis added)). (*See also* Moradi paragraph [0161] at ROXGHB004305).
selecting the control of "verifying patient registry information" "with the computer processor"	As noted above in connection, respectively, with clauses a, c, and d, *supra*, Moradi, Borsand, and Lilly each disclose a computer processor. Additionally, as Williams discusses a "computer readable storage medium" (*see* Williams col. 2 ln. 50-60 at ROXGHB004322) a computer processor is described or suggested.

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	Williams discloses consulting a ***computer readable storage medium*** to assure that the patient is registered: "[t]he present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a ***computer readable storage medium*** has been ***consulted*** to ***assure*** that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the ***patient*** is ***registered in the medium*** and approved to receive the drug" (*See* Williams col. 2 ln. 49-60 at ROXGHB004322 (emphasis added)). "[s]imilarly, the ***drugs*** generally ***may not be prescribed and/or dispensed to patients*** who are ***not registered in*** a ***computer readable storage medium***" (*See* Williams col. 13 ln. 31-33 at ROXGHB004328 (emphasis added)). *See also* Moradi paragraphs [0031] at ROXGHB004297 and [0161] at ROXGHB004305. One skilled in the art would have been motivated to modify one or more of Lilly, "An Interview with Orphan Medical about Xyrem," Moradi, Ukens, Borsand, and Deutsch to have selected the control of verifying patient registry information as taught by Williams at least to ensure patient compliance with taking a drug (*see* Williams col. 3 ln. 56-59 at ROXGHB004323).
the "control" of "providing comprehensive education information to the patient"	Williams discloses: "Preferably the patient is provided ***full*** disclosure of ***all*** the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	drug. Such ***counsel*** may be provided verbally, as well as in ***written form***. In preferred embodiments, the prescriber provides the patient with ***literature materials*** on the drug for which a prescription is contemplated, such ***as product information, educational brochures, continuing education monographs, and the like***." (*See* Williams col. 8 ln. 57 - col. 9 ln. 2, ROXGHB004325-26 (emphasis added)). *See also* the 6/19/06 OA and the Examiner's Answer wherein the Examiner found that Califano disclosed "confirming with the patient that educational material has been read prior to shipping the drug." *See*, Califano, paragraph [0084] at ROXGHB004163. The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "providing comprehensive education information to the patient" "with the computer processor"	As noted above in connection, respectively, with clauses a, c, and d, *supra*, Moradi, Borsand, and Lilly each disclose a computer processor. As noted above in the instant clause in connection with the control of "verifying patient registry information," Williams discloses a computer processor. *See also* Califano's paragraph [0052] at ROXGHB004159 for disclosure of a computer processor. Williams discloses the control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, ***in order to become registered in the computer readable storage medium, the prescriber may be required*** to comply with various aspects of the methods described herein including, for example, ***providing patient education and counseling***, and the like, as described in detail below."

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	(*See* Williams col. 4 ln. 43-54 at ROXGHB004323 (emphasis added)). *See also* Califano paragraphs [0052] at ROXGHB004159 and [0084] at ROXGHB004163. One skilled in the art at the time would have been motivated to modify one or more of Lilly, "An Interview with Orphan Medical about Xyrem," Moradi, Ukens, Borsand, Deutsch, and Williams to have selected with a computer processor the control of providing comprehensive education information to the patient as taught by Califano at least to, as noted by the Examiner in connection with the 6/19/06 OA and the Examiner's Answer, "ensure that the patient knows about the risks and dangers associated with the drug (para. 43 of Califano)."
the "control" of "verifying the patient has reviewed the educational materials"	Williams discloses: "In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the ***patient to fill out an informed consent form*** which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. ***Verification that the patient*** has given his/her informed consent may also be registered in the computer readable storage medium … By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. ***In the informed consent form***, the patient preferably ***agrees to*** comply with the risk avoidance measures provided, and to ***behave in a manner which is consistent with the prescriber's counsel***." (*See* Williams col. 10 ln. 23-46, ROXGHB004326 (emphasis added)). *See also* the 6/19/06 OA and the Examiner's Answer wherein the Examiner found that paragraph [0084] of Califano disclosed "confirming with the patient

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	that educational material has been read prior to shipping the drug." The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "verifying the patient has reviewed the educational materials" "with the computer processor"	Williams discloses: "In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. ***Verification*** that the patient has given his/her informed consent may also be registered ***in the computer readable storage medium.***" *(See* Williams col. 10 ln. 23-32, ROXGHB004326 (emphasis added)). *See also* Califano paragraphs [0084] and [0086] at ROXGHB004163-64.
the "control" of "verifying the home address of the patient"	Moradi discloses server-side validation of patient registration data, including postal code validation. *See, e.g.,* Moradi paragraphs [0136] at ROXGHB004304, [0139], [0140], [0141] and [0161] at ROXGHB004305.
selecting the control of "verifying the home address of the patient" "with the computer processor"	Moradi describes that the server-side validation takes place via a computer or processing device and can correspond to registration software component 218 of the computer or processing device. (*See* Moradi paragraphs [0031] at ROXGHB004297 and [0161] at ROXGHB004305).
the "control" of "shipping via US postal service or a commercial shipping service"	In the 10/18/06 OA and the Examiner's Answer, the Examiner found Moradi discloses "only ***mailing*** the drug to the patient if no potential abuse is found …." *See* Moradi, paragraphs [0006] at ROXGHB004295, [0043], and [0045] at ROXGHB004299, and Fig. 3 items 318 and 322 at ROXGHB004285 (emphasis added). The BPAI Decision held the Examiner's findings to be "accepted as

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "shipping via US postal service or a commercial shipping service" is selected "with the computer processor"	Paragraph [0022] of Moradi states that: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." ROXGHB004296 (Emphasis added). Accordingly, Moradi teaches implementing the "mailing the drug to the patient" noted by the Examiner to be disclosed by Moradi with a computer or processing device.
the "control" of "receiving the name of an at least 18 year old designee to receive the drug"	
receipt of the name of a designee to receive the drug	Moradi discloses: "The exemplary embodiment further includes providing the delivery person with a 'Route Slip' that has printed directions to the patient's address along with the scanned prescription image. The delivery person hand-delivers the medicine to the recipient if and only if the recipient is holding the original copy of the prescription that is identical to the image provided to the delivery person. This ensures that the proper patient gets the medicine and that the medicine is delivered only once." (*See* Moradi paragraph [0043] at ROXGHB004299).
the individual receiving the drug is at least 18 years old	Moradi teaches the impropriety of a child retrieving a mailed prescription: "Delivery of prescription medication by mail is also possible … This technique is also open to fraud since the individual patient typically does not

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	personally present his or her prescription to the pharmacy. This technique can also lead to an improper person receiving the prescription, such as when a child that is living with the recipient retrieves mail that contains the mailed prescription." (*See* Moradi paragraph [0006] at ROXGHB004295).
selecting the control of "receiving the name of an at least 18 year old designee to receive the drug" "with the computer processor"	Paragraph [0022] of Moradi states: "The system 100 includes several processing components that are located at various physical locations. The various physical locations, which may each have ***one or more computers or processing devices***, are connected via electronic communications, such as the Internet." ROXGHB004296 (Emphasis added).
the "control" of "confirming receipt of an initial shipment of the drug to the patient returning the drug to the pharmacy after two attempts to deliver"	Paragraph [0006] at ROXGHB004295 of Moradi discloses delivery by mail of the "initial fulfillment" of a prescription medication. Moreover, paragraph [0043] of Moradi at ROXGHB004299 discloses a delivery person communicating to Central Service Station (CSS) 102 of system 100 via Point of Delivery (POD) system 106 of system 100 status designations of "delivered, no one at the address, prescription mismatch or one of a number of other potential reasons for non-delivery." Further, in the 6/19/06 OA and the Examiner's Answer, the Examiner found the abstract of Moradi disclosed "confirming receipt by the patient of the drug." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). To require returning to the sender, especially in the case where the item to be delivered is a restricted drug, after two attempts to deliver are unsuccessful would have been obvious.
selecting the control of "confirming receipt of an initial shipment of the	Moradi discloses the communication of the status designations to be implemented via POD system 106 and CSS 102 of system 100. (*See* Moradi

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
drug to the patient returning the drug to the pharmacy after two attempts to deliver" "with the computer processor"	paragraph [0043] at ROXGHB004299).
the "control" of "launching an investigation when a shipment is lost"	Fletcher describes denying further orders "pending a satisfactory resolution" of a corresponding investigation of a lost shipment: "The invention relates to electronic commerce (e-commerce) and a system and method for the secure electronic procurement of goods or services particularly narcotics, ***controlled drugs*** and substances or other goods generally subject to a 'chain of custody' for ordering and ***delivering***." (*See* Fletcher paragraph [0002] at ROXGHB004231 (emphasis added)). "In accordance with a further aspect of the invention the procurement transaction processor comprises means for performing business rules analysis using the order, notification or confirmation of receipt; and means for ***alarming potential instances of diversion or loss of goods/services***. The means for performing business rules analysis and means for alarming are preferably configured to: upon receiving a notification of provision of goods/services at the secure procurement system, initiate a timer for a predetermined period of time within which to receive the confirmation of receipt corresponding to the notification; if the timer expires, ***alarm a potential instance of diversion or loss of goods/services*** and prevent further orders from the user." (*See* Fletcher paragraph [0054] at ROXGHB004233 (emphasis added)). "According to business rules implemented by SPS 38, if a 856 message is not properly confirmed by the qualified person to whom the product was shipped with a digitally signed and certified 861 message, further orders for narcotics or other controlled substances will be denied ***pending a satisfactory resolution***. The 861 message must be received by SPS 38 within a predefined period of time. Currently the defined period is five days under the Canadian regulatory framework. Additional rules ensure that variances between quantity

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	shipped and quantity confirmed received are promptly noted to VAS or a regulatory authority (eg. DEA)." (*See* Fletcher paragraph [0087] at ROXGHB004235 (emphasis added)).
selecting the control of "launching an investigation when a shipment is lost" "with the computer processor"	As noted above in connection, respectively, with clauses a, c, and d, *supra*, Moradi, Borsand, and Lilly each disclose a computer processor. As noted above in connection with the control of "verifying patient registry information," Williams discloses a computer processor. As noted above in connection with the control of "providing comprehensive education information to the patient," Califano discloses a computer processor. Additionally, Fletcher states: "Further illustrated in FIG. 2 is a preferred ***SPS 38***. In the preferred embodiment, SPS 38 comprises ***web server hardware and software*** such as a Compaq. Proliant 5000 Pentium Pro server running Microsoft. Windows NT operating system (not shown) and Netscape. Suitespot integrated software for the network enterprise (not shown)." (*See* Fletcher paragraph [0073] at ROXGHB004234 (emphasis added)). Fletcher indicates the control to be a business rule "implemented" by web server hardware and software SPS 38: "According to business rules ***implemented by SPS 38***, if a 856 message is not properly confirmed by the qualified person to whom the product was shipped with a digitally signed and certified 861 message, further orders for narcotics or other controlled substances will be denied pending a satisfactory resolution." (*See* Fletcher paragraph [0087] at ROXGHB004235 (emphasis added)). One skilled in the art at the time would have been motivated to modify one or more of Lilly, "An Interview with Orphan Medical about Xyrem," Moradi, Ukens, Borsand, Deutsch, Williams, and Califano, to have selected with a

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	computer processor the control of launching an investigation when a shipment is lost as taught by Fletcher at least to prevent diversion and loss in connection with the delivery of a controlled drug. (*See* Fletcher paragraph [0024] at ROXGHB004231-32).
the "control" of "shipping to another pharmacy for delivery"	Ukens' just-in-time inventory system wherein drugs are provided from specialty pharmacy TheraCom to an independent pharmacy in response to an order from that independent pharmacy discloses shipping to "another" pharmacy: "Declaration of independents Not content to just sit on the sidelines and watch patients and business shunted to their old nemesis, mail-service pharmacies, the National Community Pharmacists Association is attempting to build a national network of ***independent pharmacies*** willing to stock specialty products and care for the patients who need them. Teaming up with the *specialty pharmacy TheraCom*, NCPA launched the Specialty Drugs Network in January. So far, about 4,000 independents have agreed to be part of a primary distribution channel for specialty pharmaceutical manufacturers and payer programs. The free network is designed to give independents access to new products, increased revenue streams, and strategic alliances with manufacturers, insurers, and PBMs. 'Our conception of the Specialty Drugs Network was to gain access to products primarily not available through retail today,' said Todd Dankmyer, NCPA executive v.p. communications. 'There's a wide range of these products, primarily injectables, that are extremely expensive and usually for very limited patient populations where reimbursement and insurance coverage are the major challenges.' Independent members of the specialty Drugs Network can pick and choose which drugs they want to stock and provide patient support for. There's also a ***just-in-time inventory system. 'The members don't have to order anything until they know they have a patient coming in who needs this***

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	medication,' said Dankmyer. 'Second, all major medical claims are handled by TheraCom, so the members don't get into any battling to get the reimbursement, and they don't obligate themselves to accept certain levels of reimbursement.'" (*See* Ukens p. 4 at ROXGHB004316 (emphasis added)). Moradi also discloses shipping to such an independent pharmacy "for" delivery: "The pharmacy router 210 of the exemplary embodiment determines a ***pharmacy*** or other type of POD 106 *that is to deliver the prescription* by determining a POD 106 that is registered with the automated prescription delivery system 100 and that was selected by the patient or that is closest to the patient's registered address." (*See* Moradi paragraph [0040] at ROXGHB004298 (emphasis added)).
selecting the control of "shipping to another pharmacy for delivery" "with the computer processor"	Moradi discloses CSS 102 of system 100 to implement the dispatch of a medicine where the recipient of that dispatch acts to deliver the medicine to a patient by explaining that CSS 102 tracks such dispatch in CSS database 204: "The PMS system assigns the prescription a prescription number, and the pharmacist enters that prescription number and the number of refills into the PODP 216, which then communicates that data back to the CSS 102 with an identification of the prescription. The pharmacist then ***gives***, at step 322, ***the ordered medicine*** and a copy of the prescription image to a prescription deliverer, which is a delivery person in the exemplary embodiments, ***for delivery to the patient***. The ***CSS 102*** is notified that the delivery person is in the process of delivering the medication and the ***status of the prescription is changed to 'delivery' within the CSS database 204***." (*See* Moradi paragraph [0043] at ROXGHB004299 (emphasis added)). CSS 102 would also, in the context of the Specialty Drugs Network of Ukens, correspond to a computer or processing device that implements the shipment of a drug to an independent pharmacy of Ukens from specialty pharmacy TheraCom

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	of Ukens.
the "control" of "requiring manufacture at a single location"	Gibson discloses at pages 5 and 6, ROXGHB004247-48, that control of Schedule I drugs can be made at the manufacturer tier, distributor tier or supplier tier, and dispenser tier. Ukens teaches that "restricting distribution of a specialty medication to only one pharmacy," "product going to only one distributor," "going with one pharmacy provider," and "let[ting] only one pharmacy have access" (*see* Ukens, p. 3 at ROXGHB004315) provides control of drug distribution by limiting distribution and dispensing to a sole entity. In view of such teaching by Ukens, it would have been obvious to similarly limit to a sole entity the manufacture tier, and additionally to manufacture at a single location, to further control distribution. *See also*, Borsand's teaching regarding the problems that arise "[a]s a result of the numerous entities involved in a pharmaceutical transaction." (*See* Borsand paragraph [0003] at ROXGHB004124).
selecting the control of "requiring manufacture at a single location" "with the computer processor"	As noted, Moradi discloses a computer processor that controls ***distribution*** of the drug. Ukens teaches "restricting ***distribution*** of a specialty medication to only one pharmacy" (*see* Ukens p. 3 at ROXGHB004315 (emphasis added)). Extending the computer processor to require manufacture at a single location would be obvious. One skilled in the art at the time would have been motivated to modify one or more of Lilly, "An Interview with Orphan Medical about Xyrem," Moradi, Ukens, Borsand, Deutsch, Williams, Califano, and Fletcher to have selected the control of requiring manufacture at a single location as taught by Gibson in view of one or more of Ukens, Borsand, and Moradi to make certain that only authorized individuals may obtain a drug. (*See* Gibson p. 5 at ROXGHB004247).

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
the "control" of "releasing inventory in a controlled manner to the central pharmacy"	Ukens' disclosure of "product going to ***only***" the exclusive central pharmacy describes releasing inventory in a controlled manner to the exclusive central pharmacy: "She pointed out that by restricting distribution of a specialty medication ***to only one pharmacy***, a manufacturer exposes patients to the risk of not receiving their medications in a timely manner if there's a disruption in the delivery system. In addition, shunting one part of therapy away from a patient's regular pharmacist can create the potential for undiscovered drug interactions. 'If you have ***a product going to only one distributor***, you have no safety net for the patient,' said Winckler. 'It creates problems if there are any issues of drug interactions or coordinating therapy. Using an 800 number for patient care may work for some patients, but if they don't want that, what's their alternative? They have to use whatever the system provides.'" (*See* Ukens p. 3 at ROXGHB004315 (emphasis added)).
selecting the control of releasing inventory in a controlled manner to the central pharmacy "with the computer processor"	Ukens discloses the implementation of inventory release in a controlled manner. Borsand's disclosure of computerized system 20 "track[ing]" pharmaceutical 28 involves pharmacy 40: "The ***pharmacy 40*** can confirm the lack of drug interactions, allergic reactions, protocol compliance, and otherwise confirm that the issued prescription 28 is pre-certified 38 and in compliance with the appropriate rules and policies 34. The ***system 20*** provides functionality for ***tracking pharmaceutical 28***, prescription 32, and related information. The system 20 can temporarily or permanently link together the prescription 32 with the diagnosis resulting in the provider's 30 pharmaceutical 28 decision. Such linkage can allow the system 20 to track diagnosis information at potentially any time that

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	prescription 32 information is also being tracked." (*See* Borsand paragraphs [0033] and [0034] at ROXGHB004126 (emphasis added)).
the "control" of "questioning early refills"	Borsand discloses: "The ***system 20*** can ***track*** whether or not a patient 22 has ***attempted to refill a prescription 32 before*** the pharmaceutical 28 in ***the initial prescription 32 was to have run out*** in accordance with the prescribed use of the pharmaceutical 28." (*See* Borsand paragraph [0034] at ROXGHB004126 (emphasis added)).
selecting the control of "questioning early refills" "with the computer processor"	Borsand describes use of computer 26 to perform the tracking for system 20. (*See* Borsand paragraphs [0033] and [0034] at ROXGHB004126).
the "control" of "flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions"	Lilly, in paragraphs [0068] and [0070] at ROXGHB004263, discloses aberrant use flags and the issuance of a flag if a "prescription presents a problem," and that system 100 "may require or suggest declining or approving the prescriptive medication." Additionally, the flagging of repeat instances of an individual reporting that an order has not been received is well-known. For instance, Changing Times p. 68 at ROXGHB004174, describing that "a ***second*** shipment [is sent] without question when a customer complains that he didn't receive his order," teaches that a record is kept pertaining to the quantity of such complaints that a customer makes. Moreover, by discussing at paragraph [0011] at ROXGHB004256 fraud with the aim of obtaining "drugs for resale on the street." Lilly teaches flagging an attempt to obtain excess of a drug, such as by claims of lost, stolen, destroyed or spilled prescriptions.
selecting the control of "flagging repeat instances of lost, stolen, destroyed, or	Lilly discloses issuing a flag and declining to fill the prescription via system 100:

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
spilled prescriptions" "with the computer processor"	"For instance, if a pharmacist is checking on a prescriptive medication prior to dispensing the prescriptive medication, ***a red flag as indicated at 140 may be issued if the prescription presents a problem***, e.g., is a conflicting type of drug (contraindicated prescriptive medication) or perhaps a similar type of drug which in combination with a previous prescriptive medication might be harmful to the consumer. *Red flags may be issued* as a result of *automatic* or manual operation. *System 100* and/or the pharmacist and/or the doctor *may require or suggest declining or approving the prescriptive medication*, and otherwise add notes, comments, and flags, as desired." (*See* Lilly paragraph [0070] at ROXGHB004263 (emphasis added)). One skilled in the art at the time would have been motivated to modify one or more of Lilly, "An Interview with Orphan Medical about Xyrem," Moradi, Ukens, Borsand, Deutsch, Williams, Califano, Fletcher, and Gibson to have selected the control of flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions as is obvious in view of one or more of Lilly and Changing Times at least to employ a major element for success in mail order. (*See* Changing Times p. 67-68 at ROXGHB004173-74).
the "control" of "limiting the prescription to a one month supply"	Williams discloses: "In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably ***no more than about 28 days***. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below." (*See* Williams col. 12 ln. 3-8 at ROXGHB004327 (emphasis added)).
selecting the control of "limiting the prescription to a one month supply" "with the computer processor"	Williams discloses the control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, ***in order to become registered in the computer readable storage medium***, the ***prescriber may be required to comply with various aspects of the methods described herein*** including, for example, providing patient education and counseling, and the like, as described in detail below." (*See* Williams col. 4 ln. 43-54 at ROXGHB004323 (emphasis added)).
the "control" of "requiring rewriting of the prescription periodically"	Williams discloses: "In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will ***not be permitted*** without a ***renewal prescription from the prescriber***, as discussed in detail below." (*See* Williams col. 12 ln. 3-8 at ROXGHB004327 (emphasis added)). *See also* Moradi paragraph [0098] at ROXGHB004302.
selecting the control of "requiring rewriting of the prescription periodically" "with the computer processor"	Williams discloses this control as "required" in order for a "prescriber" to become registered "in the computer readable storage medium": "The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, ***in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein*** including, for example, providing patient education and counseling, and the like, as described in detail below." (*See* Williams col. 4 ln. 43-54 at ROXGHB004323 (emphasis added)).
the "control" of "making the database	Lilly discloses making available to the DEA from the central database data

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
available to the DEA for checking for abuse patterns in the data, for cash payments, and for inappropriate questions"	required to reach the DEA's goals such as "determin[ing] where violations may be occurring." The data would be available to the DEA "for" checking for abuse patterns, for cash payments, and for inappropriate actions: "Many different types of entities/organizations may be electronically interconnected in accord with the present invention with respect to pharmaceutical information control organization 12. The ***types of data available to each organization*** maybe filtered depending on the type of organization/entity and the ***need thereof*** for the various types of pharmaceutical information available from pharmaceutical information control organization 12." (*See* Lilly paragraph [0052] at ROXGHB004260 (emphasis added)). "Government oversight entities 14, such as the ***DEA***, FBI, CDC, and so forth, may be able to ***utilize data as required to reach the organization goals*** and within the limitations required therefore. For instance, the DEA may review data to determine areas where violations may be occurring." (*See* Lilly paragraph [0054] at ROXGHB004260-61 (emphasis added)).
selecting the control of "making the database available to the DEA for checking for abuse patterns in the data, for cash payments, and for inappropriate questions" "with the computer processor"	Lilly discloses making, via computer interconnection arrangement 10, the needed data available to the DEA: "Referring now to the drawings and, more particularly to FIG. 1, there is shown one possible ***computer*** interconnection arrangement 10 between various entities/organizations and pharmaceutical information control organization 12 that may be utilized to implement the method of the present invention." (*See* Lilly paragraph [0051] at ROXGHB004260 (emphasis added)). "Many different types of entities/organizations may be electronically interconnected in accord with the present invention with respect to pharmaceutical information control organization 12. The ***types of data available to each organization*** maybe filtered depending on the type of

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	organization/entity and the ***need thereof*** for the various types of pharmaceutical information available from pharmaceutical information control organization 12" (S*ee* Lilly paragraph [0052] at ROXGHB004260 (emphasis added)).
the selected "controls" are "for distribution by said exclusive central pharmacy"	The 6/19/06 OA and the Examiner's Answer each found Moradi disclosed "a method of ***distributing a drug under exclusive control of an exclusive central pharmacy***." *See*, Moradi, paragraphs [0003] at ROXGHB004295 and [0024] at ROXGHB004296. Also, the 10/18/06 OA and the Examiner's Answer each found Ukens disclosed an exclusive central pharmacy at page 3, paragraphs 3-5, ROXGHB004315. The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). The noted ***controls*** would, in the context of such distribution under ***control*** of such exclusive central pharmacy, be ***controls*** for distribution by that exclusive central pharmacy.
5. The method of claim 4 wherein initially selected controls comprise communicating prescriptions from a physician to the central pharmacy; identifying the physician's name, license, and DEA registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the GHB by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has reviewed the educational materials; verifying the home address of the patient; shipping via US postal service;	

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
confirming receipt of an initial shipment of the drug to the patient; releasing inventory in a controlled manner to the central pharmacy; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; and making the database available to the DEA for checking for abuse patterns in the data.	
the "control" of "communicating prescriptions from a physician to the central pharmacy"	As noted above in connection with clause e of claim 4, *supra*, in the Examiner's Answer the Examiner found that Moradi, Lilly and Ukens disclosed "***receiving all prescription requests at the exclusive central pharmacy from a medical doctor*** containing information identifying a patient, the sensitive drug, and various credentials of the doctor" (emphasis added). The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the "control" of "communicating prescriptions from a physician to the central pharmacy"	As noted, in the Examiner's Answer the Examiner found Moradi, Lilly, and Ukens disclosed prescription request receipt. As noted above in connection with clause e of claim 4, *supra*, such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260.
the selection is initial	Performance of prescription submission step 310 of Moradi, relating to the portions of Moradi cited by the Examiner's Answer in connection with recognizing the disclosure of prescription request receipt, is indicated by Fig. 3 of Moradi at ROXGHB004285 to be initial as performance of step 310 is depicted by Fig. 3 as occurring prior to performance of subsequent steps.
the "control" of "identifying the physician's name, license, and DEA registration information"	As noted above in connection with clause e of claim 4, *supra*, Moradi discloses this control in relation to physician registration (*see* Moradi paragraph [0118] at ROXGHB004304).
selecting the "control" of "identifying the	As noted above in connection with clause e of claim 4, *supra*, Moradi discloses

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
physician's name, license, and DEA registration information"	this control selection (*see* Moradi paragraph [0109], ROXGHB004303).
the selection is initial	Fig. 7 of Moradi at ROXGHB004290 depicts physician registration as occurring prior to further actions (e.g., prior to "Display Successful Registration to user" step 730 and "Notify Admin of new Registration form" step 732).
the "control" of "verifying the prescription"	As noted above in connection with clause e of claim 4, *supra*, Moradi discloses this control in relation to step 316 of verifying the prescription (*see* Moradi paragraph [0042] at ROXGHB004299).
selecting the "control" of "verifying the prescription"	As noted above in connection with clause e of claim 4, *supra*, Moradi discloses this control selection (*see* Moradi paragraph [0028] at ROXGHB004297).
the selection is initial	Fig. 3 of Moradi at ROXGHB004285 depicts the processing of prescription verification step 316 as occurring prior to the processing of subsequent steps.
the "control" of "obtaining patient information"	As noted above in connection with clause e of claim 4, *supra*, in the Examiner's Answer the Examiner found that Moradi, Lilly and Ukens disclosed "***receiving*** all prescription requests at the exclusive central pharmacy from a medical doctor containing ***information identifying a patient***, the sensitive drug, and various credentials of the doctor" (emphasis added). The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756). As further noted in connection with clause e of claim 4, *supra*, *see also* Moradi paragraph [0035] at ROXGHB004297-98.
selecting the "control" of "obtaining patient information"	As noted, in the Examiner's Answer the Examiner found that Moradi, Lilly, and Ukens disclosed receipt of prescription requests containing patient information. As noted above in connection with clause e of claim 4, *supra*, such prescription request receipt is in view of Moradi and Lilly performed with a computer processor. *See* Moradi paragraph [0022] at ROXGHB004296 and Lilly paragraph [0051] at ROXGHB004260. As further noted above in connection with clause e

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	of claim 4, *supra*, *see also* Moradi paragraph [0031] at ROXGHB004297.
the selection is initial	Performance of prescription submission step 310 of Moradi, relating to the portions of Moradi cited by the Examiner's Answer in connection with recognizing the disclosure of the receipt of prescription requests containing patient information, is indicated by Fig. 3 of Moradi at ROXGHB004285 to be initial as performance of step 310 is depicted by Fig. 3 as occurring prior to performance of subsequent steps. *See also* Fig. 3 of Moradi at ROXGHB004285 depicting patient registration as occurring prior to further actions.
the "control" of "verifying the physician is eligible to prescribe" the drug "by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician"	As noted above in connection with clause e of claim 4, *supra*, this control selection is obvious in view of one or more of Deutsch, Moradi, and Borsand (*see* Moradi paragraphs [0113] – [0116] at ROXGHB004303, Deutsch pp. 252-254 at ROXGHB004196-98 and 269-272 at ROXGHB004213-16, and Borsand paragraph [0120] at ROXGHB004134).
selecting the "control" of "verifying the physician is eligible to prescribe" the drug "by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician"	As noted above in connection with clause e of claim 4, *supra*, Moradi discloses the performance of validation of physician data (*see* Moradi paragraph [0022] at ROXGHB004296). *See also* Moradi paragraph [0109] at ROXGHB004303 and Borsand paragraph [0120] at ROXGHB004134.
the selection is initial	Moradi indicates such validation to be initial by indicating such validation to correspond to physician registration and by Fig. 7 of Moradi at ROXGHB004290 indicating such physician registration as occurring prior to further actions (e.g., prior to "Display successful Registration to user" step 730 and "Notify Admin of new Registration form" step 732). Borsand indicates such checking to be initial as paragraph [0120] of Borsand at ROXGHB004134 explains the checking to occur prior to, as is found to be

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	appropriate, either performing or not performing prescription modification or cancellation.
the "control" of "verifying patient registry information"	As noted above in connection with clause e of claim 4, *supra*, Williams discloses this control in relation to consultation of a computer readable storage medium in which patients are registered (*see* Williams col. 2 ln. 49-60 at ROXGHB004322, col. 5 ln. 61 - col. 6 ln. 3 at ROXGHB004324, and col. 13 ln. 19-41 at ROXGHB004328). *See also* Moradi paragraph [0161] at ROXGHB004305.
selecting the control of "verifying patient registry information"	As noted above in connection with clause e of claim 4, *supra*, Williams discloses this control selection (*see* Williams col. 2 ln. 49-60 at ROXGHB004322, and col. 13 ln. 31-33 at ROXGHB004328). *See also* Moradi paragraphs [0031] at ROXGHB004297 and [0161] at ROXGHB004305.
the selection is initial	Williams indicates such consultation to be initial by indicating such consultation to occur prior to filling a prescription for a drug: "[t]he present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which ***prescriptions for the drug*** are ***filled only after*** a computer readable storage medium has been ***consulted*** to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug" (*See* Williams col. 2 ln. 49-59 at ROXGHB004322 (emphasis added)). *See also* Moradi Fig. 3 at ROXGHB004285.
the "control" of "providing comprehensive education information to the patient"	As noted above in connection with clause e of claim 4, *supra*, Williams discloses this control in relation to patient counseling (*see* Williams col. 8 ln. 57 - col. 9 ln. 2 at ROXGHB004325-26). As also noted above in connection with clause e of claim 4, *supra*, in the in the 6/19/06 OA and the Examiner's Answer the

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	Examiner found Califano disclosed "confirming with the patient that educational material has been read prior to shipping the drug." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting that the control of "providing comprehensive education information to the patient"	As noted above in connection with clause e of claim 4, *supra*, Williams disclosed this control selection (*see* Williams col. 4 ln. 43-54 at ROXGHB004323). As further noted above in connection with clause e of claim 4, *supra*, *see also* Califano paragraphs [0052] at ROXGHB004159 and [0084] at ROXGHB004163.
the selection is initial	Col. 8 ln. 45-59 of Williams at ROXGHB004325 discuss the patient counseling as occurring "[p]rior to prescribing the drug." *See also* paragraph [0084] of Califano at ROXGHB004163 which discusses occurrence "before participation in a study begins."
the "control" of "verifying the patient has reviewed the educational materials"	As noted above in connection with clause e of claim 4, *supra*, Williams discloses this control in relation to informed consent verification (*see* Williams col. 10 ln. 23-46 at ROXGHB004326). As also noted above in connection with clause e of claim 4, *supra*, in the 6/19/06 OA and the Examiner's Answer the Examiner found Califano disclosed "confirming with the patient that educational material has been read prior to shipping the drug." The BPAI Decision held the Examiner's findings "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "verifying the patient has reviewed the educational materials"	As noted above in connection with clause e of claim 4, *supra*, Williams disclosed this control selection (*see* Williams col. 10 ln. 23-32 at ROXGHB004326). As further noted above in connection with clause e of claim 4, *supra*, *see also* Califano paragraphs [0084] and [0086] at ROXGHB004163-64.
the selection is initial	Col. 10 ln. 23-32 of Williams at ROXGHB004326 discuss the informed consent verification as occurring "[p]rior to receiving a prescription for the drug." *See also* paragraph [0084] of Califano at ROXGHB004163 which discusses

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	occurrence "before participation in a study begins."
the "control" of "verifying the home address of the patient"	As noted above in connection with clause e of claim 4, *supra*, Moradi disclosed this control in relation to server-side validation of patient registration data (*see, e.g.,* Moradi paragraphs [0136] at ROXGHB004304, [0139], [0140], [0141] and [0161] at ROXGHB004305).
selecting the control of "verifying the home address of the patient"	As noted above in connection with clause e of claim 4, *supra*, Moradi disclosed this control selection (*see* Moradi paragraphs [0031] at ROXGHB004297 and [0161] at ROXGHB004305).
the selection is initial	Moradi indicates such validation to be initial by indicating such validation to correspond to patient registration and by Fig. 3 of Moradi at ROXGHB004285 depicting such patient registration as occurring prior to further actions (e.g., prior to prescription submission step 310).
the "control" of "shipping via US postal service"	As noted above in connection with clause e of claim 4, *supra*, in the 10/28/06 OA and the Examiner's Answer the Examiner found "only ***mailing*** the drug to the patient if no potential abuse is found …" to be disclosed by Moradi (emphasis added). The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "shipping via US postal service"	As noted above in connection with clause e of claim 4, *supra*, Moradi teaches implementing the "mailing the drug to the patient" noted by the Examiner to be disclosed by Moradi with a computer or processing device (*see* Moradi paragraph [0022] at ROXGHB004296).
the selection is initial	Moradi indicates such shipping to be initial as Fig. 3 of Moradi at ROXGHB004285 depicts items 318 and 322 of Moradi cited by the 10/28/06 OA and the Examiner's Answer in connection with recognizing the disclosure of "only mailing the drug to the patient if no potential abuse is found …" as corresponding to steps occurring prior to further actions (e.g., prior to "Route to Admin Office for Further Action" step 320 and "Delivery Person Returns with

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
	Patient's Signature, Stamps Prescription Signifying Delivery, Update POD System" step 324).
the "control" of "confirming receipt of an initial shipment of the drug to the patient"	As noted above in connection with clause e of claim 4, *supra*, Moradi discloses delivery by mail of the "initial fulfillment" of a prescription medication and a delivery person communicating to Central Service Station (CSS) 102 of system 100 via Point of Delivery (POD) system 106 of system 100 status designations of "delivered, no one at the address, prescription mismatch or one of a number of other potential reasons for non-delivery" (*see* Moradi paragraphs [0006] at ROXGHB004295 and [0043] at ROXGHB004299). As also noted above in connection with clause e of claim 4, *supra*, in the 6/19/06 OA and the Examiner's Answer, the Examiner found that "confirming receipt by the patient of the drug" is disclosed by Moradi. The BPAI Decision held the Examiner's findings to be "accepted as being undisputed." (BPAI Decision, p. 6, ROXGHB004756).
selecting the control of "confirming receipt of an initial shipment of the drug to the patient"	As noted above in connection with clause e of claim 4, *supra*, Moradi discloses the communication of the status designations to be implemented via POD system 106 and CSS 102 of system 100 (*see* Moradi paragraph [0043] at ROXGHB004299).
the selection is initial	Paragraph [0006] of Moradi at ROXGHB004295, discussing the "initial fulfillment" of a prescription medication and "refills" for that prescription medication, explains that the communication of the status designations for the "initial fulfillment" is initial by indicating it to occur prior to those "refills."
the "control" of "releasing inventory in a controlled manner to the central pharmacy"	As noted above in connection with clause e of claim 4, *supra*, Ukens' disclosure of "product going to ***only***" the exclusive central pharmacy describes releasing inventory in a controlled manner to the exclusive central pharmacy (*see* Ukens p. 3 at ROXGHB004315).
selecting the control of "releasing	As noted above in connection with clause e of claim 4, *supra*, Ukens discloses

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
inventory in a controlled manner to the central pharmacy"	the implementation of inventory release in a controlled manner. As also noted above in connection with clause e of claim 4, *supra,* Borsand's disclosure of computerized system 20 "track[ing]" pharmaceutical 28 involves pharmacy 40.
the selection is initial	Ukens indicates inventory release in a controlled manner to the exclusive central pharmacy of Ukens to be initial as Ukens, by discussing patients being exposed "to the risk of not receiving their medications in a timely manner" in connection with "product going to only" the exclusive central pharmacy, indicates that inventory being released in a controlled manner to the exclusive central pharmacy of Ukens occurs prior to medication receipt by patients.
the "control" of "flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions"	As noted above in connection with clause e of claim 4, *supra*, this control selection is obvious in view of one or more of Lilly and Changing Times (*see* Lilly paragraphs [0011] at ROXGHB004256, [0068] and [0070] at ROXGHB004263 and Changing Times p. 68 at ROXGHB004174).
selecting the control of "flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions"	As noted above in connection with clause e of claim 4, *supra*, Lilly discloses issuing a flag and declining to fill the prescription via system 100 (*see* Lilly paragraph [0070] at ROXGHB004263).
the selection is initial	Lilly indicates the flagging to be initial by indicating such flagging to relate to step 140 of Fig. 2 of Lilly at ROXGHB004255 and by Fig. 2 of Lilly depicting step 140 as occurring prior to further actions.
the "control" of "making the database available to the DEA for checking for abuse patterns in the data"	As noted above in connection with clause e of claim 4, *supra*, Lilly discloses making available to the DEA from the central database data required to reach the DEA's goals such as "determin[ing] where violations may be occurring." The data would be available to the DEA "for" checking for abuse patterns (*see* Lilly paragraphs [0052] and [0054] at ROXGHB004260-61).
selecting the control of "making the database available to the DEA for checking	As noted above in connection with clause e of claim 4, *supra*, Lilly discloses making, via computer interconnection arrangement 10, the needed data available

Claims of U.S. Patent No. 7,765,107	Description in Prior Art:
for abuse patterns in the data" the selection is initial	to the DEA (*see* Lilly paragraphs [0051] and [0052] at ROXGHB004260). Lilly indicates making the needed data available to the DEA to be initial by explaining making the needed data available to the DEA to occur prior to the DEA "review[ing] data to determine areas where violations may be occurring" (*see* Lilly paragraphs [0052] and [0054] at ROXGHB004260-61).
6. The method of claim 4 which further comprises consulting a separate database to verify that the medical doctor is eligible to prescribe the drug.	Moradi discloses validation of physician data: "The CSS program 202 performs the following validations and if there are any validation errors, an error message is displayed to the user identifying the field or fields in error: Physician License Number: The Physician License number consists of an alphabetical prefix (used as license type) followed by a number assigned to licensed physician. It is used to identify physician to various payers. ***Existing*** Internet data resources are used by the exemplary embodiment to verify the physician license number" (*See* Moradi paragraphs [0113] - [0114] at ROXGHB004303 (emphasis added)). Moradi indicates the data resources employed in the validation to be separate from CSS database 204 of Moradi by characterizing the data resources as "[e]xisting." That a data resource can be a database is well-known.

Dated: April 14, 2011

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CERTIFICATE OF SERVICE

I hereby certify that on this 14th day of April, 2011, I caused a true and correct copy of the foregoing ROXANE LABORATORIES, INC.'S INITIAL INVALIDITY AND NONINFRINGEMENT CONTENTIONS PURSUANT TO LOCAL PATENT RULE 3.6 to be delivered by overnight delivery to:

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC.,	)	
	)	
	)	
Plaintiff,	)	CIVIL ACTION NO.:
	)	2:10-cv-06108 (ES) (CLW)
vs.	)	(consolidated)
	)	
ROXANE LABORATORIES, INC.,	)	
	)	
Defendant,	)	
	)	

ROXANE LABORATORIES, INC.'S OPENING *MARKMAN* BRIEF
IN SUPPORT OF ITS CLAIM CONSTRUCTIONS

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OTHER AUTHORITIES

Roxane Laboratories, Inc. ("Roxane") respectfully submits this brief in support of the proper construction of certain claim terms of U.S. Patent Nos. 6,472,431 ("the '431 patent"), 6,780,889 ("the '889 patent"), 7,262,219 ("the '219 patent"), 7,851,506 ("the '506 patent"), 7,668,730 ("the '730 patent"), 7,765,106 ("the '106 patent"), 7,765,107 ("the '107 patent"), and 7,895,059 ("the '059 patent"), which are attached as Exhibits A-H[1].

I. BACKGROUND

Sodium oxybate, also known as sodium gamma-hydroxybutyrate (NaGHB), is a pharmaceutically active salt that has been in medical use for over forty years for treating certain sleep- and pain-related conditions. (Ex. A, '431 patent, 1:23-2:6[2].) The drug has potential for abuse as a euphoric and a date-rape drug, resulting in FDA and DEA regulation as a controlled substance. In 2002, Jazz Pharmaceutical, Inc.'s ("Jazz") predecessor, Orphan Medical, received approval to market sodium oxybate to treat narcolepsy under the brand name Xyrem®. Roxane filed an Abbreviated New Drug Application with FDA in 2010 seeking permission to market a generic sodium oxybate product.

In this lawsuit, Jazz has asserted against Roxane eight patents with fifty-six claims. The patents can be broken into two families based on their earliest-filed common application, the '431 patent family and the '730 patent family. The '431 patent family includes the '431, '889, '219, and '506 patents. The '730 patent family includes the '730, '106, '107, and '059 patents. The parties currently dispute the meaning of thirty-four claim terms—nine in the '431 patent family and twenty-five in the '730 patent family. Many of these terms appear in multiple claims.

II. ARGUMENT

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[1] All exhibits are attached to the Certification of Theodora McCormick in Support of Roxane Laboratories, Inc.'s Opening Markman Brief.

[2] An "X:Y-Z" citation to a patent stands for column X, line numbers Y through Z.

A. Legal Standards for Claim Construction

The scope and meaning of patent claims are legal questions for the Court. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 372 (1996). The goal of claim construction is to determine how a person of ordinary skill in the art[3] would understand terms used in the patent claims at issue when the application was filed. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*).

The proper meaning of claim terms is based first and foremost on the intrinsic evidence. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Intrinsic evidence includes the claims, the patent specification, and the prosecution history. *V-Formation, Inc. v. Benetton Group SpA*, 401 F.3d 1307, 1311 (Fed. Cir. 2005). Extrinsic evidence may not be used to contradict the definition of a claim term derived from the otherwise unambiguous intrinsic evidence. *Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 716 (Fed. Cir. 1998). A court may, however, look to extrinsic evidence (*e.g.*, dictionaries) to *support* a claim construction based on the intrinsic evidence, to understand the technology at issue, or to show that a term in the patent has a particular meaning in the relevant field.*Phillips*, 415 F.3d at 1318.

Terms that appear in more than one claim should be construed consistently throughout the patent. *Id.* at 1314. A patent applicant, however, "may choose to be his own lexicographer and use terms in a manner other than their ordinary meaning, as long as the special definition is

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[3] Roxane proposes that the person of ordinary skill for the '431, '889, and '219 patents would in December 1999 have an undergraduate or graduate degree in chemistry or chemical engineering with 2-6 years of experience, depending on education level, in preparing or familiarity with the techniques for preparing pharmaceutically acceptable solutions that are chemically stable and resistant to microbial growth. For the '506 patent, the person of ordinary skill in December 1999 would be a doctor practicing for at least 4-6 years in the field of sleep disorders. For the '730 patent family, the person of ordinary skill in December 2002 would have an undergraduate degree in computer science or work experience equivalent thereto and, in either case, two years of work experience designing or programming business applications, and experience with inventory control software.

clearly stated in the patent specification or file history." *Vitronics*, 90 F.3d at 1582.

B. The '431 Patent Family

The patents in the '431 patent family all have the same specification and, therefore, Roxane will cite only to the '431 patent, unless expressly noted.

1. "resistant to microbial growth"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"resistant to microbial growth" ('431 patent, claim 1; '889 patent, claim 1; '219 patent, claims 1, 4)	"formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days, including but not limited to formulations containing greater than about 150 mg/ml GHB to GHB's maximal solubility in an aqueous medium"	The formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles.

The patent applicants ("applicants") acted as their own lexicographers with respect to this claim term, expressly defining it in the '431 patent using the classic terms applicants use to signal they are setting forth their own special definition. That is, applicants stated that "as used herein" the claim term "means"—and then set forth the exact language contained in Roxane's proposed construction. (*See e.g.*, Ex. A. 3:22-31); *see also Housey Pharms., Inc. v. Astrazeneca UK Ltd.*, 366 F.3d 1348, 1354 (Fed. Cir. 2004) (applicants act as own lexicographers to define a term expressly by using language "as used herein"); *Prima Tek II v. Polypap*, 318 F.3d 1143, 1152 (Fed. Cir. 2003) (applicants acted as own lexicographers by using language "The term [ ] as used herein, means…").

There is no dispute that applicants, by using the words "as used herein" and "means," acted as their own lexicographers. The only dispute is whether the term's definition should: (i) comprise the entire definition that applicants set forth, as Roxane proposes; or (ii) stop mid-sentence and lop off much of applicants' explicit definition, as Jazz contends. Both the law and common sense compel adopting the entire definition, not some arbitrarily truncated version. *See, e.g.*, *PrimaTek II*, 318 F.3d at 1152 (construing term "band" to be defined by all words following " as used herein, means" within the same sentence in the patent specification regardless of internal commas).

2. "salt"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"salt" ('431 patent, claims 1-2)	"a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base"	A compound formed by the interaction of an acid and a base.

Method claims 1 and 2 of the '431 patent both add a "salt" of GHB when making the resulting composition. As above, applicants specifically defined the term "salt" in the '431 patent. (*See* Ex. A, 7:2-5 ("A 'salt' is understood herein to mean [in] certain embodiments to mean…").) And again, the parties' dispute centers only on whether the Court should artificially truncate applicants' chosen definition at an internal comma.

Neither logic nor prevailing authority dictate that the definition of "salt" should terminate midway through applicants' articulated definition. Even worse, Jazz's proposed definition defies basic scientific tenets. The "interaction of an acid and a base" can form a wide range of compounds, many of which are not salts. For example, adding HCl (an acid) to NaOH (a base) results in two products—table salt (NaCl) and water (H_2O).

$$HCl + NaOH \dashrightarrow NaCl + H_2O$$

Yet Jazz's proposed construction results in the illogical conclusion that water is a salt. Applicants did not end their definition at an internal comma, so neither should the Court.

3. "adding the gamma-hydroxybutyrate salt to the aqueous medium"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"adding the gamma-hydroxybutyrate salt to the aqueous medium" ('431 patent, claim 1)	"externally adding a pre-made gamma-hydroxybutyrate salt into a pre-existing aqueous medium"	Including gamma-hydroxybutyrate in a liquid comprising more than 50% water.

Roxane's construction calls for "adding" an already existing "salt" to an aqueous medium, *i.e.* water, as the plain language and the '431 patent and prosecution history teach. Jazz, on the other hand, says that the NaGHB "salt" does not need to be ***added*** to the water, and that it is good enough if the salt's components, Na and GHB, are merely found in a water solution.

Roxane's proposed construction properly addresses the claim's literal requirement that a NaGHB "salt" be "added" to the aqueous medium. And while the '431 patent does not explicitly define "adding," the examples in the patent implicitly define the term. The specification repeatedly describes "dissolving or mixing" already existing NaGHB salt into an aqueous medium. (*See* Ex. A, 3:37-40, 46-48; 4:25-28; 8:45-49, 63-67; 10:14-16, 20-23, 28-29.) You cannot "dissolve" or "mix" something in water unless you first "add" it to the water.

Further, applicants inserted the "adding" limitation to overcome a patentability rejection. So clearly the concept of "adding" was important to the claimed invention. It cannot be glossed

over here, as Jazz proposes. (*See*Ex. I, '431 PH[4], 4/6/02 Notice of Allowability at 2, ROXGHB02926.)

Jazz's construction is wrong for at least three reasons. First, Jazz's construction is contrary to the claim language because Jazz's construction does not require "adding" and improperly allows for the NaGHB salt components to be formed for the first time within the aqueous medium. Second, Jazz's construction allows NaGHB to be present in the aqueous medium in its component parts, *i.e.*, as an acid and a base, without ever having existed as the "salt" that the claim language requires. And third, Jazz's construction ignores the patent teachings. Specifically, the patent describes only a method that takes the already existing NaGHB salt and ***adds*** it into an already present aqueous medium. Thus, Jazz's proposed construction, which eliminates the "adding" requirement, is incorrect. *See General American Transp. Corp. v. Cryo-Trans, Inc.*, 93 F.3d 766, 770 (Fed. Cir. 1996) (rejecting construction that would read out claim term).

4. "about"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"about" ('431 patent, claims 1, 3, 5; '889 patent, claim 1; '219 patent, claims 1, 2, 4; '506 patent claim 1)	"20% of the number modified in the appropriate direction(s)"	Reasonably close to.

Applicants expressly defined this term in the '431 patent. (*See* Ex. A, 4:8-9.) Roxane properly incorporated applicants' explicit definition, "[a]s used herein, the term 'about' generally means within about 10-20%," in its proposed construction. (*Id.*) Jazz has not.

When used in patent claims, the term "about" can mean different things. *See Pall Corp.*

[4] '___ PH stands for the prosecution history of the corresponding patent number.

v. Micron Separations, Inc., 66 F.3d 1211, 1217 (Fed. Cir. 1995) ("[T]he word 'about' does not have a universal meaning in patent claims, and [its] meaning depends on the technological facts of the particular case.") The Federal Circuit, however, has explained that when "about" is used in association with numerical values, it should be construed consistent with the intrinsic evidence. *See Conopco, Inc. v. May Dept. Stores Co.*, 46 F.3d 1556, 1560-61 (Fed. Cir. 1994)(rejecting construction of "about" that did not comport with use in the patent's specification). If the patent assigns a meaning to the term "about," the patent governs, even if that meaning differs from dictionary definition, "approximately." *See Vitronics*, 90 F.3d at 1582.

Here, the patent assigns a specific definition to "about." The inquiry should stop there.

Jazz proposes an imprecise construction that would postpone an authoritative interpretation until later. The goal of claim construction, however, and the purpose of the New Jersey rule requiring an early *Markman* hearing, is to try to eliminate ambiguity to assist in the resolution of the legal claims. *Phillips*, 415 F.3d at 1312. Roxane's proposed construction would accomplish that goal, while Jazz's proposed construction would thwart it.

5. "does not contain a preservative" or "free of preservatives"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"does not contain a preservative"; "free of preservatives" ('431 patent, claim 4; '889 patent, claim 1; '219 patent, claims 1, 4)	"does not contain any substance added to inhibit chemical change or microbial action"	Free of conventional exogenous substances that are added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action.

Save for one aspect, the parties' proposed constructions of these terms are the same, although Jazz's proposed construction is more prolix. The only substantive difference is that Jazz's construction imports into the term "substances" two limitations that do not appear in the

patent, "conventional" and "exogenous." *See Phillips*, 415 F.3d at 1320 (it is improper to import limitations into a patent claim that were not intended by applicants)

The Court should not construe these claim terms to contain these limitations. For here too, applicants used the signals "is understood herein" and "means" to indicate that they were acting as their own lexicographers in defining the term "preservative." (Ex. A, 7:42-44.)

6. "pH-adjusting agent"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"pH-adjusting agent" ('431 patent, claims 1, 6; '889 patent, claim 1; '219 patent, claims 1, 3, 4)	"an agent, which is an acid or base, directly added primarily to alter the pH"	No construction necessary.

Although this term does not appear in claim 1 of the '431 patent, claim 1 requires "adjusting the pH of the medium to a final pH of about 6 to about 10…" Claim 6 of the same patent, however, depends from claim 1 and claims "[t]he method of claim 1, wherein ***said*** pH-adjusting agent is an organic acid." (Emphasis added). Thus, applicants plainly contemplated that a pH-adjusting agent performed the pH adjustment in claim 1 . Accordingly, that term needs to be construed in connection with claim 1. *See* 35 U.S.C. § 112, ¶ 4 (a further limitation placed in a dependent claim must also appear in an independent claim). Indeed, if claim 1 were not construed to include the "pH-adjusting agent," then claims 6 and 7 would be invalid, which would run afoul of the requirement that claims must be construed, whenever possible, to preserve their validity. *SeeRhine v. Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999)("Claims should be so construed, if possible, to sustain their validity.") (internal citation omitted). With that in mind, we turn to the proper construction of the claim term.

The '431 patent consistently describes "pH-adjusting agents" as agents, specifically

"acids" or "bases," that are mixed "sequentially or simultaneously" with the NaGHB salt and other components in the composition in order to "adjust" the composition's pH.(*See* Ex. A, 6:36-39; 8:45-59; 12:50-63.) In other words, the term "pH-adjusting agent" refers to an acid or base added directly to the composition whose primary purpose is to alter the composition's pH.(*See* Ex. J,'889 PH, 3/18/04 Notice of Allowability at 2, ROXGHB003187 (noting adding malic acid as pH-adjusting agent in Reasons for Allowance).)

Jazz proposes that no construction of the term is necessary. Again, Jazz's approach would only leave clarification of the term's meaning for another day, contrary to the purpose of *Markman*proceedings. *See Phillips*, 415 F.3d at 1312.

7. "organic acid"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"organic acid" ('431 patent, claim 6)	"an acid containing at least one carbon atom that directly acidifies a solution"	A substance containing one or more carbon atoms that is capable of yielding a proton (hydrogen ion) in aqueous solution, turning blue litmus paper red in aqueous solutions, ionizing in solution to yield the positive ion of the solvent, reacting with bases to form salts, or accepting electrons in an acid-base reaction.

The '431 patent discloses that "[i]n certain embodiments, the acid may be an organic acid…" and notes that "in certain other embodiments, the acid is selected from…" a list of other acids, including many containing at least one carbon atom. (Ex. A, 6:39-51.) These carbon-containing acids are the very acids the specification describes as being added in the method of claim 1 to lower the pH of the solutions, *i.e.,* to acidify. Accordingly, "organic acid" should be construed to mean "an acid containing at least one carbon atom that directly acidifies a solution."

Jazz's proposed construction strays far from descriptions of organic acids described in the

'431 patent and improperly imports limitations into the claim term that appear nowhere in the intrinsic evidence. In fact, Jazz's proposed construction goes one step further, seeking to import limitations from the extrinsic evidence (a technical dictionary) into the claim term. Jazz's approach violates the tenet of claim construction that one should not limit a claim based on extrinsic evidence. *Key Pharms.*, 161 F.3d at 716.

8. "wherein…is…"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"wherein ... is …" ('219 patent, claims 1, 3, 4)	"one of the listed components and no others"	No construction necessary.

When used in patent claims, phrases beginning with the transition word "wherein" have specific significance, namely that the words that follow "wherein" serve to limit the claim. *See* MPEP § 2111.04. And when a claim includes a transitional phrase designed to limit the claim to a specific group, such as "composed of" or "wherein…is…," the claim should be specifically limited to only members of the listed group. *See* MPEP § 2111.03. Thus, Roxane proposes that the Court construe these claims consistent with the legal meaning of "wherein…is…"

Curiously, Jazz proposes that this claim term requires no construction, yet refuses to agree that the phrase should be given a construction in accord with its well-known legal meaning. But what else could the claim term mean? Jazz's refusal to propose an alternate construction is an implicit concession to give the phrase its proper legal meaning.

9. "dose"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"dose" ('506 patent, claim 1)	"a therapeutic amount of a pharmaceutical composition	No construction necessary.

	comprising chemically stable gamma-hydroxybutyrate in an aqueous medium resistant to microbial growth taken by a patient"	

The '506 patent does not specifically define the term "dose," but consistently discusses "dose" in the context of giving to a patient "a therapeutic amount of … GHB...." (Ex. D, 8:60-65.) The context of the claim itself also discusses the "dose" in terms of what a patient takes—stating "orally administering to a patient . . . a first dose." (Ex. D, 72:20-22). The patent later describes such a "therapeutic amount" as a "dosage" or "dose" the patient takes or needs. (Ex. A, 8:66-9:34.) Thus, "dose" is what the patient takes.

Roxane's proposed construction finds further support in the extrinsic evidence. (*See* Ex. K, WEBSTER'S NINTH NEW COLLEGIATE DICTIONARY 376 (1991) (defining "dose" as "the measured quantity of a therapeutic agent to be taken at one time").)

Jazz, once again, proposes that the Court need not construe the term, yet offers no reason to deviate from Roxane's proposed construction.

C. '730 Patent Family

The patents in the '730 patent family all have the same specification and, therefore, Roxane will cite only to the '730 patent, unless expressly noted.

For the construction of the claim terms in the '730 patent family, the prosecution history is of particular import. At first, the Examiner rejected the claims as obvious over certain prior-art references. Applicants appealed the rejection, but the Board of Patent Appeals and Interferences ("the Board") construed the claims and affirmed the rejection. Only after the appeal, when applicants amended the claims and made further representations to the Examiner, did applicants distinguish their claims from the prior art.

Applicants relied on two distinguishing features to overcome the prior-art rejections.

First, they repeatedly argued that the prior art did not require a "single" pharmacy with a "single" central database for distribution of all of the prescription drug. (*See*, *e.g.*, Ex. L, '730 PH, 12/3/07 Reply Brief at 2-4, ROXGHB004733-35; 1/17/07 Amdt. at 9-10, ROXGHB004611-12; 7/31/06 Interview Agenda at 6, ROXGHB004563; 7/18/07 Substitute Appeal Br. at 16-23, ROXGHB004689-96; 11/2/09 Amdt. at 9-14, ROXGHB004779-84; Ex. M, '106 PH, 3/11/10 Amdt. at 11-12, ROXGHB005046-47; Ex. N, '107 PH, 11/3/09 Amdt. at 8-12, ROXGHB005271-75.) Second, applicants amended the claims to require that all prescriptions be "received *only* at the central pharmacy and that *all* prescriptions [be] processed *only* by the exclusive pharmacy and using *only*the exclusive computer database." (Ex. L, 11/2/09 Amdt. at 9, ROXGHB004779; Ex. N, 11/3/09 Amdt. at 6, ROXGHB005269.) As such, for claim construction, applicants' representations to the Patent Office must be taken into account.

This prosecution history informs the claim constructions for all the terms in the '730 patent family, even terms such as "dispense," ". . . to . . . the patient," and "shipping." In the context of the '730 patent, the "exclusive central pharmacy" must always perform all of the claimed acts, from receiving the drug product to dispensing and shipping the finished drug product. When the exclusive central pharmacy dispenses the drug product, it must be in a form ready for receipt and use by the patient. It would be contrary to the patent's teachings and applicants' representations to the Patent Office to construe the claims to include a situation where the exclusive central pharmacy sends a bulk stock to another pharmacy to keep as inventory for later dispensing to a patient. (Ex. E, 3:34-45; Ex. L, 11/2/09 Amdt. at 10-11, ROXGHB004780-81.)

Inexplicably, however, with the exception of the term, "prescription drug," Jazz has not proffered a construction for any '730 patent family claim term. Instead, Jazz pretends that this

extensive prosecution history did not occur and that the Board did not make any claim construction findings. Leaving the terms unconstrued would introduce the very ambiguity that the *Markman* process was designed to prevent. *See*, *e.g.*, *Amgen, Inc. v. F. Hoffmann-La Roche Ltd.*, 494 F. Supp. 2d 54, 60 (D. Mass. 2007) (*citing Markman*, 517 U.S. at 391).

1. "prescription drug"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"prescription drug" ('730 patent, claims 1, 2, 4, 6, 7, 11; '106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 2, 3; '059 patent claims 1, 3, 5, 6, 7, 8, 10, 14, 15, 16)	"a product containing an active pharmaceutical ingredient available by prescription and not based on brand manufacture"	An FDA approved finished dosage form that may be dispensed only upon a prescription.

The '730 patent discloses that: a prescription drug is identified by the active pharmaceutical ingredient and not the brand manufacturer; and a prescription is required to obtain it. (*Seee.g.*, Ex. E, 1:38-42; 3:14-24 (identifying the drug as sodium oxybate).) Jazz recognized this fact; and later filed a continuation application to limit the prescription drug to a particular manufacturer by changing the claims to specifically identify the prescription drug by a company or trademark, in contrast to the claims-in-suit that merely refer to the drug as a "prescription drug." (*See*, *e.g.*, Ex. P, U.S. Pat. Appl. No. 2011/0119085, claims 1 ("company's prescription drug"), 30 ("prescription drug… sold or distributed under a single trademark").)

The parties' constructions further diverge on Jazz's proposed requirement that the drug be "FDA approved." A person of ordinary skill would know, however, that some drugs available only by prescription have been on the market since before the FDA began approving drugs (*e.g.*, codeine, quinine). These drugs, while still available only by prescription, do not require FDA

approval. *See*21 U.S.C. § 321(p)(1); *see also USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 662-66 (1973).

2. "exclusive"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"exclusive" ('730 patent, claims 1-3, 7-11; '106 patent, claims 1-8; '107 patent, claims 1, 4; '059 patent, claims 1-2, 6, 7, 9-10, 12-15)	"sole"	No construction necessary.

The term "exclusive" can be found in every independent claim in the '730 patent family because its inclusion was necessary for allowance of the claims. During prosecution of the '730 patent, applicants defined "exclusive" to mean "single" or "sole" to distinguish the claims from the prior art. (*See* Ex. L, 12/3/07 Reply Br. at 2, ROXGHB004733.) This definition comports with applicants' other amendments and arguments to the Patent Office—that all prescriptions be "received *only* at the central pharmacy and that *all* prescriptions [must be] processed *only* by the exclusive pharmacy and using *only* the exclusive computer database." (*See*, *e.g.*, Ex. L, 7/31/06 Interview Agenda at 6, ROXGHB004563; 11/2/09 Amdt. at 9, ROXGHB004779; Ex. N, 11/3/09 Amdt. at 8-12, ROXGHB005271-75.)

Jazz disingenuously proposes that no construction is necessary for this term. But applicants, during prosecution, assigned a special definition to "exclusive," which they cannot ignore or disavow during litigation.

3. "pharmacy"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"pharmacy"	"a place where drugs are	No construction necessary.

('730 patent, claims 1-3, 7-11; '106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 2, 4-5; '059 patent, claims 1, 2, 6-16)	compounded or dispensed from a supply stock"	

Roxane's proposed construction of "pharmacy" comports with the intrinsic evidence. The '730 patent refers to the pharmacy as a place from which the prescription drug is dispensed from inventory. (Ex. E, 3:38-42.) Dictionary references agree. (*See*Ex. Q, DORLAND'S POCKET MEDICAL DICTIONARY, 25th ed., 627 (1995) (defining "pharmacy" as "a place where drugs are compounded or dispensed").)

4. "only"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"only" ('730 patent, claims 1-2, 7-11; '106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 12-14)	"and no other"	No construction necessary.

The term "only" should receive Roxane's proposed construction of "and no other," which meaning the intrinsic evidence fully supports. Here too, applicants' amendments and arguments to overcome an obviousness rejection comport with Roxane's proposed construction. (*See*, *e.g.*, Ex. L, 11/2/09 Amdt. at 9-14, ROXGHB004779-84; 12/3/07 Reply Br. at 2-4, ROXGHB004733-35; 1/17/07 Amdt. at 9-10, ROXGHB004611-12; 7/31/06 Interview Agenda at 6-11, ROXGHB004563-68; 7/18/07 Substitute Appeal Br. at 16-23, ROXGHB004689-96; Ex. M, 3/11/10 Amdt. at 11-12, ROXGHB005046-47; Ex. N, 11/3/09 Amdt. at 6, 8-12, ROXGHB005269, 71-75.) Specifically, the Board affirmed a rejection based on prior art because the claims without "only" could have been read to contemplate a distribution system

with more than one central pharmacy or central database. (Ex. L, 8/31/09 Board Decision at 12, ROXGHB4762.) In response, applicants amended the claims to include the term "only" and represented to the Patent Office that "only" the central pharmacy and no other pharmacy receives all prescriptions; "only" the exclusive pharmacy and no other pharmacy processes the prescriptions; and "only" the exclusive computer database and no other database could be used by the exclusive pharmacy to process the prescriptions. (*See*, *e.g.*, Ex. L, 11/2/09 Amdt. at 9, ROXGHB004779.)

The specification comports with Roxane's proposed construction. (See, Ex. E, Figs. 2A-2C; 3:35-45, 3:62-4:1; 4:7-5:58; 7:37-45.) So does the extrinsic evidence. (Ex. R, WEBSTER'S NEW UNIVERSAL UNABRIDGED DICTIONARY at 1250 (1983); *see also*, Ex. K, WEBSTER'S NINTH at 825 ("solely, exclusively").)

5. "at"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"at" ('730 patent, claims 1-2, 7-11; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 12-14)	"located at"	No construction necessary.

The intrinsic and extrinsic evidence supports Roxane's proposed construction of "at." First, the claim context supports the construction. When used in the '730 patent claims, "at" conveys the location of the computer processor that receives all prescription requests—"only *at* the exclusive central pharmacy." (Ex. E, claim 1 (emphasis added).) For example, claim 1 requires that "receiving" be ***both*** "in" the computer processor and "***only at***" the exclusive central pharmacy. Thus, the computer processor must be located at the pharmacy. Further, applicants argued during prosecution that the claims require one exclusive central pharmacy that receives

and processes the prescription requests. Thus, the claimed computer processor that receives the prescription requests must be *located at* that exclusive central pharmacy. (*See*, *e.g.*, Ex. L, 11/2/09 Amdt. at 9, ROXGHB004779-84.)

Extrinsic evidence is in accord. (Ex. K, WEBSTER'S NINTH at 111 (defining "at" as "used as a function word to indicate presence or occurrence in, on or near <staying~a hotel>").)

6. "prescription requests"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"prescription requests" ('730 patent, claims 1-2, 7-11; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 12-14)	"requests to fill prescriptions"	No construction necessary.

Claim context supports Roxane's construction. The claims discuss what is received at the exclusive central pharmacy, *i.e.*, requests for a prescription to be filled. And according to the patent, after a doctor writes the prescription, the prescription request is forwarded to the exclusive central pharmacy for processing and filling. (*See* Ex. E, 4:7-12, 5:27-28.) Only a doctor could write the ***prescription***, but the ***request*** could be made by a doctor, nurse, or patient. In other words, there is a distinction between a doctor's prescription and a request for the prescription to be filled.

The extrinsic evidence agrees. (*See*Ex. K, WEBSTER'S NINTH at 1001 (dictionary definition for "request"); Ex. Q, DORLAND'S POCKET at 660 (defining "prescription" as "a written directive for the preparation and administration of a remedy").)

7. "all"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction

"all" ('730 patent, claims 1, 2, 7-11; '106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 12-14[5])	"every single one, no exceptions"	No construction necessary.

The '730 patent family claims require receiving in a computer processor located only at the exclusive central pharmacy "all prescription requests, for any and all patients being prescribed the prescription drug,…from any and all medical doctors". (*See, e.g.*, Ex. E, claim 1.) The use of "all" and "any and all" in the claims indicates that none—whether the subject be prescription requests, patients, or doctors—is excluded. Again, applicants' representations to the Patent Office in order to obtain their patents dictates this construction. Only after applicants amended the claims to include these terms, and argued that these terms meant that there were none to be excluded, did the Examiner allow the claims. (Ex. L, 11/2/09 Amdt. at 2-13, ROXGHB004772-83; 12/31/09 Notice of Allowability at 10-11, ROXGHB004805-06; Ex. M, 3/11/10 Amdt. at 2, 4, 6, 8, 11-12, ROXGHB005037, 39, 41, 43, 46-47; 4/30/10 Notice of Allowability at 2, ROXGHB005071; Ex. N, 11/3/09 Amdt. at 2, 4, 6, 8, 11, ROXGHB005265, 67, 69, 71, 74; 3/10/10 Notice of Allowability at 5-6, ROXGHB005326-27; Ex. O, '059 PH, 12/21/10 Notice of Allowability at 2-3, ROXGHB028032-33.) Jazz's representations must be taken into account in construing these claim terms.

Extrinsic evidence supports Roxane's proposed claim construction. (*See*Ex. K,

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[5] When preparing this brief, Roxane realized that, for a few claim terms, the claim construction chart that the parties previously submitted inadvertently failed to identify every single claim in the patents-in-suit where the given term appears. The charts in this brief are complete, and they identify the few instances where the claim listing for a given term differs from the claim listing in the chart previously submitted. There is no prejudice to Jazz from the earlier omission because Roxane is not adding any additional claim terms to be construed; it is just identifying additional claims where the given claim terms appear and Roxane's proposed claim constructions are unchanged.

WEBSTER'S NINTH at 70-71 (defining "all" as "every").)

8. "database"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"database" ('730 patent, claims 1-3, 7-11; '106 patent, claims 1, 3, 5-7; '107 patent, claims 1, 4; '059 patent, claims 1, 2, 6, 9, 12-14)	"database containing all relevant data related to the distribution of the drug and the process of distributing it, including patient, physician and prescription information"	No construction necessary.

Like the Board, Roxane relies on the intrinsic evidence for its proposed construction of "database." The Board found that applicants acted as their own lexicographers with respect to this term and that applicants described the central computer database as being exclusive of other databases because it "contain[s] all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information." (Ex. L, 8/31/09 Board Decision at 9, ROXGHB004759 (citing '730 patent at 2:10-12).) Because applicants' definition controls, the Court should construe "database" as applicants and the Board did. *See Vitronics*, 90 F.3d at 1582. (*See also* Ex. E, 1:37-43.)

9. "associated"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"associated" ('730 patent, claims 1-2; '106 patent, claims 1, 3, 7; '059 patent, claim 1)	"located either at or remote from, but not both"	No construction necessary.

The intrinsic evidence supports Roxane's construction of "associated"—a construction that permits only one computer database. Claim 1 of the '730 patent contemplates but a single database. Figure 1 of the patent and the corresponding text describe a computer system of an

exclusive central pharmacy that contains one internal database. The patent also describes an alternate embodiment in which an external database is connected via "a network, phone connection, local area network, wide area network [*i.e.*, a long distance connection] *or* other mechanism." (Emphasis added). However, when the patent allows for the alternate embodiment, it dictates that the external database is "***used in place of***" the internal database." (Ex. E, 3:62-4:1 (emphasis added).) Thus, the database is located either at the computer system/pharmacy or remote from it but not both.

10. "control"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"control" ('730 patent, claims 7-11; '059 patent, claims 6, 9, 12-14)	"write accessibility"	No construction necessary.

The claim context dictates that the term "control" means "write accessibility." Claim 7 of the '730 patent, for example, requires information to be entered into an "exclusive computer database [that is] under exclusive *control* of the central pharmacy." (Ex. E, claim 7 (emphasis added).) The patent explains that the only individuals who have "control" over the central database are those individuals at the central pharmacy who have the ability to enter data into the database. (*Seee.g.*, Ex. E, 4:7-7:25 (explaining that pharmacy specialists enter information into computer database to initiate processing of prescription requests and refill requests).)

While some person or entity other than the central pharmacy (*e.g.*, the DEA) may access the database to check for potential abuse or diversion, only a person at the exclusive central pharmacy (*i.e.*, technician, specialist, or pharmacist) can input information into the database. It is the ability to *input information* that is the touchstone of "control." (*See* Ex. E, 4:7-7:25.) Thus, only those with write accessibility have "control."

11. "prescriptions…are processed;" "processing…prescriptions"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"prescriptions . . . are processed"; "processing . . . prescriptions" ('730 patent, claims 1, 2, 7-11; '107 patent, claims 1, 4; '059 patent, claims 1, 6, 9, 12-14)	"all actions from the receipt of the prescription for the prescription drug through filling of the prescription in a form suitable for providing to the patient"	No construction necessary.

The intrinsic evidence supports Roxane's construction of these terms as encompassing "all actions from the receipt of the prescription for the prescription drug through filling of the prescription in a form suitable for providing to the patient." The '730 patent describes in detail the steps taken from the time a prescription request is received until the prescription is filled. (*See* Ex. E, 4:7-5:67; Figs. 2A-2C.) Because the '730 patent describes the prescription processing as encompassing all of these steps, Roxane's construction is correct.

12. "prescriptions…processed for authorization"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"prescriptions...processed for authorization" ('106 patent, claims 1, 3, 5, 7)	"all actions from receipt of the prescription for the prescription drug up to but not including the filling of the prescription"	No construction necessary.

The intrinsic evidence and the doctrine of claim differentiation inform the proper construction of this term. Whereas the claim term "processing" discussed immediately above contains no modifier or further limitation, this claim term adds the modifier "for authorization." Therefore, this claim term should have a different, narrower meaning. The activity contemplated in this claim term proceeds only to the point where the prescription is authorized for filling. In

the '730 patent, the processing is shown diagrammatically, separating the authorization steps from the filling steps. (*See* Ex. E, Figs 2A-2C; 2:22-24; 4:7-5:28.) Roxane's proposed claim construction properly accounts for this distinction drawn in the '730 patent.

13. "confirming…patient"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"confirming...patient" ('730 patent, claims 1, 2, 7-19; '106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 2, 4, 5; '059 patent, claims 1, 6, 8-14, 16)	"contacting the patient and the patient responding"	No construction necessary.

The "confirming" claim terms of the '730 patent family all require communication with the patient. Claim 1 of the '730 patent, for example, requires (1) "confirming with a patient that the educational material has been read" and (2) "confirming receipt by the patient of the prescription drug." (*See* Ex. E, claim 1.) The '730 patent further explains that the central pharmacy must contact the patient to inquire whether the patient received and read the educational material and that the patient received the prescription drug, and further that the patient must provide a confirming response. (*See id.*, 1:53-56; 5:27-41, 61-63.)

Accordingly, this claim term must be defined to mean "contacting the patient and the patient responding." This construction not only comports with the intrinsic evidence, but also with the doctrine of claim differentiation as discussed in connection with the claim term "verifying" immediately below.

14. "verifying"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"verifying" ('106 patent, claims 1-	"contacting another source for affirming"	No construction necessary.

8; '107 patent claims 1-2, 4-5)		

As mentioned above, under the doctrine of claim differentiation, this claim term must be construed differently than "confirming." Here, the claims explicitly recite "verifying whether a physician is eligible to prescribe a prescription drug, involves contacting the National Technical Information Services ("NTIS") to determine whether the physician has an active DEA number and to check whether any actions are pending against the physician." (*See, e.g.*,Ex. F, claim 1.) The NTIS unquestionably is not part of the central pharmacy, and thus, "verifying" contemplates contacting ***another source*** to affirm the information. The '730 patent further supports this construction because whenever it uses the term "verifying," a second source of affirmance of the act or information is required. (*See* Ex. E, 1:44-50; 4:7-25, 45-46; 5:27-41.)

15. "dispensed"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"dispensed" ('059 patent, claims 7, 10, 15)	"prepared in a form suitable for providing to an individual patient"	No construction necessary.

The claim context supports Roxane's proposed construction. Claim 7 of the '059 patent states that "providing the prescription drug to the patient comprises the central pharmacy authorizing the prescription drug to be dispensed to the patient by another pharmacy." Thus, in the context of the claim, "dispensing" entails providing the drug product "to the patient."

Extrinsic evidence further supports Roxane's construction. Roxane's dictionary citation defines "dispense" as to "prepare[ ] and distribute medicines to those who are to use them." (Ex. U, DORLAND'S ILLUSTRATED MEDICAL DICTIONARY, 28th ed., 496 (1995).) And even Jazz's dictionary citations agree with Roxane's proposed construction, respectively, defining "dispense" as "[t]o give out medicine and other necessities to the sick; to fill a medical

prescription;" and "to prepare and distribute (medication)." (*Compare*Ex. V, STEDMAN'S MEDICAL DICTIONARY, 26th ed., 510 (1995) (relied upon by Jazz) *and*Ex. W, MERRIAM-WEBSTER'S COLLEGIATE DICTIONARY, 10th ed., 335 (1997) (relied upon by Jazz)*with*Ex. U, DORLAND'S ILLUSTRATED at 496.)

16. ". . . to . . . patient"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"...to...patient" ('730 patent, claims 1, 2, 7-11[6]; '107 patent, claims 1, 4; '106 patent, claims 1, 3, 5, 7; '059 patent, claims 1, 6, 7, 9-10, 12-15)	"to the patient in a dispensed form"	No construction necessary.

Roxane's proposed construction of this term is consistent with its proposed construction of "dispensed" and is supported by the intrinsic evidence. The claims recite "providing," "mailing," "sending by courier," "delivering," or "shipment of" the prescription drug to the patient. (*See e.g.*, Ex. E, claim 1; Ex. H, claim 1.) As discussed above with regard to the claim term "dispensing," the '730 patent and claims are directed to a prescription drug that must be prepared in a form suitable for providing to the individual patient. Then the dispensed drug is shipped directly to the patient or to another pharmacy for patient pick-up. (*See* Ex. E, FIG. 2C, 5:27-62 ("the shipment must be sent to the patient's home address"); 1:65-66.) Without question, the drug must be in a dispensed form before the patient receives the prescription drug; thus, the intrinsic evidence supports Roxane's construction.

17. "shipping" and "shipment"

---

[6] *See* fn. 5, above.

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"shipping"; "shipment" ('106 patent, claims 1, 3, 5, 7; '107 patent, claims 1-2, 4-5[7])	"sending of the prescription drug in dispensed form by carrier"	No construction necessary.

As discussed above, the claims and the specification support Roxane's construction that the prescription drug must be prepared in a form suitable for the patient. After the central pharmacy dispenses the drug, the central pharmacy sends the dispensed drug product to the patient via carrier. (*See* Ex. E, 1:61-62 ("courier service's tracking system is used to confirm delivery"); 3:42-45 (dispensed Xyrem is shipped via "overnight carriers or by US mail"); 5:57-58 ("shipped by USPS").) Thus, these claim terms must mean "sending of the prescription drug in dispensed form by carrier."

18. "therapeutic"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"therapeutic" ('106 patent, claims 1, 3, 5, 7)	"only for approved on-label indications"	No construction necessary.

The intrinsic evidence supports Roxane's proposed construction. The '730 patent states that the scope is the distribution of sensitive drugs. (*See* Ex. E, 1:6-7.) Because of the potential for abuse, "sensitive drugs" are approved only for "therapeutic" uses, *i.e.*, medical indications. The FDA determines what those indications are. Thus, "[s]ensitive drugs are controlled [and] are ***approved for specific uses*** by the [FDA], and must be prescribed by a licensed physician." (*Id.* at 1:11-15 (emphasis added).) It is well-known in the art that the only FDA-approved indications for a drug are listed on the drug's label. With respect to sodium oxybate, the FDA-

[7] *See* fn. 5, above.

approved indication is for daytime cataplexy associated with narcolepsy, and the '730 patent discloses that the "therapeutic purpose" of sodium oxybate is for this on-label indication. (*Id.* at 1:21-25.) Accordingly, "therapeutic" means "only for approved on-label indications."

19. "computer system"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"computer system" ('106 patent, claims 1-5, 7-8)	"a computer system that is located at the exclusive central pharmacy"	No construction necessary.

This term must be construed in view of the patent and prosecution history. The '106 patent only discloses a "computer system" in reference to Figure 1. And that "computer system" is located at the exclusive central pharmacy. (*See* Ex. G, 2:19-37 and accompanying text describing exclusive central pharmacy personnel operating the computer system). Further, in seeking the '106 patent claims, applicants amended the claims to require that all prescription requests be received only into an exclusive central computer system (or for claim 5 into an exclusive computer database in a computer system). (Ex. M, 3/11/10 Amdt. at 2-11, ROXGHB005037-46.) The patent, of course, requires that all prescription requests must be received at the exclusive central pharmacy. (*See* Ex. E, Fig. 2A; 4:8-12.) Thus, logic dictates that if all of the requests are received at the exclusive central pharmacy and into the exclusive central computer system, then the exclusive central computer system must be located at the exclusive central pharmacy.

20. "selecting…multiple controls;" "places controls"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"selecting... multiple controls";	"deciding to select more than one control"	No construction necessary.

"places controls" ('106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 2, 4-5; '059 patent, claims 8, 11, 16)		

This claim construction includes two parts. First, whether the claim requires more than one control; and second whether selecting requires a decision to select. First, the terms "multiple controls" and "controls," plainly require more than one "control." The prosecution history is in accord. The Examiner found that the prior art taught "selecting…multiple controls" because the prior art taught two of the controls listed in the claim. (*See e.g.*, Ex. M, 11/17/09 Office Action at 6, ROXGHB005018.) Regarding the "selecting" portion of the claim term, the plain and ordinary meaning of "selecting" and "placing" have a decision component. (*See* K, WEBSTER'S NINTH at 1064 (defining "select" as "take by preference"); 897 (defining "place" as "put in…a particular place").)

21. "controls selected from the group consisting of"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"controls selected from the group consisting of" ('106 patent, claims 1, 3, 5, 7; '059 patent, claims 8, 11, 16)	"selected from the group consisting of the listed controls and no others"	No construction necessary.

In patent law, "consisting of" is a term of art "signifying restriction and exclusion." *See Vehicular Tech. Corp. v. Titan Wheel Int'l Inc.*, 212 F.3d 1377, 1382 (Fed. Cir. 2000); *see also*MPEP§ 2111.03. The Federal Circuit has held that "consisting of" means "I claim what follows and nothing else." *Vehicular*, 212 F.3d at 1382. *See also, In re Gray*, 53 F.2d 520 (C.C.P.A. 1931); MPEP§ 2111.03. This limitation applies to *Markush*groups as well. *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1372 (Fed. Cir. 2005). Here, applicants used the

phrase "consisting of" to restrict the types of controls that may be selected.

22. "maintains"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"maintains" ('107 patent, claims 1, 4)	"has write access to"	No construction necessary.

The intrinsic evidence supports Roxane's proposed construction of "maintains." The claims recite an "exclusive central pharmacy that maintains a central database," which is a computer database. (Ex. G, claims 1, 4.) Nearly half of the specification details the steps from prescription intake to shipping the prescription drug to the patient. (*See* Ex. E, 4:7-7:25.) This process includes the ability of exclusive central pharmacy personnel, and no one else, to enter information or change information within the database, *i.e.*, having "write access" to the database. (*See, e.g.*, Ex. E, 4:28-33 ("specialist entering the patient and physician information into [a] database"); 5:10-11 ("enters all findings in the database"); *see also* Ex. E, 5:19-20, 39, 50; 6:5, 20-21, 24, 33-34, 47-48; 7:11-13, 16-17.) Regardless of how the database is designed, in order to enter information into the database, one must have write access.

23. "the controls comprising"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"the controls comprising" ('107 patent, claim 1, 4)	"including all of the recited controls but open to additional controls"	No construction necessary.

In patent law, "comprising" is a term of art that "means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *See Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); *see also*MPEP§ 2111.03. Here, applicants claimed controls that comprise twenty-three essential

elements. (*See* Ex. G, claims 1, 4.) In fact, applicants amended the claims from "selected from the group consisting of" to "comprising" to overcome a rejection based on the Examiner's finding of at least two of the controls, but not all of them, in the prior art. (*See* Ex. N, 9/14/09 Office Action at 6-7, ROXGHB005239-40; 11/3/09 Amdt. at 2, ROXGHB005265.) As such, the applicants intended "comprising" to require all twenty-three listed elements.

24. "a separate database"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"a separate database" ('107 patent, claims 3, 6)	"a database other than the exclusive central database"	No construction necessary.

Roxane's construction is based on the claim language, the specification, and extrinsic evidence. This claim term appears in claim 3, which depends from claim 1. Claim 1 refers to the exclusive central pharmacy that maintains a central database. Thus, when claim 3 refers to a "separate" database, it must be referring to a database other than the exclusive central database.

The '730 patent discloses that one can "consult[ ] a separate database" to verify a physician's eligibility to prescribe a drug further supports Roxane's construction. (Ex. E, 1:44-50.)

The plain meaning of "separate" further supports Roxane's proposed construction. Separate means "autonomous" or "distinct." (Ex. K, WEBSTER'S NINTH at 1073.) The only other database cited in the claim is the exclusive central database. Thus, a separate database is a database distinct from the exclusive central database.

25. "making the database available to the DEA for checking...for cash payments and for inappropriate questions"

Term(Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction

"making the database available to the DEA for checking . . . for cash payments and for inappropriate questions" ('106 patent, claims 1, 3, 5, 7; '107 patent claims 1, 4)	"the database includes fields designated for cash payments and for inappropriate questions and the DEA can access the database to check for such payments and questions"	No construction necessary.

The intrinsic evidence supports Roxane's proposed construction. The '730 patent discloses that the database "contains multiple fields of information" and that "all the entries described with respect to the above processes are included in the fields." (*See* Ex. E, FIG. 7; 7:41-52; *see also* Ex. T, AppleWorks 5 User's Manual at 8-2 (teaching that a computer database is a collection of data made up of fields and records).)

In order for the DEA to check the database for the two situations identified in the claim, it must have access. Further, the DEA can check this information only if it is stored in fields, as with all entries of information in a database. (*See id.* ("[e]ach category of information is a *field*" and "information in each field is a *value*") (emphasis in original).)

CONCLUSION

For the above reasons, Roxane respectfully asks that the Court construe the terms consistent with Roxane's proposed constructions.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that, on December 5, 2011, I electronically filed the foregoing ROXANE LABORATORIES, INC.'S OPENING *MARKMAN* BRIEF IN SUPPORT OF ITS CLAIM CONSTRUCTIONS with the clerk of the Court by using the Court's CM/ECF system, and accordingly served the parties who receive notice of the filing via the Court's CM/ECF system.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC.,	)	
	)	
Plaintiff,	)	CIVIL ACTION NO.:
	)	2:10-cv-06108 (ES) (CLW)
vs.	)	(consolidated)
ROXANE LABORATORIES, INC.,	)	
	)	
Defendant,	)	

ROXANE LABORATORIES, INC.'S RESPONSIVE *MARKMAN* BRIEF
IN SUPPORT OF ITS CLAIM CONSTRUCTIONS

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CASES

Roxane respectfully submits this brief in response to Jazz's Opening *Markman* Brief, (D.I. 80) regarding the construction of certain claim terms in the '431 and '730 patent families.

I. INTRODUCTION

Jazz's brief commits several cardinal sins with respect to claim construction. In ascertaining the meaning of claim terms, it is insufficient simply to adopt general definitions of the type you would find in a dictionary. Rather, the cases teach over and over again that the first place to look to derive the meaning of claim terms is the intrinsic evidence, which comprises the patent claims, specification, and prosecution history. If the applicants defined their claim terms in a certain way in the specification or before the United States Patent Office, those definitions must prevail over any contrary general dictionary definitions.

In contrast, Roxane's constructions are faithful to the specific meanings that the applicants ascribed to the claim terms, both in the specification (where the applicants acted as their own lexicographers) and in the prosecution history. Jazz's constructions, on the other hand, ignore these critical guiding definitions and unmistakable disavowals. For at least these reasons, the Court should adopt Roxane's proposed constructions set forth in Roxane's opening brief.

II. ARGUMENT

There are thirty-four claim terms in dispute, yet Jazz's brief offers substantive arguments supporting constructions for only eleven terms. It would be wrong for Jazz to offer, in its responsive brief, constructions of additional claim terms based on information gleaned from a recent document production by Roxane reflecting the most up-to-date details of Roxane's proposed distribution system. That would not only be improper sandbagging, but it would also violate fundamental tenets of claim construction. For claims must be construed based on the intrinsic evidence—which has not changed—and may *not* be construed in light of the accused product or method. *See Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1580

(Fed. Cir. 1991) ("[i]n 'claim construction' the words of the claims are construed independent of the accused product, in light of the specification, the prosecution history, and the prior art.") *overruled on other grounds by Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009).

A. The '431 patent family

The patents in the '431 patent family all have the same specification and, therefore, Roxane will cite only to the '431 patent specification, unless expressly noted.

1. "resistant to microbial growth"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"resistant to microbial growth" ('431 patent, claim 1; '889 patent, claim 1; '219 patent, claims 1, 4)	"formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days, including but not limited to formulations containing greater than about 150 mg/ml GHB to GHB's maximal solubility in an aqueous medium"	The formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles.

Jazz concedes that the applicants acted as their own lexicographers to set forth a special definition for the term "resistant to microbial growth" in the '431 patent specification. (*See* D.I. 80 at 5-7.) Jazz, however, proposes to adopt only a portion of the applicants' definition, chopping off a big chunk of it, in mid-sentence no less. But where the applicants act as their own lexicographers, courts typically adopt the applicants' entire definition, not some arbitrary portion of it. *See Prima Tek II v. Polypap*, 318 F.3d 1143, 1152 (Fed. Cir. 2003) (applicants'

definition for term "band" includes all words following "as used herein, means" within the same sentence in the patent specification).

The entire paragraph in the specification that contains the disputed term and the applicants' intended definition is as follows:

> **As used herein in certain embodiments, "resistant to microbial growth" or "resistant to microbial challenge" means that the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days.** As used herein in certain embodiments, an "aqueous medium" may mean a liquid comprising more than about 50% water. In certain preferred embodiments, an "aqueous medium" may be a solution, suspension, gel or emulsion of GHB, with a solution of GHB being most preferred. Preferred gels are thixotropic gels. **Compositions that are resistant to microbial growth are created by dissolving or mixing GHB in an aqueous medium to a concentration or content of greater than of about 150 mg/ml GHB to the maximal solubility of GHB.** The solubility of GHB is up to about 750 mg/ml at room temperature (20°C. to about 25°C.), however, heating the aqueous medium during preparation up to 100°C. will increase GHB solubility to at least about 1000 mg/ml. A preferred concentration or content of GHB is about 500 mg/ml.

(D.I. 78, Ex. A, 3:22-45) (emphasis added). The added emphasis highlights the source of Roxane's proposed construction.

Jazz first focuses on the portion of the specification that reads: ", which for bacteria....and 28 days." Jazz says that it lopped this phrase off because the language merely explains the U.S. Pharmacopoeia's requirements for resistance to microbial growth, and thus is surplusage. (*See* D.I. 80 at 6.) But this argument improperly disregards the applicants' specific choice to define the term as they understood it *when they filed their patent application*. FDA and pharmacopoeial requirements change over time, so the specification sets out the level of microbial resistance that the applicants incorporated into their claims.

This is in full accord with established principles of claim construction. A claim term cannot have different meanings at different times and, thus, claims must be construed as of the application's effective filing date. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 986 (Fed. Cir. 1995) (*en banc*) ("[T]he focus is on the objective test of what one of ordinary skill in the art at the time of the invention would have understood the term to mean."), *aff'd*, 517 U.S. 370 (1996); *see alsoPC Connector Solutions LLC v. SmartDisk Corp.*, 406 F.3d 1359, 1363 (Fed. Cir. 2005) (district court did not err in construing implicit time-dependent claim terms by limiting those terms to "technologies existing at the time of the invention").

Jazz's construction would have these bacterial levels—which were plainly fixed in the applicants' minds—become a moving target open to some later interpretation that might contradict the precise parameters that the applicants set forth in describing their purported invention. That would be improper.

This leaves for consideration only the final portion of Roxane's construction ("including but not limited to formulations containing greater than about 150 mg/ml GHB…into an aqueous medium."). Jazz excludes this portion of the construction because it views the language as exemplary. (D.I. 80 at 6-7.) But that does not make it improper in the claim construction. *See MSMInvs. Co. v. Carolwood Corp.*, 259 F.3d 1335, 1339-40 (Fed. Cir. 2001) (taking into account definitional examples provided in patent specification in claim construction). Indeed, the applicants included this language in the same paragraph where they set forth their own definition of "resistant to microbial growth," indicating that this phrase further animates the meaning of the claim term in the context of their claimed invention. Jazz's proposed construction lacks the precision that the applicants envisioned and, thus, the Court should adopt Roxane's proposed construction, which remains faithful to the applicants' vision.

2. "salt"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"salt" ('431 patent, claims 1-2)	"a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base"	A compound formed by the interaction of an acid and a base.

Once again, the parties agree that the specification sets forth a specific definition for this term. (*See* D.I. 77 at 4-5; D.I. 80 at 9-11.) And again, the parties' dispute revolves around whether the Court should artificially truncate the applicants' chosen definition mid-sentence. And once again, Roxane believes that the proper construction should include the entire definition, not just a portion of the applicants' definition. The relevant sentence in the specification reads:

> A "salt" is understood herein to mean certain embodiments [sic] to mean a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base.

(D.I. 78, Ex. A, 7:2-5.) Following this sentence the specification sets forth a host of examples.

Jazz misreads the specification when it argues that the disputed phrase ", the hydrogen atoms of the acid being replaced by the positive ion of the base," constitutes an "example" of a salt. (D.I. 80 at 10.) In fact, the phrase at issue is a necessary limitation of the term salt. As one of ordinary skill in the art surely knows from high-school chemistry, the interaction of an acid and a base necessarily yields a salt, but not only a salt. (*See* example of water discussed in D.I. 77 at 4-5). But when hydrogen atoms of the acid are replaced by the positive ions of the base, the only compound obtained is a salt. Thus, contrary to Jazz's assertions, Roxane is not trying to incorporate an example into its proposed construction.

To be sure, the paragraph of the specification that contains the full definition of "salt" also contains a multitude of examples of salts. But these examples appear *after* the complete sentence that Roxane relies on defining the necessary parameters of a salt. The clause at issue is most assuredly not an example, but is essential to the full definition that the applicants supplied in their patent specification.

3. "adding the gamma-hydroxybutyrate salt to the aqueous medium"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"adding the gamma-hydroxybutyrate salt to the aqueous medium" ('431 patent, claim 1)	"externally adding a pre-made gamma-hydroxybutyrate salt into a pre-existing aqueous medium"	Including gamma-hydroxybutyrate in a liquid comprising more than 50% water.

Under patent law, a method claim has a fundamental nature—the method must include discrete action steps. *See* McCormick Declaration, Ex. X, R. Faber, FABER ON MECHANICS OF PATENT CLAIM DRAFTING § 4.1 (6 ed. 2011) ("A very important rule to remember is that the 'elements' of a method claim, instead of being structural parts, are, and must be, *acts* or manipulative steps that are performed upon an article, workpiece, or chemical substance.") (emphasis in original). Roxane's proposed construction takes this fundamental nature into account: it requires that an act whereby a GHB salt not already present in the aqueous medium is *added* into an aqueous medium. Jazz, however, knows that Roxane does not practice this "adding" step and, therefore, proposes a construction that improperly reads out this "adding" step entirely—allowing the NaGHB salt components to be formed for the first time within the aqueous medium or even be present in the aqueous medium in its component parts, *i.e.*, as a Na^+cation and GHB^- anion, without ever having existed as a "salt" at all. *See General American*

Transp. Corp. v. Cryo-Trans, Inc., 93 F.3d 766, 770 (Fed. Cir. 1996) (rejecting construction that would read out claim term).

Roxane's construction of the "adding" step is correct. Unlike Jazz's litigation-inspired argument, Roxane's construction finds support in the specification and prosecution history. The parties agree on the specific passages in the '431 patent that describe the claimed chemical method. (*See* D.I. 77 at 5; D.I. 80 at 8.) These passages consistently describe an action step, *i.e.*, "adding," whereby NaGHB salt is "dissolved or mixed" into an aqueous medium. (*See* D.I. 78, Ex. A, 3:37-40, 46-48; 4:25-28; 8:45-49, 63-67; 10:14-16, 20-23, 28-29.); *see also Powell v. Home Depot U.S.A., Inc.*, 663 F.3d 1221, 1233 (Fed. Cir. 2011) (claim term should be construed consistent with specification's repeated description of claimed invention). It is impossible to "dissolve" or "mix" something into water if you don't first *introduce* it into the water. Moreover, the applicants included this "adding" step to overcome a patentability rejection, so its significance cannot be glossed over, as Jazz does. (*See* McCormick Decl. Ex. Y, '431 PH[1], JPI-00000668-JPI-00000671; D.I. 78, Ex. I, '431 PH, 4/6/02 Notice of Allowability at 2, ROXGHB02926.) Thus, Roxane's construction is required by the intrinsic evidence.

Jazz, on the other hand, proposes a construction that improperly relies on extrinsic evidence that contradicts the intrinsic evidence. *See Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 716 (Fed. Cir. 1998) (extrinsic evidence may not be used to contradict the definition of a claim term derived from the otherwise unambiguous intrinsic evidence). That is, Jazz disregards the plain language of claim 1 and urges that a general-purpose dictionary definition of "adding" compels its construction. (*See* D.I. 80 at 7-8.) Based on the dictionary definition, Jazz

[1] '___ PH stands for the prosecution history of the corresponding patent number.

asks the Court to construe "adding" so as not to require a step of adding a component that was not originally present in the solution.

Not only does Jazz's proposed construction violate Federal Circuit precedent by relying on contradictory extrinsic evidence, but Jazz compounds its error by cherry-picking the dictionary definition. Jazz neglects to tell the Court that the definition of "add" that it relies on is not the first, or the second, or even the third listed definition of "add," but rather is the fourth. (D.I. 80, Decl. of G. Brier, Ex. 9 at 13.) Further, Jazz omits from its brief the usage portion of the fourth definition ("<don't forget to ~ me in>"), probably because the usage example shows that the context of Jazz's chosen definition is far removed from the context of this patent claim. (*Id.*)

Indeed, the more appropriate definition of "add" is the dictionary's first—and most common—definition: "1: to join or unite so as to bring about an increase or improvement <~s 60 acres to his land><wine ~s a creative touch to cooking>." (D.I. 80, Decl. of G. Brier, Ex. 9 at 13.) In this context, the definition comports with how the applicants used the term in the specification—to join or unite NaGHB salt with the aqueous medium where it was not present in the aqueous medium before.

Jazz also disregards the specification to the extent its proposed construction requires a "liquid comprising more than 50% water." As shown in the quotation from the specification set forth in Section II.A.1 above, the specification states that the aqueous medium "*may*" be a liquid comprising more than 50% water. But the specification goes on to say that the aqueous medium also "may be a solution, suspension, gel or emulsion" and preferably a "thixotropic gel." Gels, for one, are not liquids but are jelly-like solids and do not necessarily contain over 50% water. Nor do emulsions necessarily contain more than 50% water, *e.g.*, mayonnaise.

4. "about"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"about" ('431 patent, claims 1, 3, 5; '889 patent, claim 1; '219 patent, claims 1, 2, 4; '506 patent claim 1)	"20% of the number modified in the appropriate direction(s)"	Reasonably close to.

Contrary to Jazz's assertion, the parties do not agree that the '431 patent "does not provide an explicit definition of 'about.'" (D.I. 80 at 11.) As Roxane explained in its opening brief, the applicants expressly defined this term in the '431 patent. (*See* D.I. 77 at 6-7; *see also* D.I. 78, Ex. A, 4:8-9.) Roxane's construction incorporates the applicants' explicit definition stating that, "[a]s used herein, the term 'about' generally means within about 10-20%." (*Id.*) Jazz's improper construction, on the other hand, seeks to narrow the claims to contradict this definitional statement.

While "about" has no universal meaning in patent claims, prevailing authority requires that "about" be construed consistent with the intrinsic evidence when used in association with numerical values. *See Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995) ("[T]he word 'about' does not have a universal meaning in patent claims, and [its] meaning depends on the technological facts of the particular case."); *see also Conopco, Inc. v. May Dept. Stores Co.*, 46 F.3d 1556, 1560-61 (Fed. Cir. 1994) (rejecting construction of "about" that did not comport with use in the patent's specification). And "about," like any other term, must be construed consistent with an applicant's own lexicography even if that definition differs from dictionary definitions. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

None of Jazz's three arguments with respect to this claim term comports with the law or with logic.

First, Roxane *is* asserting that the applicants acted as their own lexicographers. Roxane's proposed construction merely takes into account the fact that a 20% modification necessarily subsumes a 10% modification. Further, Roxane's proposed construction recognizes the indisputable fact that "about" goes in both directions—upwards and downwards. These elements are not made up "out of whole cloth," but rather are the necessary implications of the applicants' own definition.

Second, Roxane's construction does not render the specification nonsensical. The term "about 9.8" can differ from "about 10" when "about" is defined as Roxane proposes. Of course, Jazz fails to explain how its own construction comports with the same cited string of GHB amounts. And if Jazz is proposing a narrower construction, then Jazz is contradicting the specification's own statement as to what "about" means.

Third, Jazz cites the preference in the law for constructions that do not result in invalid claims. But this is not a hard and fast rule, and courts often adopt constructions that invalidate patent claims—if those constructions are compelled by the intrinsic evidence. *See Elekta Instrument S.A. v. O.U.R. Scientific Int'l, Inc.*, 214 F.3d 1302, 1308 (Fed. Cir. 2000) (when the intrinsic record compels only one interpretation of a claim term that interpretation must govern even if it renders the claim invalid); *see also Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004) (same). Further, the law favoring valid constructions applies only when the claim term's meaning is ambiguous and needs clarification. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1327 (Fed. Cir. 2005) (*en banc*). But there is no ambiguity where, as here, the applicants specifically set forth the claim term's meaning.

In fact, the only ambiguity with respect to the term "about" appears in Jazz's proposed construction, which improperly leaves the term vague and unbounded. *See Phillips*, 415 F.3d at 1313 (the goal of claim construction proceedings is to eliminate ambiguity to assist in the resolution of legal claims).

There is no merit to Jazz's argument that Roxane's construction would result in pHs that lack support in the specification, *i.e.*, would lead to a pH range of up to 12.0 where the patent "reports a maximal pH of 10.3." (D.I. 80 at 13.) Jazz's argument fails to take into account the specification as a whole. The specification does not state that the maximal pH is 10.3, as that terminology does not appear in the specification. The only place the word "maximal" appears close to the term "pH" in the portion of the specification that Jazz cites is at column 20, lines 5-9, which states:

> The inventors contemplate that a concentration of greater than about 150 mg/ml of GHB, up to the *maximal solubility* in aqueous solution of GHB, will be suitably resistant to microbial challenge from about *pH 3 to about pH 10.3.*

(D.I. 78, Ex. A, 20:5-9) (emphasis added). Plainly, in this portion of the specification, "maximal" modifies the word "solubility" and not the word "pH."

Moreover, this section refers to solubility in solutions, while the patent specification and the claims of the '431 patent support other types of aqueous media (the '431 patent claims recite "aqueous medium"), such as, thixotropic gels and emulsions. (D.I. 78, Ex. A, 3:33-36.) Further, Roxane notes that the '889 and '219 patent claims refer to "aqueous solutions" instead of "aqueous medium," and the pH in those claims is recited as "pH of about 7.5" and "pH of about 6-7.5," respectively, which with 20% added on to the 7.5 would be 8.25, well below the pH 10.3 that Jazz claims is "maximal" for a solution. The other types of media, gels, and emulsions could contain amounts of GHB above the maximal solubility in a solution. And other portions of

the specification explicitly refer to preferred embodiments for the pH range in terms of "to about pH 10.3," meaning that the pH could be above 10.3. (D.I. 78, Ex. A, 3:56-4:9.) Finally, the Federal Circuit has repeatedly cautioned against limiting claim terms to the preferred embodiments where the patent as a whole requires a broader construction. *See Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327-28 (Fed. Cir. 2002).

5. "does not contain a preservative" or "free of preservatives"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"does not contain a preservative"; "free of preservatives" ('431 patent, claim 4; '889 patent, claim 1; '219 patent, claims 1, 4)	"does not contain any substance added to inhibit chemical change or microbial action"	Free of conventional exogenous substances that are added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action.

The parties agree that their proposed constructions of these terms are substantially the same because the '431 patent specification sets out an explicit definition for the term. The only substantive difference between the two constructions is that Roxane has adopted the applicants' specific definition, while Jazz has tried to add limitations into the claim term based on purported limiting statements the applicants made during prosecution. (*See* D.I. 80 at 14-15.)

The passages from the prosecution history on which Jazz relies, taken alone or in combination, do not constitute the required clear and unmistakable disavowal of claim scope needed to vary an explicit definition. *See Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1458 (Fed. Cir. 1998) (refusing to limit claim scope based on prosecution history not clearly calling for narrower limitation). With respect to the word, "conventional," the passages merely describe the prior art, without distinguishing the claimed subject matter. *See Sandisk Corp. v. Memorex*

Prods., 415 F.3d 1278, 1286-90 (Fed. Cir. 2005) (arguments describing the prior art without distinguishing from claimed subject matter did not limit definition and scope of a claim term).

As for the word "exogenous," Jazz relies on a single sentence from the prosecution history discussing a preferred embodiment of the invention. Such vague and nonspecific recitations from the prosecution history are "far too slender a reed to support the judicial narrowing" Jazz requests. *Northern Telecom Ltd. v. Samsung Elecs. Co.*,215F.3d 1281, 1294 (Fed. Cir. 2000) (disavowal of claim scope must be overt and unambiguous).

Finally, while Roxane does not disagree that the "preservative" may be exogenous, *i.e.*, originating outside the aqueous medium, such a concept is implicit in Roxane's construction that no preservative is "added." But for purposes of construing the claims at issue, neither the specification nor the prosecution history clarify what substances are considered "conventional" exogenous preservatives.

6. "pH-adjusting agent"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"pH-adjusting agent" ('431 patent, claims 1, 6; '889 patent, claim 1; '219 patent, claims 1, 3, 4)	"an agent, which is an acid or base, directly added primarily to alter the pH"	No construction necessary.

As the Court will appreciate, "pH-adjusting agent" is not a term used in everyday parlance and, thus, needs to be construed. In fact, the applicants devoted a significant portion of the specification to illuminating what this claim term means. This section of the specification states that:

> In certain other embodiments of the present invention, the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids, bases, or combinations thereof.

(D.I. 78, Ex. A., 6:36-38.) Thus, the pH-adjusting agent should be construed to be an acid or a base, and Jazz is wrong when it claims that the intrinsic evidence does not support such a construction.

Jazz argues that the term "pH-adjusting agent" has a "well-understood, ordinary meaning" and cites various snippets from the patent that purportedly describe what such an agent purportedly does (although at least one reference actually describes what a buffering agent does). (D.I. 80 at 17.) But describing what an agent does is not defining what it is or is composed of. Roxane's construction fills in that blank, whereas Jazz's construction does not illuminate the issue. And of course, even a high school chemistry student knows that compounds that adjust pH must be either acidic or basic (alkaline).

Finally, the inclusion of "directly added" and "primarily" in Roxane's proposed claim constructions is mandated by the specification. The specification teaches that the listed pH-adjusting agents are agents that are added to aqueous media without any additional step (*i.e.*, directly) for the principal purpose (*i.e.*, primarily) of adjusting the pH of the aqueous media. (*See* D.I. 78, Ex. A, 6:36-39; 8:45-59; 12:50-63; *see also* Ex. K, '889 PH, 3/23/2004 Notice of Allowability at 2.)

This claim term should not be a moving target. The intrinsic evidence contains all the information needed to construe it. Consistent with the purpose of *Markman* and the New Jersey Local Patent Rules, the Court should construe the claim term.

7. "organic acid"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"organic acid" ('431 patent, claim 6)	"an acid containing at least one carbon atom that directly acidifies a solution"	A substance containing one or more carbon atoms that is capable of yielding a proton (hydrogen

		ion) in aqueous solution, turning blue litmus paper red in aqueous solutions, ionizing in solution to yield the positive ion of the solvent, reacting with bases to form salts, or accepting electrons in an acid-base reaction.

Although the parties agree that "organic" means containing at least one carbon atom, their constructions could not be more different. Roxane bases its construction on the intrinsic evidence. Jazz, on the other hand, improperly looks solely to contrary extrinsic evidence to add limitations into the term that can be found nowhere in the intrinsic evidence. *See Key Pharms.*, 161 F.3d at 716.

Jazz argues that its proposed construction should be adopted because the term "acid" "is not defined in the specification." (D.I. 80 at 18.) But that argument ignores column six of the specification, which describes the very acids that the applicants conceived could be added in the method of claim 1 to lower the pH of the solutions, *i.e.*, to acidify. (*See* D.I. 78, Ex. A, 6:39-51.) Each of the compounds disclosed in this section—including caffeine (which acts as a weak acid in highly basic solutions), although Jazz erroneously argues otherwise, (D.I. 80 at 19)—can directly lower pH when added to a solution. Roxane's construction merely recites the most basic description of the function these compounds all have in common.

Roxane's proposed definition is consistent with the applicants' usage of the term "organic acid" in their patent. For example, at column 20, lines 27-31, the applicants state:

> The feasibility of preparing formulations containing 150 mg/mL of GHB at pH 3, 5 and 7 was established. Solutions containing 150 mg/mL GHB were prepared. The initial pH was greater than pH 7.5 and the final pH was adjusted to 3, 5 or 7 with hydrochloric acid.

(D.I. 78, Ex. A, 20:27-31.) In this passage, the applicants discuss acidifying (lowering the pH of) a solution by directly adding an acid (albeit in this case an inorganic acid, HCl). Elsewhere in the patent, however, in the Formulation Study at columns 32-35, the applicants discuss directly adding an organic acid (malic acid) to lower the pH of the GHB solutions. (*See* D.I. 78, Ex. A, 32:5-35:36.)

Jazz's construction ignores these illustrations in the specification. Instead, Jazz melds multiple definitions of "acid" plucked from two technical dictionaries to create a mish-mosh of confusing and potentially inaccurate statements, with no support from an expert. (*See* D.I. 80 at 18.) The resulting amalgam encompasses many types of compounds that differ greatly from the organic acids the '431 patent identifies. There is simply no reason to insert such confusion and ambiguity into the term's construction when applicants have already plainly laid their vision out.

8. "wherein ... is ..."

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"wherein ... is ..." ('219 patent, claims 1, 3, 4)	"one of the listed components and no others"	No construction necessary.

Jazz's proposed non-construction ignores the special place that the phrase "wherein...is" has in patent law. *See* MPEP § 2111.03;MPEP§ 2111.04. Instead, Jazz argues that no construction is necessary because the term is composed of "two ordinary English words." (*See* D.I. 80 at 20.) But many terms of art are comprised of "ordinary English words," yet they are nevertheless understood to carry special meaning to those who practice the art. The term "wherein...is" is one of them.

Jazz's citation to the *Decisioning.com* case lends no assistance. (D.I. 80 at 20.) That case considered claim terms that did not carry a special legal significance as set forth in the

MPEP, and also resulted in a claim construction that produced anomalous results, a circumstance not present here. For example, in the context of the '219 patent claims, limiting the pH adjusting agent to one of the organic acids listed after "is" ("wherein the pH adjusting agent is malic acid, citric acid, acetic acid, lactic acid, carbonic acid, formic acid, propionic acid or tartaric acid") produces no anomalous result.

9. "dose"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"dose" ('506 patent, claim 1)	"a therapeutic amount of a pharmaceutical composition comprising chemically stable gamma-hydroxybutyrate in an aqueous medium resistant to microbial growth taken by a patient"	No construction necessary.

Roxane's construction relies on the intrinsic evidence, as supported by extrinsic evidence, to present the appropriate definition of the term "dose" in the '506 patent. (*See* D.I. 77 at 10-11.) Contrary to Jazz's contention, Roxane's construction derives from explicit statements in the '506 patent defining a method of dosing a patient to treat him or her for conditions responsive to GHB:

> The invention also provides a method of treating any therapeutic category of disorder responsive to GHB, comprising administering *to a patient suspected of have such a condition a therapeutic amount of a pharmaceutical composition comprising chemically stable GHB (e.g. 1-10 gms.) in an aqueous medium resistant to microbial growth.*

(D.I. 78, Ex. D, 8:60-64 (emphasis added).)

The issue here boils down to whether a "dose" means the liquid a patient actually ingests or the liquid in the bottle of concentrate a patient receives from the pharmacy and then dilutes in a glass of water to create the liquid that actually will be ingested. The specification passage cited

above makes clear that the "dose" consists of what is "administered to" or "taken by" the patient. This conclusion also comports with the common conception of "dose" and the context in which dose appears in the '506 patent claims – "comprising *orally administering* to a patient afflicted with the condition an aqueous composition comprising a first *dose* . . ." (D.I. 78, Ex. D, 72:20-22) (emphasis added).

B. '730 Patent Family

The patents in the '730 patent family all have the same specification and, therefore, Roxane will cite only to the '730 patent, unless expressly noted.

As explained in Roxane's opening brief, the prosecution history of the '730 patent family informs the construction of many of the twenty-five disputed claim terms. (*See* D.I. 77 at 11-30.) Yet, Jazz proposes a construction for just one term, "prescription drug," and offers substantive argument on just one other, "the controls comprising." (*See* D.I. 80 at 22-29.) Thus, Jazz would prefer the Court remain blind to what the intrinsic evidence says about twenty-three of these terms. But Jazz cannot wish away the specification and extensive prosecution history simply by pretending they do not exist.

1. "prescription drug"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"prescription drug" ('730 patent, claims 1, 2, 4, 6, 7, 11; '106 patent, claims 1, 3, 5, 7; '107 patent, claims 1, 2, 3; '059 patent claims 1, 3, 5, 6, 7, 8, 10, 14, 15, 16)	"a product containing an active pharmaceutical ingredient available by prescription and not based on brand manufacture"	An FDA approved finished dosage form that may be dispensed only upon a prescription.

Jazz must recognize that its construction of this claim term is untenable because its brief offers only a confusing welter of disconnected arguments that draw on irrelevant issues such as storage regulations and FDA's definition of a different term (drug product).

Roxane's construction, on the other hand, is firmly grounded in the intrinsic evidence. As the prosecution history shows, when the applicants wanted to limit the "prescription drug" to a specific manufacturer, they did so. (*See, e.g.*, D.I. 78 at Ex. P, U.S. Pat. Appl. No. 2011/0119085, claim 1 ("company's prescription drug"), and claim 30 ("prescription drug... sold or distributed under a single trademark").) With regard to the claims-in-suit, however, the applicants did not modify "prescription drug." Accordingly, under the doctrine of claim differentiation, the claim term as issued cannot be limited to a specific manufacturer. *See Precise Exercise Equipment Inc. v. Chi HsinImpex Inc.*, No. 96-6418, 1998 WL 798163, 48 U.S.P.Q. 2d 1621, 1625 (C.D. Cal. 1998) (applying the doctrine of claim differentiation to related patents in the same family).

Further, a person of ordinary skill in the art would know that there are prescription drugs that have been available before FDA's approval process began, including sensitive drugs such as codeine or quinine, that do not require FDA approval to be marketed. *See*21 U.S.C. § 321(p)(1); *see also USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 662-66 (1973). The Court should not limit the claim term to only Jazz's preferred embodiments. *See Teleflex*, 299 F.3d at 1327-28.

2. "the controls comprising"

Term (Patent Claims)	Roxane's Proposed Construction	Jazz's Proposed Construction
"the controls comprising" ('107 patent, claim 1, 4)	"including all of the recited controls but open to additional controls"	No construction necessary.

Although Jazz disputes Roxane's construction of this term, it never offers a construction of its own. (*See* D.I. 80 at 24-25.) And it ignores the fact that when used in a patent, the term "comprising" has specific legal significance—"mean[ing] that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *See Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); *see also* MPEP§ 2111.03. Here, the applicants specifically used the term to claim controls that comprise twenty-three essential elements. (*See* D.I. 78, Ex. G, claims 1, 4.) Further, the prosecution history contains an unmistakable disavowal that comports with Roxane's construction. In the prosecution history, the applicants amended the claims from the phrase:

> "selecting . . . multiple controls . . ., the controls selected from the group consisting of,"

which terminology allows fewer than all members to be selected from a group (known in patent parlance as a "Markush" grouping, *see*MPEP § 803.02), to:

> "selecting . . . multiple controls . . ., the controls comprising"

to overcome a rejection based on the Examiner's finding of at least two of the controls, but not all of them, in the prior art. (*See* D.I. 78 at Ex. N, 9/14/09 Office Action at 6-7, ROXGHB005239-40; 11/3/09 Amdt. at 2, ROXGHB005265.) Thus, the applicants intended "comprising" to require all twenty-three listed elements. This is a clear disavowal of claim scope in the prosecution history that merits inclusion in a claim construction. *See Northern Telecom Ltd.*,215 F.3d at 1294.

Jazz, however, urges that Roxane's construction "would improperly read other limitations out of the claims," in particular the beginning portion of the phrase "selecting…multiple controls," because it includes twenty-three controls. (D.I. 80 at 24-25.) But Jazz overlooks that

the patent does not identify all the possible controls that a person of ordinary skill in the art would know exist. Moreover, unlike Jazz, Roxane has proposed a separate, and consistent, construction of "selecting...multiple controls." (*See*D.I. 77 at 26-27.)

Finally, in amending the claims, the applicants provided a specific instruction on how both claim terms ("selecting multiple controls" and "the controls comprising") should be interpreted within the context of the claim. The Court may not restructure the claim to have a different meaning than the applicants' intention, even if, as Jazz argues, that construction would render the claim invalid. *See Elekta*, 214 F.3d at 1308.

3. The remaining claim terms in the '730 patent family.

Even though there are twenty-three more claim terms in dispute, Jazz argues that the Court should not construe them. Jazz provides no term-specific justification or reasoning, but rather raises a host of nonspecific allegations about "redundancy" and "imported limitations." (*See* D.I. 80 at 29.) Since Jazz has not offered any specific argument with respect to these claim terms, Roxane will not burden the Court by merely restating the arguments in its opening brief, but reserves its right to address any new arguments Jazz makes during any *Markman* hearing the Court may schedule. As Jazz has failed to offer substantive argument, Roxane's constructions of these terms should be adopted.

Roxane suspects that Jazz can offer no counter-argument to these claim terms because Roxane's reasoning is unassailable. For instance, with respect to the claim term "only," the documented disavowals in the '730 patent prosecution history are crystal clear that the applicants amended their claims to limit their claimed distribution method to one central pharmacy or central database *and no other*, and that without the concept "and no other," the claims would not have issued. (*See* D.I. 77 at 15-16.) Likewise, with respect to the claim term "exclusive," to overcome a rejection the applicants convinced the examiner that the claimed methods could be

distinguished from, and thus issue despite, the prior art because the claimed methods used a "single" or "sole" central pharmacy or central database. (*See id.* at 14.) Thus "exclusive" must be construed to mean "sole."

III. CONCLUSION

For the above reasons, Roxane respectfully asks that the Court construe the terms consistent with Roxane's proposed constructions.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that, on February 21, 2012, I electronically filed the foregoing ROXANE LABORATORIES, INC.'S RESPONSIVE *MARKMAN* BRIEF IN SUPPORT OF ITS CLAIM CONSTRUCTIONS with the clerk of the Court by using the Court's CM/ECF system, and accordingly served the parties who receive notice of the filing via the Court's CM/ECF system.

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Electronic Acknowledgement Receipt

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Application Number:	13592202
International Application Number:	
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Title of Invention:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
First Named Inventor/Applicant Name:	Dayton T. Reardan
Customer Number:	21186
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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Warnings:					
Information:					
4	Non Patent Literature	0003_2__jazz_v_roxane_complaint_11_22_10_2.pdf	176563 efe38bf3f9dc7bcb9ffafdc2539c4e3f6fefae02	no	14
Warnings:					
Information:					
5	Non Patent Literature	0004_5__jazz_opening_markman_brief.pdf	448201 91c87a780a89ad89309a8e380f16a8efb05b6752	no	34
Warnings:					
Information:					
6	Non Patent Literature	0005_8__jazz_responsive_markman_brief_106108_2_21_12.pdf	5275551 2e4aa20982489d8f90134ef88280cee014e1cbc5	no	41
Warnings:					
Information:					
7	Non Patent Literature	0006_4__statement_joint_claim_struction.pdf	243829 8d39990daf4261ffd35cd6b615a0402cc93fff1b	no	31
Warnings:					
Information:					

8	Non Patent Literature	0007_1__10_14_10__roxane_letter_to_jazz__roxane_paragraph_iv_certification_received1.pdf	1483974 5569c5adf519ce1a0e46f90909d8ddf12cbf48f4	no	11
Warnings:					
Information:					
9	Non Patent Literature	0008_11__ltr_roxane_to_court_re_amend_tentions_22712.pdf	4527569 00237ab43e28ad21d187206cdcc96099d0e39a3c	no	60
Warnings:					
Information:					
10	Non Patent Literature	0009_12__2093851v1roxanes_march_19_2012_reply_letter_w_exhibits.pdf	8723592 cdc2596d3e769998b1f2c6f8d2fa3f9d37bd6e90	no	89
Warnings:					
Information:					
11	Non Patent Literature	0010_13__ltr_re_tentions_329122.pdf	319353 7d70d39b53d90055367890695dca91fb91379ff7	no	4
Warnings:					
Information:					
12	Non Patent Literature	0011_7__answer_to_counterclaim.pdf	118605 121efcfc51ccaf3a9ddd864b7ef652a7365cb1f6	no	7
Warnings:					
Information:					
13	Non Patent Literature	0012_10__reply_to_counterclaims.pdf	495137 30ebcf411d72cebf6e19ba3786ab4652d372b296	no	6
Warnings:					
Information:					
14	Non Patent Literature	0013_3__answer.pdf	2206320 e402e8b89b0bb644b0ab69c259ed7fbe70e980ea	no	21
Warnings:					
Information:					
15	Non Patent Literature	0014_14__roxanes_invalidity_tentions_41411.pdf	1925211 3af12ebac360fe1826f042440dc3095d3d2dca50	no	317
Warnings:					
Information:					
16	Non Patent Literature	0015_6__roxanes_opening_markman_brief.pdf	368760 486e930e38e13a07f3694fb74b6f7166fafc6dcf	no	37
Warnings:					
Information:					

17	Non Patent Literature	0016_9__roxanes_responsive_markman_brief.pdf	1969168 551aac2d65a281703de420120c30ad1b3155ce5e	no	27
Warnings:					
Information:					
			Total Files Size (in bytes):	31936112	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/097,651	04/01/2005	Dayton T. Reardan	101.031US3	6798

21186 7590 05/27/2010

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER	
FUELLING, MICHAEL	
ART UNIT	**PAPER NUMBER**
3626	

NOTIFICATION DATE	DELIVERY MODE
05/27/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@slwip.com
request@slwip.com

Interview Summary	Application No.	Applicant(s)	
	11/097,651	REARDAN ET AL.	
	Examiner	Art Unit	
	Michael Fuelling	3626	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Michael Fuelling*. (3)_____.

(2) *David D'Zurilla, Esq., Reg. No. 36,776*. (4)_____.

Date of Interview: *21 May 2010*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *N/A*.

Identification of prior art discussed: *N/A*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Applicant had questions about the Rule 105 request and it is anticipated the requested exemplar documents will be provided for the identified time periods*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Michael Fuelling/ Examiner, Art Unit 3626	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

———

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Dayton T. Reardan Ph.D et al.	Examiner:	Unknown
Serial No.:	13/592,202	Group Art Unit:	3626
Filed:	August 22, 2012	Docket:	101.031US9
Customer No.:	21186	Confirmation No.:	5805
Title:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD		

COMMUNICATION CONCERNING PRIOR OR COPENDING APPLICATION(S)

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Pursuant to the guidance of MPEP §§ 2001.06(b) and 2004(9), Applicants would like to bring the following additional application(s) to the Examiner's attention. The identification of these applications is not intended to suggest that the subject matter claimed in any listed application is, or has been, substantially similar to any claim or claims in the present application.

Serial No./ Patent No.	Filing Date	Attorney Docket	Title
13/595,676	August 27, 2012	101.031U10	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
13/595,757	August 27, 2012	101.031U11	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
10/322,348 7,668,730	December 17, 2002	101.031US1	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
10/979,665 7,765,106	November 2, 2004	101.031US2	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
11/097,651 7,797,171	April 1, 2005	101.031US3	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
12/704,097 7,895,059	February 11, 2010	101.031US5	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
13/013,680	January 25, 2011	101.031US6	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
11/097,985 7,765,107	April 1, 2005	101.031US4	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

13/453,915	April 23, 2012	101.031US7	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
13/495,047	June 13, 2012	101.031US8	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 371-2140

Date October 4, 2012 By /David D'Zurilla/
David D'Zurilla
Reg. No. 36,776

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Dayton T. Reardan Ph.D et al.

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

Docket No.:	101.031US9	Serial No.:	13/592,202
Filed:	August 22, 2012	Due Date:	N/A
Examiner:	Unknown	Group Art Unit:	3626
Customer No.:	21186	Confirmation No.:	5805

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We are transmitting herewith the following attached items (as indicated with an "X"):

X Communication Concerning Prior and Copending Applications (2 pgs.)
X Information Disclosure Statement (2 pgs.), Form 1449 (5 pgs.) Copies of Cited References (16).
Other documents NOT enclosed, cited in Parent Application.

If not provided for in a separate paper filed herewith, please consider this a PETITION FOR EXTENSION OF TIME for sufficient number of months to enter these papers and please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
Customer No.: 21186

By: /David D'Zurilla/
David D'Zurilla
Reg. No. 36,776

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
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SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. BOX 2938
MINNEAPOLIS MN 55402

MAILED

OCT 04 2012

OFFICE OF PETITIONS

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/592,202

1. THE REQUEST FILED August 22, 2012 IS **GRANTED**.

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to **Michelle R. Eason** at (571) 272-4231. In his/her absence, calls may be directed to Brian W. Brown at (571) 272-5338.

/Michelle R. Eason/
(*Signature*)

Paralegal Specialist, Office of Petitions
(Title)

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13592202	REARDAN ET AL.
	Examiner	Art Unit
	LENA NAJARIAN	3686

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	01/11/2013								
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/592,202	08/22/2012	Dayton T. Reardan	101.031US9	5805

21186 7590 01/16/2013

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

NOTIFICATION DATE	DELIVERY MODE
01/16/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@slwip.com
SLW@blackhillsip.com

Office Action Summary	Application No.	Applicant(s)	
	13/592,202	REARDAN ET AL.	
	Examiner	Art Unit	
	LENA NAJARIAN	3686	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-26* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *1-26* are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-22, drawn to database, schema, and data structure creation and/or modification, classified in class 707, subclass 803.

   II. Claim 23-26, drawn to health care management, classified in class 705, subclass 2.

2. The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct if they do not overlap in scope and are not obvious variants, and if it is shown that at least one subcombination is separately usable. In the instant case, subcombination I has separate utility such as database, schema, and data structure creation and/or modification. Subcombination II has separate utility such as health care management. See MPEP § 806.05(d).

The examiner has required restriction between subcombinations usable together. Where applicant elects a subcombination and claims thereto are subsequently found allowable, any claim(s) depending from or otherwise requiring all the limitations of the allowable subcombination will be examined for patentability in accordance with 37 CFR 1.104. See MPEP § 821.04(a). Applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to

provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

3. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LENA NAJARIAN whose telephone number is (571)272-7072. The examiner can normally be reached on Monday - Friday, 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jerry O'Connor can be reached on (571) 272-6787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LENA NAJARIAN/
Primary Examiner, Art Unit 3686
1/11/13

Mark S. Olinsky
Theodora McCormick
Brian N. Biglin
SILLS CUMMIS & GROSS P.C.
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(973) 643-7000
Attorneys for Defendant
Roxane Laboratories, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **vs.** **ROXANE LABORATORIES, INC.,** **Defendant.**	**C.A. No. 2:12-cv-06761 (ES) (CLW)**

ROXANE LABORATORIES, INC.'S ANSWER,
AFFIRMATIVE DEFENSES AND COUNTERCLAIMS TO PLAINTIFF'S COMPLAINT

Defendant, Roxane Laboratories, Inc. ("Roxane"), for its Answer, Affirmative Defenses and Counterclaims to Plaintiff Jazz Pharmaceuticals, Inc.'s ("Jazz Pharmaceuticals") Complaint for Patent Infringement ("the Complaint"), states as follows:

Nature of the Action

1. Roxane admits that the Complaint purports to be a civil action for patent infringement. Roxane also admits that it filed an Abbreviated New Drug Application ("ANDA") No. 202090 with the United States Food and Drug Administration ("FDA"), seeking approval to commercially market a generic version of Jazz Pharmaceuticals' XYREM® drug product prior to

the expiration of United States Patent No. 8,263,650 ("the '650 patent"). Roxane denies all other allegations contained in paragraph 1 of the Complaint.

The Parties

2. Roxane admits on information and belief that Jazz Pharmaceuticals is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304. Roxane denies all other allegations contained in paragraph 2 of the Complaint.

3. Roxane admits the allegations contained in paragraph 3 of the Complaint.

4. Roxane admits that it is registered to do business in the State of New Jersey and maintains a registered agent for service of process in New Jersey. Roxane further admits that it sells generic drug products throughout the United States, including this judicial district. Roxane further admits that it has litigated patent cases in this district and that, in at least some of those actions, Roxane has asserted counterclaims. Roxane denies all other allegations contained in paragraph 4 of the Complaint.

Jurisdiction and Venue

5. Roxane admits the allegations contained in paragraph 5 of the Complaint.

6. For purposes of this action, Roxane consents to this Court's jurisdiction. Roxane denies all other allegations contained in paragraph 6 of the Complaint.

7. For purposes of this action, Roxane consents that venue is proper in this district. Roxane denies all other allegations contained in paragraph 7 of the Complaint.

The Patents in Suit

8. Roxane admits that what purports to be a copy of the '650 patent is attached to the Complaint as Exhibit A. Roxane further admits that Exhibit A (a) is entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy,"

and (b) lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan as "Inventors." Roxane denies all other allegations contained in paragraph 8 of the Complaint.

The XYREM® Drug Product

9. Roxane admits that New Drug Application ("NDA") No. 21-196 was approved by the FDA and that Jazz Pharmaceuticals is listed as the applicant for that NDA. Roxane denies all other allegations contained in paragraph 9 of the Complaint.

10. Roxane admits that the '650 patent is listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to XYREM®. Roxane denies all other allegations contained in paragraph 10 of the Complaint.

Acts Giving Rise to this Suit

11. Roxane admits that it filed ANDA No. 202090. Roxane's ANDA speaks for itself as to its contents. Roxane denies all other allegations contained in paragraph 11 of the Complaint.

12. Roxane admits that it provided a written certification to the FDA pursuant to Section 505 of the Federal Food Drug and Cosmetics Act ("FFDCA"). Roxane's certification speaks for itself as to its contents. Roxane denies all other allegations contained in paragraph 12 of the Complaint.

13. Roxane admits that by letter dated October 5, 2012 ("Roxane's Notice Letter"), Roxane notified Jazz Pharmaceuticals of its ANDA certification that the claims of the '650 patent are invalid, unenforceable, and/or will not be infringed by Roxane. Roxane's ANDA speaks for itself as to its contents. Roxane further admits that in Roxane's Notice Letter, Roxane informed Jazz Pharmaceuticals that Roxane seeks FDA approval for Roxane's sodium oxybate oral solution. Roxane denies all other allegations contained in paragraph 13 of the Complaint.

Count I: Infringement of the '650 Patent

14. Roxane repeats, reasserts and incorporates by reference its answers to paragraphs 1-13 of the Complaint above, as if fully set forth herein.

15. Roxane denies the allegations contained in paragraph 15 of the Complaint.

16. Roxane admits the allegations contained in paragraph 16 of the Complaint.

17. Roxane denies the allegations contained in paragraph 17 of the Complaint.

18. Roxane denies the allegations contained in paragraph 18 of the Complaint.

19. Roxane denies the allegations contained in paragraph 19 of the Complaint.

20. Roxane denies the allegations contained in paragraph 20 of the Complaint.

21. Roxane denies the allegations contained in paragraph 21 of the Complaint.

22. Roxane denies the allegations contained in paragraph 22 of the Complaint.

PRAYER FOR RELIEF

Roxane specifically denies that Jazz Pharmaceuticals is entitled to the general or specific relief requested against Roxane, or to any relief whatsoever, and prays for judgment in favor of Roxane dismissing this action with prejudice, and awarding Roxane its reasonable attorneys' fees pursuant to 35 U.S.C. § 285, interest, and costs of this action, and such other or further relief as this Court may deem just and proper.

AFFIRMATIVE DEFENSES

Without prejudice to the denials set forth in its Answer and without admitting any allegations of the Complaint not otherwise admitted, Roxane avers and asserts the following Affirmative Defenses to the Complaint of Plaintiff Jazz Pharmaceuticals.

FIRST AFFIRMATIVE DEFENSE
(Noninfringement of U.S. Patent No. 8,263,650)

The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that is the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 8,263,650 ("the '650 patent") either literally or under the doctrine of equivalents.

SECOND AFFIRMATIVE DEFENSE
(Invalidity of U.S. Patent No. 8,263,650)

Upon information and belief, the claims of the '650 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

THIRD AFFIRMATIVE DEFENSE
(Inequitable Conduct)

Upon information and belief, the claims of the '650 patent are unenforceable because of Jazz Pharmaceutical's inequitable conduct, as alleged more specifically in Roxane's Counterclaim set forth below.

FOURTH AFFIRMATIVE DEFENSE
(Patent Misuse)

Upon information and belief, the claims of the '650 patent are unenforceable due to Jazz Pharmaceutical's inequitable conduct committed during its prosecution with unclean hands including, without limitation, the failure of the applicants, inventors, and/or those involved in the prosecution, with the intent to deceive the United States Patent and Trademark Office, to disclose prior art that was material to the examination of the '650 patent, as alleged more specifically in Roxane's Counterclaims set forth below.

COUNTERCLAIM

1. Counterclaimant Roxane Laboratories, Inc. ("Roxane") is a corporation organized under the laws of Nevada having a principal place of business at 1809 Wilson Road, Columbus, Ohio 43228-8601.

2. Upon information and belief, Plaintiff and Counterclaim Defendant Jazz Pharmaceuticals Inc. ("Jazz Pharmaceuticals") is a corporation organized under the laws of Delaware having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304.

3. As a consequence of Jazz Pharmaceuticals' Complaint against Roxane, there is now an existing, continuing actual controversy between Jazz Pharmaceuticals and Roxane regarding the alleged infringement, validity and enforceability of U.S. Patent No. 8,263,650 ("the '650 patent").

4. This Court has jurisdiction over the subject matter of these counterclaims pursuant to §§ 1331 and 1338(a) of Title 28 of the U.S. Code, as they involve substantial claims arising out of the United States Patent Act, 35 U.S.C. § 1, et. seq.

5. This Court may declare the rights and legal relations for the parties pursuant to §§ 2201 and 2202 of Title 28 of the U.S. Code and § 271(e)(5) of Title 35 of the U.S. Code because Roxane's Counterclaims present an actual controversy within the Court's jurisdiction that the patent asserted by Jazz Pharmaceuticals against Roxane are not infringed and/or are invalid.

6. Venue for these Counterclaims is proper within this District in which Jazz Pharmaceuticals' Complaint is pending.

COUNT 1
Declaratory Judgment of Noninfringement of the '650 Patent

7. The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that is the subject matter of ANDA No.

202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of the '650 patent either literally or under the doctrine of equivalents.

COUNT 2
Declaratory Judgment of Invalidity of the '650 Patent

8. Upon information and belief, the claims of the '650 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

COUNT 3
Declaratory Judgment of Unenforceability of the '650 Patent

9. Counterclaimant Roxane incorporates paragraphs 1-8 of its Counterclaim by reference, as though fully set forth herein.

10. The '650 patent and its claims are unenforceable due to inequitable conduct committed during the prosecution, as set forth more fully below.

11. Title 37 of the Code of Federal Regulations §1.56 and the Manual for Patent Examining Procedure §2000.01 et seq. impose a duty of candor and good faith on each individual associated with the filing and prosecution of a patent application before the United States Patent and Trademark Office ("USPTO"), which requires that he or she disclose to the USPTO all information that is material to the patentability of the application under examination. Breach of this duty of candor, good faith and honesty with an intent to deceive the USPTO constitutes inequitable conduct so as to render at least the affected patent unenforceable.

12. Upon information and belief, the '650 patent is void, unenforceable and of no legal effect by reason of inequitable conduct on the part of the inventors thereof and/or those acting on their behalf before the USPTO. Jazz Pharmaceuticals, the inventors and/or those acting on their behalf committed acts of inequitable conduct by failing to disclose information

material to the prosecution of the application. Specifically, Jazz Pharmaceuticals, the inventors, and/or those acting on their behalf withheld material invalidating prior art from the USPTO. Such acts were committed with an intent to deceive the USPTO.

13. The '650 patent is entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt For the Treatment of Narcolepsy" and issued from Application Serial No. 13/446,940, which Jazz filed with the USPTO on April 13, 2012.

14. Claim 1 of the '650 patent claims "[a] pharmaceutical composition, comprising an aqueous solution of about 500 mg/ml sodium gamma-hydroxybutyrate, wherein the composition has a pH of about 7.3 to about 8.5, wherein the composition is chemically stable and resistant to microbial growth, and wherein the composition is free of preservatives."

15. The '650 patent issued from an application which is a continuation of U.S. Application No. 12/913,644, which is a continuation of the application which issued as U.S. Patent No. 7,851,506 ("the '506 patent"), which is a divisional of the application which issued as U.S. Patent No. 7,262,219 ("the '219 patent"), which is a divisional of the application which issued as U.S. Patent No. 6,780,889 ("the '889 patent"), which is a divisional of the application which issued as U.S. Patent No. 6,472,431 ("the '431 patent").

16. The validity and enforceability of the claims of the '431, '889, '219 and '506 patents (collectively, "the '431 patent family") are already at issue in Civil Action No. 10-cv-6108 currently pending in this Court.

17. The '650 patent and the other individual patents of the '431 patent family each identifies the same individuals as inventors. The named inventors are as follows: Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad, and Dayton Reardan.

18. All of the named inventors of the '650 patent and the other patents in the '431 patent family signed a declaration under oath stating that:

> I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 C.F.R. §1.56 (attached hereto). I also acknowledge my duty to disclose all information known to be material to patentability which became available between a filing date of a prior application and the national PCT international filing date in the event this is a Continuation-in-Part application in accordance with 37 C.F.R. §1.63(e).

19. The applications that matured into the '650, '431, '889, '219 and '506 patents were all prosecuted by attorneys and/or patent agents, including Ms. Monique M. Perdok Shonka from the law firm of Schwegman, Lundberg & Woessner, P.A.

20. Under 37 C.F.R. §1.56, patent attorneys prosecuting patent applications are individuals subject to the duty of candor and good faith in dealing with the USPTO, which includes a duty to disclose to the USPTO all information known to those individuals to be material to patentability.

21. Upon information and belief, during the prosecution of the '650 patent, Jazz Pharmaceuticals, the inventors and/or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, such as the attorneys and/or patent agents from the law firm of Schwegman, Lundberg & Woessner, P.A., including Ms. Perdok Shonka, were each aware of his or her duty to disclose information material to patentability to the USPTO.

22. Upon information and belief, Jazz Pharmaceuticals, the inventors and/or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, failed to disclose Chem

Abstract ES302338 ("CA 338"), a non-cumulative prior art reference material to the patentability of the claims of the '650 patent, to the USPTO during prosecution of that application.

23. CA 338 sets forth information contained in Spanish Patent No. ES 302338, entitled "Solutions of 4-hydroxybutyric acid salts for injection," issued on January 16, 1965, from application number ES 1964-30233864 filed on July 22, 1964.

24. CA 338 teaches the preparation of chemically stable, microbial growth resistant, preservative free, pH 7.2-7.7 solutions of the sodium salt of gamma-hydroxybutyrate by reacting pure sodium hydroxide (NaOH) with gamma-butyrolactone (GBL) so as not to prepare solutions that "have far too high a pH for injection." CA 338, therefore, would have been material to claim 1 in the application that matured into the '650 patent, alone or in combination with other references. Furthermore, CA 338 is not cumulative of any reference that was already in front of the USPTO.

25. On April 14, 2011, over a year before the application that matured into the '650 patent was filed, Roxane provided to Jazz Pharmaceuticals its Initial Invalidity Contentions regarding the '431 patent family in Civil Action No. 10-cv-6108, as required by the Local Patent Rules of this Court. Roxane contended in its Initial Invalidity Contentions that one or more of the claims of the '431 patent are invalid in light of CA 338 in combination with other references.

26. Roxane provided its Initial Invalidity Contentions with respect to the '431 patent, as well as the other patents-in-suit, to Jazz Pharmaceuticals on a non-confidential basis. Upon information and belief, these Initial Invalidity Contentions were provided by Jazz Pharmaceuticals, or those acting on its behalf, to attorneys and/or patent agents from the law firm of Schwegman, Lundberg & Woessner, P.A., including Ms. Perdok Shonka, who have

subsequently filed copies of the Initial Invalidity Contentions during prosecution of related patent applications, such as U.S. Patent Application No. 13/453,915.

27. Upon information and belief, as of at least April 14, 2011, Jazz Pharmaceuticals, the inventors and/or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent were aware of CA 338.

28. Specifically, CA 338 was known to Ms. Perdok Shonka, who disclosed CA 338 to the USPTO in an Information Disclosure Statement during the prosecution of a co-pending, related Application Serial No. 13/446,892 ("the '892 application"), which also claims priority to the '431 patent and was co-pending at the same time as the application for the '650 patent. The '892 application, instead of claiming the pH of sodium oxybate liquid formulation, claims a method of orally dosing a liquid formulation of sodium oxybate with no mention of formulation specifics or pH.

29. Upon information and belief, Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, knew that CA 338 was material to the patentability of at least claim 1 of the '650 patent and not cumulative of any prior art that is already in front of the USPTO.

30. Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, did not disclose CA 338 to the USPTO during the pendency of the application that matured into the '650 patent.

31. Failure to disclose CA 338 to the USPTO was an omission by Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation,

filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, in contravention of their duties to the USPTO during the prosecution of the '650 patent.

32. Upon information and belief, Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, had knowledge of, and intentionally withheld, CA 338 from the USPTO with intent to deceive the USPTO.

33. This omission was material to patentability because, among other things, CA 338 was relevant to the question of whether the claims of the '650 patent would have been novel or obvious to one of ordinary skill in the art and because there is a substantial likelihood that a reasonable examiner would have considered CA 338 important in deciding whether to allow at least claim 1 of the '650 patent because this reference either alone or in combination with other art, teaches or implies elements of, or renders obvious, at least claim 1 of the '650 patent.

34. CA 338 was not cumulative of any prior art that was already before the examiners who examined the '431 patent family or the application for the '650 patent.

35. Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including on information and belief Ms. Perdok Shonka, believed the CA 338 reference was sufficiently relevant to this family of patent applications and not cumulative of any prior art already in front of the USPTO to cite CA 338 to the USPTO during the prosecution of the '892 application. CA 338 has less direct relevance to the '892 application claims, which relate to a dosing schedule, than to the '650 patent claims, which relate to liquid formulation pH.

36. Citation of CA 338 during the prosecution of the less relevant '892 application but not the more relevant '650 patent evidences an intent to deceive the USPTO into granting the '650 patent by Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including, on information and belief Ms. Perdok Shonka.

37. But for the material omission of Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, the USPTO would not have issued at least claim 1 of the '650 patent.

38. By failing to cite CA 338 during prosecution of the '650 patent, Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, materially misrepresented the patentability of at least claim 1 of the '650 patent.

39. On information and belief, this material misrepresentation was part of a deliberately planned and carefully executed scheme carried out by Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, to defraud the USPTO and the courts and effect issuance of at least claim 1 of the '650 patent.

40. This material omission of Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, amounted to affirmative egregious misconduct in dealing with the USPTO.

41. For each of the aforesaid reasons, Roxane is entitled to a declaratory judgment that the '650 patent is unenforceable due to inequitable conduct.

ROXANE'S PRAYER FOR RELIEF

WHEREFORE, Roxane respectfully requests that the Court enter judgment against Jazz Pharmaceuticals as follows:

(A) Declaring that Roxane would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 8,263,650 either literally or under the doctrine of equivalents by submitting ANDA No. 202090;

(B) Declaring that Roxane's proposed sodium oxybate oral solution that is the subject of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 8,263,650 either literally or under the doctrine of equivalents;

(C) Declaring that U.S. Patent No. 8,263,650 is invalid for failure to comply with one or more provisions of 35 U.S.C. § 101, 102, 103, and/or 112;

(D) Declaring that U.S. Patent No. 8,263,650 is unenforceable due to inequitable conduct;

(E) Granting an injunction permanently preventing Jazz Pharmaceuticals from asserting or enforcing U.S. Patent No. 8,263,650 against Roxane, its divisions, subsidiaries, licensees, customers or agents;

(F) Awarding Roxane its reasonable costs and attorneys' fees incurred in connection with this action pursuant to 35 U.S.C. § 285;

(G) Such further and other relief as this Court may deem just and proper.

Dated: November 9, 2012

Respectfully Submitted,

s/ THEODORA MCCORMICK
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Theodora McCormick
Brian N. Biglin
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CERTIFICATION PURSUANT TO L. CIV. R. 11.2

Pursuant to L. Civ. R. 11.2, I hereby certify that to the best of my knowledge, information, and belief, aside from this action, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: November 9, 2012

s/ THEODORA MCCORMICK
Theodora McCormick

CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 201.1(D)(1)

I hereby certify that this action does not fall within the requirement for compulsory arbitration set forth in Local Civil Rule 201(d)(1) because the relief sought consists of non-monetary relief (i.e., permanent injunction).

Dated: November 9, 2012

s/ THEODORA MCCORMICK
Theodora McCormick

CERTIFICATE OF SERVICE

I hereby certify that, on November 9, 2012, I electronically filed the attached Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint with the clerk of the Court by using the Court's CM/ECF system, and accordingly served all parties who receive notice of the filing via the Court's CM/ECF system.

s/ THEODORA MCCORMICK
Theodora McCormick

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **vs.** **ROXANE LABORATORIES, INC.,** **Defendant.**	**C.A. No. 2:11-cv-02523 (SDW) (MCA)**

ROXANE LABORATORIES, INC.'S ANSWER,
AFFIRMATIVE DEFENSES AND COUNTERCLAIMS TO PLAINTIFF'S COMPLAINT

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Nature of the Action

1. Roxane admits that the Complaint purports to be a civil action for patent infringement. Roxane also admits that it filed an amendment to its Abbreviated New Drug Application ("ANDA") No. 202090 with the United States Food and Drug Administration ("FDA"), seeking approval to commercially market a generic version of Jazz Pharmaceuticals'

XYREM® drug product prior to the expiration of United States Patent No. 7,895,059 ("the '059 patent"). Roxane denies all other allegations contained in paragraph 1 of the Complaint.

The Parties

2. Roxane admits on information and belief that Jazz Pharmaceuticals is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304. Roxane denies all other allegations contained in paragraph 2 of the Complaint.

3. Roxane admits the allegations contained in paragraph 3 of the Complaint.

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The Patents in Suit

8. Roxane admits that what purports to be a copy of the '059 patent is attached to the Complaint as Exhibit A. Roxane further admits that Exhibit A (a) is entitled "Sensitive Drug Distribution System and Method," and (b) lists Dayton T. Reardan, Patti A. Engle, and Bob

Gagne as "Inventors." Roxane denies all other allegations contained in paragraph 8 of the Complaint.

The XYREM® Drug Product

9. Roxane admits that New Drug Application ("NDA") No. 21-196 was approved by the FDA and that Jazz Pharmaceuticals is listed as the applicant for that NDA. Roxane denies all other allegations contained in paragraph 9 of the Complaint.

10. Roxane admits that the '059 patent is listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to XYREM®. Roxane denies all other allegations contained in paragraph 10 of the Complaint.

Acts Giving Rise to this Suit

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13. Roxane admits that by letter dated March 22, 2011 ("Roxane's Notice Letter"), Roxane notified Jazz Pharmaceuticals of its ANDA certification that the '059 patent is invalid, unenforceable, and/or will not be infringed by Roxane. Roxane's ANDA speaks for itself as to its contents. Roxane further admits that in Roxane's Notice Letter, Roxane informed Jazz Pharmaceuticals that Roxane seeks FDA approval for Roxane's sodium oxybate oral solution. Roxane denies all other allegations contained in paragraph 13 of the Complaint.

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AFFIRMATIVE DEFENSES

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FIRST AFFIRMATIVE DEFENSE
(Noninfringement of U.S. Patent No. 7,895,059)

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SECOND AFFIRMATIVE DEFENSE
(Invalidity of U.S. Patent No. 7,895,059)

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COUNTERCLAIMS

1. Counterclaimant Roxane Laboratories, Inc. ("Roxane") is a corporation organized under the laws of Nevada having a principal place of business at 1809 Wilson Road, Columbus OH 43228-8601.

2. Upon information and belief, Plaintiff and Counterclaim Defendant Jazz Pharmaceuticals Inc. ("Jazz Pharmaceuticals") is a corporation organized under the laws of Delaware having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304.

3. As a consequence of Plaintiff's Complaint against Roxane, there is now an existing, continuing actual controversy between Jazz Pharmaceuticals and Roxane regarding the alleged infringement and validity of U.S. Patent No. 7,895,059 ("the '059 patent").

4. This Court has jurisdiction over the subject matter of these counterclaims pursuant to §§ 1331 and 1338(a) of Title 28 of the U.S. Code, as they involve claims arising out of the United States Patent Act, 35 U.S.C. § 1, et. seq.

5. This Court may declare the rights and legal relations for the parties pursuant to §§ 2201 and 2202 of Title 28 of the U.S. Code and § 271(e)(5) of Title 35 of the U.S. Code because Roxane's Counterclaims present an actual controversy within the Court's jurisdiction.

6. Venue for these Counterclaims is proper within this District in which Jazz Pharmaceuticals' Complaint is pending.

Plaintiff's Improper Listing Of the '059 Patent In The Orange Book

7. The '059 patent relates to a "drug distribution system and method [which] utilizes a central pharmacy and database to track all prescriptions for a sensitive drug" and does not claim an approved method of using the drug (21 U.S.C. 355(j)(5)(C)(ii)), *e.g.*, "indications or other conditions of use" required by 21 C.F.R. § 314.53(b)(1).

8. Thus, the '059 patent was improperly listed in the Orange Book.

9. The listing of the '059 patent must be removed from the Orange Book because the patent does not claim an approved indication or method of using the drug.

Plaintiff's REMS Program

10. Upon information and belief, Plaintiff submitted a risk minimization action plan or risk evaluation and mitigation strategy as part of its NDA No. 21-196 ("REMS Program"), pursuant to section 355-1 of Title 21 of the United States Code.

11. Upon information and belief, Plaintiff's '059 patent constitutes an attempt to cover, or claim some or all aspects of Plaintiff's REMS Program.

12. Plaintiff's '059 patent has been listed in the Orange Book relating to Plaintiff's XYREM® drug product, thereby improperly serving to block or delay approval of Roxane's ANDA No. 202090 under section 355(j) of Title 21 of the U.S. Code.

COUNT 1
Declaratory Judgment of Noninfringement of U.S. Patent No. 7,895,059

13. The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that is the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 7,895,059 ("the '059 patent") either literally or under the doctrine of equivalents.

COUNT 2
Declaratory Judgment of Invalidity of U.S. Patent No. 7,895,059

14. Upon information and belief, the claims of the '059 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

COUNT 3
Order Requiring Removal of the '059 Patent From the Orange Book

15. Counterclaimant Roxane incorporates paragraphs 1-14 of its Counterclaim by reference.

16. Under 21 U.S.C. § 355(j)(5)(C)(ii), Roxane seeks an order requiring Plaintiff to remove the '059 patent from the Orange Book listing for XYREM®.

17. Roxane is entitled to an Order requiring Plaintiff to correct the patent information submitted by Plaintiff for the '059 patent on the ground that the patent does not claim any approved method of using sodium oxybate.

ROXANE'S PRAYER FOR RELIEF

WHEREFORE, Roxane respectfully requests that the Court enter judgment against Jazz Pharmaceuticals as follows:

(A) Declaring that Roxane would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of the '059 patent either literally or under the doctrine of equivalents by submitting ANDA No. 202090;

(B) Declaring that Roxane's proposed sodium oxybate oral solution that is the subject of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of the '059 patent either literally or under the doctrine of equivalents;

(C) Declaring that U.S. Patent No. 7,895,059 is invalid for failure to comply with one or more provisions of 35 U.S.C. § 101, 102, 103, and/or 112;

(D) An Order requiring Plaintiff to remove the '059 patent from the Orange Book listing for XYREM®;

(E) Declaring that Plaintiff's REMS Program for XYREM® is in violation of 21 U.S.C. § 355-1(f)(8) and cannot be used to block or delay approval of Roxane's ANDA;

(F) Awarding Roxane its reasonable costs and attorneys' fees incurred in connection with this action pursuant to 35 U.S.C. § 285;

(G) Such further and other relief as this Court may deem just and proper.

Dated: June 1, 2011

Respectfully Submitted,

s/Theodora McCormick
Mark S. Olinsky
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CERTIFICATION PURSUANT TO L. CIV. R. 11.2

Pursuant to L. Civ. R. 11.2, I hereby certify that to the best of my knowledge, information, and belief, aside from this action, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: June 1, 2011

s/Theodora McCormick
Theodora McCormick

CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 201.1(D)(1)

I hereby certify that this action does not fall within the requirement for compulsory arbitration set forth in Local Civil Rule 201(d)(1) because the relief sought consists of non-monetary relief (i.e., permanent injunction).

Dated: June 1, 2011

s/Theodora McCormick
Theodora McCormick

CERTIFICATE OF SERVICE

I hereby certify that, on June 1, 2011, I electronically filed the attached Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint with the clerk of the Court by using the Court's CM/ECF system, and accordingly served all parties who receive notice of the filing via the Court's CM/ECF system.

s/Theodora McCormick_____
Theodora McCormick

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Dayton T. Reardan Ph.D et al.	Examiner:	Lena Najarian
Serial No.:	13/592,202	Group Art Unit:	3686
Filed:	August 22, 2012	Docket:	101.031US9
Customer No.:	21186	Confirmation No.:	5805
Title:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD		

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In compliance with the duty imposed by 37 C.F.R. § 1.56, and in accordance with 37 C.F.R. §§ 1.97 *et. seq*., the enclosed materials are brought to the attention of the Examiner for consideration in connection with the above-identified patent application. Applicants respectfully request that this Information Disclosure Statement be entered and the documents listed on the attached PTO 1449 Form be considered by the Examiner and made of record. Pursuant to the provisions of MPEP 609, Applicant requests that a copy of the PTO 1449 Form, initialed as being considered by the Examiner, be returned to the Applicant with the next official communication.

Pursuant to 37 C.F.R. § 1.97(b), it is believed that no fee or statement is required with the Information Disclosure Statement. However, if an Office Action on the merits has been mailed after filing of the application or after the filing of the most recent RCE, the Commissioner is hereby authorized to charge the required fees to Deposit Account No. 19-0743 in order to have this Information Disclosure Statement considered.

Pursuant to 37 C.F.R. § 1.98(a)(2), copies of cited U.S. Patents and Published Applications, and Non-Published Applications identifiable by USPTO Serial Number, are no longer required to be provided to the Office. Applicants acknowledge the requirement to submit copies of foreign patent documents and non-patent literature in accordance with 37 C.F.R § 1.98(a)(2).

The Examiner is invited to contact the undersigned at the telephone number indicated if there are any questions regarding this communication.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 371-2140

Date February 14, 2013 By / /

David D'Zurilla
Reg. No. 36,776

DDZ:vam

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Dayton T. Reardan Ph.D et al.

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

Docket No.:	101.031US9	Serial No.:	13/592,202
Filed:	August 22, 2012	Due Date:	N/A
Examiner:	Lena Najarian	Group Art Unit:	3686
Customer No.:	21186	Confirmation No.:	5805

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We are transmitting herewith the following attached items (as indicated with an "X"):

X Supplemental Information Disclosure Statement (2 pgs.), Form 1449 (1 pg.) Copies of Cited References (6).

If not provided for in a separate paper filed herewith, please consider this a PETITION FOR EXTENSION OF TIME for sufficient number of months to enter these papers and please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
Customer No.: 21186

By: / /
David D'Zurilla
Reg. No. 36,776

Electronic Acknowledgement Receipt

EFS ID:	14957297
Application Number:	13592202
International Application Number:	
Confirmation Number:	5805
Title of Invention:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
First Named Inventor/Applicant Name:	Dayton T. Reardan
Customer Number:	21186
Filer:	Eric B. Andersland/Valerie Murphy
Filer Authorized By:	Eric B. Andersland
Attorney Docket Number:	101.031US9
Receipt Date:	14-FEB-2013
Filing Date:	22-AUG-2012
Time Stamp:	11:10:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13592202_SIDS_2-14-13.pdf	254730 5413a5557df0d4cc8417fbc54828d58ab74ff84b	yes	4

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Miscellaneous Incoming Letter		1	1	
	Transmittal Letter		2	3	
	Information Disclosure Statement (IDS) Form (SB08)		4	4	
Warnings:					
Information:					
2	Non Patent Literature	0001_101031u11_oarn_011713.pdf	753631 dbee4a67b3a5e48569246305e0d39301af9eed79	no	6
Warnings:					
Information:					
3	Non Patent Literature	0002_markman_opinion.pdf	464541 5357677c82158061a791ec9e9daa982a1dee59d4	no	43
Warnings:					
Information:					
4	Non Patent Literature	0003_jazz_v_roxane_5.pdf	126805 74a2f6e46e098c77d8705cdaefb6991dc2805597	no	8
Warnings:					
Information:					
5	Non Patent Literature	0004_jazz_v_roxane_2.pdf	159506 e43390e161c5c0364fddad2116e0fcd73fd6f6ff	no	13
Warnings:					
Information:					
6	Non Patent Literature	0005_jazz_v_roxane_3.pdf	155712 cbb51927bac3d4491db20d822949f33fdb9d2bd7	no	12
Warnings:					
Information:					
7	Non Patent Literature	0006_jazz_v_roxane_4.pdf	188709 9347bc1ea82d13a870fbd936366608a89c6ac447	no	18
Warnings:					
Information:					
		Total Files Size (in bytes):	2103634		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Mark S. Olinsky
Theodora McCormick
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The Legal Center
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Attorneys for Defendant
Roxane Laboratories, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **vs.** **ROXANE LABORATORIES, INC.,** **Defendant.**	**C.A. No. 2:11-cv-00660 (SDW) (MCA)**

ROXANE LABORATORIES, INC.'S ANSWER, AFFIRMATIVE DEFENSES AND COUNTERCLAIMS TO PLAINTIFF'S COMPLAINT

Defendant, Roxane Laboratories, Inc. ("Roxane"), for its Answer, Affirmative Defenses and Counterclaims to Plaintiff Jazz Pharmaceuticals, Inc.'s Complaint for Patent Infringement ("the Complaint"), states as follows:

Nature of the Action

1. Roxane admits that the Complaint purports to be a civil action for patent infringement. Roxane also admits that it filed an amended Abbreviated New Drug Application ("ANDA") No. 202090 with the United States Food and Drug Administration ("FDA"), seeking approval to commercially market a generic version of Jazz Pharmaceuticals' XYREM® drug product prior to the expiration of United States Patent Nos. 6,472,431 (the "'431 patent") and

7,851,506 (the "'506 patent"). Roxane denies all other allegations contained in paragraph 1 of the Complaint.

The Parties

2. Roxane admits on information and belief that Jazz Pharmaceuticals is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304. Roxane denies all other allegations contained in paragraph 2 of the Complaint.

3. Roxane admits the allegations contained in paragraph 3 of the Complaint.

4. Roxane admits that it is registered to do business in the State of New Jersey and maintains a registered agent for service of process in New Jersey. Roxane further admits that it sells generic drug products throughout the United States, including this judicial district. Roxane further admits that it has litigated patent cases in this district and that, in at least some of those actions, Roxane has asserted counterclaims. Roxane denies all other allegations contained in paragraph 4 of the Complaint.

Jurisdiction and Venue

5. Roxane admits the allegations contained in paragraph 5 of the Complaint.

6. For purposes of this action, Roxane consents to this Court's jurisdiction. Roxane denies all other allegations contained in paragraph 6 of the Complaint.

7. For purposes of this action, Roxane consents that venue is proper in this district. Roxane denies all other allegations contained in paragraph 7 of the Complaint.

The Patents in Suit

8. Roxane admits that what purports to be a copy of the '431 patent is attached to the Complaint as Exhibit A. Roxane further admits that Exhibit A (a) is entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy,"

and (b) lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan as "Inventors." Roxane denies all other allegations contained in paragraph 8 of the Complaint.

9. Roxane admits that what purports to be a copy of the '506 patent is attached to the Complaint as Exhibit B. Roxane further admits that Exhibit B (a) is entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," and (b) lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan as "Inventors." Roxane denies all other allegations contained in paragraph 9 of the Complaint.

The XYREM® Drug Product

10. Roxane admits that New Drug Application ("NDA") No. 21-196 was approved by the FDA and that Jazz Pharmaceuticals is listed as the applicant for that NDA. Roxane denies all other allegations contained in paragraph 10 of the Complaint.

11. Roxane admits that the '506 patent is listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to XYREM®. Roxane denies all other allegations contained in paragraph 11 of the Complaint.

Acts Giving Rise to this Suit

12. Roxane admits that it filed ANDA No. 202090. Roxane's ANDA speaks for itself as to its contents. Roxane denies all other allegations contained in paragraph 12 of the Complaint.

13. Roxane admits that it provided a written certification to the FDA pursuant to Section 505 of the Federal Food Drug and Cosmetics Act ("FFDCA"). Roxane's certification speaks for itself as to its contents. Roxane denies all other allegations contained in paragraph 13 of the Complaint.

14. Roxane admits that by letter dated January 10, 2011 ("Roxane's Notice Letter"), Roxane notified Jazz Pharmaceuticals of its ANDA certification that the '506 patent is invalid, unenforceable, and/or will not be infringed by Roxane. Roxane's ANDA speaks for itself as to its contents. Roxane further admits that in Roxane's Notice Letter, Roxane informed Jazz Pharmaceuticals that Roxane seeks FDA approval for Roxane's sodium oxybate oral solution. Roxane denies all other allegations contained in paragraph 14 of the Complaint.

Count I: Infringement of the '431 Patent

15. Roxane repeats, reasserts and incorporates by reference its answers to paragraphs 1-14 of the Complaint above, as if fully set forth herein.

16. Roxane denies the allegations contained in paragraph 16 of the Complaint.

17. Roxane admits the allegations contained in paragraph 17 of the Complaint.

18. Roxane denies the allegations contained in paragraph 18 of the Complaint.

19. Roxane denies the allegations contained in paragraph 19 of the Complaint.

20. Roxane denies the allegations contained in paragraph 20 of the Complaint.

21. Roxane denies the allegations contained in paragraph 21 of the Complaint.

22. Roxane denies the allegations contained in paragraph 22 of the Complaint.

23. Roxane denies the allegations contained in paragraph 23 of the Complaint.

Count II: Infringement of the '506 Patent

24. Roxane repeats, reasserts and incorporates by reference its answers to paragraphs 1-23 of the Complaint above, as if fully set forth herein.

25. Roxane denies the allegations contained in paragraph 25 of the Complaint.

26. Roxane admits the allegations contained in paragraph 26 of the Complaint.

27. Roxane denies the allegations contained in paragraph 27 of the Complaint.

28. Roxane denies the allegations contained in paragraph 28 of the Complaint.

29. Roxane denies the allegations contained in paragraph 29 of the Complaint.

30. Roxane denies the allegations contained in paragraph 30 of the Complaint.

31. Roxane denies the allegations contained in paragraph 31 of the Complaint.

32. Roxane denies the allegations contained in paragraph 32 of the Complaint.

AFFIRMATIVE DEFENSES

Without prejudice to the denials set forth in its Answer and without admitting any allegations of the Complaint not otherwise admitted, Roxane avers and asserts the following Affirmative Defenses to the Complaint of Plaintiff Jazz Pharmaceuticals, Inc.

FIRST AFFIRMATIVE DEFENSE
(Noninfringement of U.S. Patent No. 6,472,431)

The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that is the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 6,472,431 ("the '431 patent") either literally or under the doctrine of equivalents.

SECOND AFFIRMATIVE DEFENSE
(Invalidity of U.S. Patent No. 6,472,431)

Upon information and belief, the claims of the '431 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

THIRD AFFIRMATIVE DEFENSE
(Noninfringement of U.S. Patent No. 7,851,506)

The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that is the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any

validly construed claim of U.S. Patent No. 7,851,506 ("the '506 patent") either literally or under the doctrine of equivalents.

FOURTH AFFIRMATIVE DEFENSE
(Invalidity of U.S. Patent No. 7,851,506)

Upon information and belief, the claims of the '506 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

COUNTERCLAIMS

1. Counterclaimant Roxane Laboratories, Inc. ("Roxane") is a corporation organized under the laws of Nevada having a principal place of business at 1809 Wilson Road, Columbus OH 43228-8601.

2. Upon information and belief, Plaintiff and Counterclaim Defendant Jazz Pharmaceuticals Inc. ("Jazz Pharmaceuticals") is a corporation organized under the laws of Delaware having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304.

3. As a consequence of Plaintiff's Complaint against Roxane, there is now an existing, continuing actual controversy between Jazz Pharmaceuticals and Roxane regarding the alleged infringement and validity of U.S. Patent Nos. 6,472,431 ("the '431 patent") and 7,851,506 ("the '506 patent").

4. This Court has jurisdiction over the subject matter of these counterclaims pursuant to §§ 1331 and 1338(a) of Title 28 of the U.S. Code, as they involve claims arising out of the United States Patent Act, 35 U.S.C. § 1, et. seq.

5. This Court may declare the rights and legal relations for the parties pursuant to §§ 2201 and 2202 of Title 28 of the U.S. Code and § 271(e)(5) of Title 35 of the U.S. Code because Roxane's Counterclaims present an actual controversy within the Court's jurisdiction.

6. Venue for these Counterclaims is proper within this District in which Jazz Pharmaceuticals' Complaint is pending.

Plaintiff's Improper Listing Of the '506 Patent In The Orange Book

7. XYREM® is required to be taken in two doses. Prior to dosing XYREM®, the XYREM® label requires that XYREM® be diluted with a specific amount of water. This dilution causes the doses to fall outside the scope of the claims of the '506 patent. Hence, the '506 patent does not claim an approved method of using the drug (21 U.S.C. 355(j)(5)(C)(ii)), *e.g.,* "indications or other conditions of use" required by 21 C.F.R. § 314.53(b)(1).

8. Thus, the '506 patent was improperly listed in the Orange Book.

9. The listing of the '506 patent must be removed from the Orange Book because the patent does not claim an approved indication or method of using the drug.

COUNT 1
Declaratory Judgment of Noninfringement of U.S. Patent No. 6,472,431

10. The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that are the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 6,472,431 ("the '431 patent") either literally or under the doctrine of equivalents.

COUNT 2
Declaratory Judgment of Invalidity of U.S. Patent No. 6,472,431

11. Upon information and belief, the claims of the '431 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

COUNT 3
Declaratory Judgment of Noninfringement of U.S. Patent No. 7,851,506

12. The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that are the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 7,851,506 ("the '506 patent") either literally or under the doctrine of equivalents.

COUNT 4
Declaratory Judgment of Invalidity of U.S. Patent No. 7,851,506

13. Upon information and belief, the claims of the '506 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

COUNT 5
Order Requiring Removal of the '506 Patent From the Orange Book

14. Counterclaimant Roxane incorporates paragraphs 1-13 of its Counterclaim by reference.

15. Under 21 U.S.C. § 355(j)(5)(C)(ii), Roxane seeks an order requiring Plaintiff to remove the '506 patent from the Orange Book listing for XYREM®.

16. Roxane is entitled to an Order requiring Plaintiff to correct the patent information submitted by Plaintiff for the '506 patent on the ground that the patent does not claim the approved method of using sodium oxybate.

ROXANE'S PRAYER FOR RELIEF

WHEREFORE, Roxane respectfully requests that the Court enter judgment against Jazz Pharmaceuticals as follows:

(A) Declaring that Roxane would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of the '431 and '506 patents either literally or under the doctrine of equivalents by submitting ANDA No. 202090;

(B) Declaring that Roxane's proposed sodium oxybate oral solution that is the subject of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of the '431 patent either literally or under the doctrine of equivalents;

(C) Declaring that U.S. Patent No. 6,472,431 is invalid for failure to comply with one or more provisions of 35 U.S.C. § 101, 102, 103, and/or 112;

(D) Declaring that Roxane's proposed sodium oxybate oral solution that is the subject of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of the '506 patent either literally or under the doctrine of equivalents;

(E) Declaring that U.S. Patent No. 7,851,506 is invalid for failure to comply with one or more provisions of 35 U.S.C. § 101, 102, 103, and/or 112;

(F) An Order requiring Plaintiff to remove the '506 patent from the Orange Book listing for XYREM®;

(G) Awarding Roxane its reasonable costs and attorneys' fees incurred in connection with this action pursuant to 35 U.S.C. § 285;

(H) Such further and other relief as this Court may deem just and proper.

Dated: March 9, 2011

Respectfully Submitted,

s/Mark S. Olinsky
Mark S. Olinsky
Theodora McCormick
SILLS CUMMIS & GROSS P.C.
The Legal Center
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and

s/Alan B. Clement
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(312) 443-0700

Attorneys for Defendant
Roxane Laboratories, Inc.

CERTIFICATION PURSUANT TO L. CIV. R. 11.2

Pursuant to L. Civ. R. 11.2, I hereby certify that to the best of my knowledge, information, and belief, aside from this action, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: March 9, 2011

s/ Mark S. Olinsky
Mark S. Olinsky

CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 201.1(D)(1)

I hereby certify that this action does not fall within the requirement for compulsory arbitration set forth in Local Civil Rule 201(d)(1) because the relief sought consists of non-monetary relief (i.e., permanent injunction).

Dated: March 9, 2011

s/Mark S. Olinsky
Mark S. Olinsky

CERTIFICATE OF SERVICE

I hereby certify that, on March 9, 2011, I electronically filed the attached Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint with the clerk of the Court by using the Court's CM/ECF system, and accordingly served all parties who receive notice of the filing via the Court's CM/ECF system.

s/Mark S. Olinsky
Mark S. Olinsky

Modified form PTO/SB/08A(04-07) OMB 651-0031
US Patent & Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)	*Complete if Known*	
	Application Number	13/592,202
	Filing Date	August 22, 2012
	First Named Inventor	Dayton T. Reardan Ph.D
	Group Art Unit	3686
	Examiner Name	Lena Najarian
Sheet 1 of 1	Attorney Docket No: 101.031US9	

OTHER DOCUMENTS – NON PATENT LITERATURE DOCUMENTS		
Examiner Initial *	**Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.**	**T 1**
	"Application Serial No. 13/595,757, Non Final Office Action mailed 01-17-13", 6 pgs	
	"Markman Opinion, filed September 14, 2012, in the case of Jazz Pharmaceuticals, Inc., Plaintiff, v. Roxane Laboratories, Inc., Defendant (United States District Court for the District of New Jersey, Civil 10-6108 ES)", 43 pgs.	
	"Roxane Laboratories, Inc.'s Answer and Affirmative Defenses to Plaintiff's Complaint", (January 4, 2013), 8 pgs.	
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint", (March 9, 2011), 13 pgs.	
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint", (June 1, 2011), 12 pgs.	
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint", (November 9, 2012), 18 pgs.	

EXAMINER **DATE CONSIDERED**

* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant is to place a check mark here if English language Translation is attached

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **v.** **ROXANE LABORATORIES, INC.,** **Defendant.**	**Civil Action No. 12-07459 (ES) (SCM)**

ROXANE LABORATORIES, INC.'S ANSWER AND AFFIRMATIVE DEFENSES TO PLAINTIFF'S COMPLAINT

Defendant, Roxane Laboratories, Inc. ("Roxane"), for its Answer and Affirmative Defenses to Plaintiff Jazz Pharmaceuticals, Inc.'s ("Jazz Pharmaceuticals") Complaint for Patent Infringement ("the Complaint"), states as follows:

Nature of the Action

1. Roxane admits that the Complaint purports to be a civil action for patent infringement. Roxane also admits that it filed an Abbreviated New Drug Application ("ANDA") No. 202090 with the United States Food and Drug Administration ("FDA"), seeking approval to commercially market a generic version of Jazz Pharmaceuticals' XYREM® drug product prior to

the expiration of United States Patent No. 8,324,275 ("the '275 patent"). Roxane denies all other allegations contained in paragraph 1 of the Complaint.

The Parties

2. Roxane admits on information and belief that Jazz Pharmaceuticals is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304. Roxane denies all other allegations contained in paragraph 2 of the Complaint.

3. Roxane admits the allegations contained in paragraph 3 of the Complaint.

4. Roxane admits that it is registered to do business in the State of New Jersey and maintains a registered agent for service of process in New Jersey. Roxane further admits that it sells generic drug products throughout the United States, including this judicial district. Roxane further admits that it has litigated patent cases in this district and that, in at least some of those actions, Roxane has asserted counterclaims. Roxane denies all other allegations contained in paragraph 4 of the Complaint.

Jurisdiction and Venue

5. Roxane denies the allegations contained in paragraph 5 of the Complaint.

6. For purposes of this action, Roxane consents to this Court's personal jurisdiction. Roxane denies all other allegations contained in paragraph 6 of the Complaint.

7. For purposes of this action, Roxane consents that venue is proper in this district. Roxane denies all other allegations contained in paragraph 7 of the Complaint.

The Patent in Suit

8. Roxane admits that what purports to be a copy of the '275 patent is attached to the Complaint as Exhibit A. Roxane further admits that Exhibit A (a) is entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," and (b) lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan as "Inventors." Roxane denies all other allegations contained in paragraph 8 of the Complaint.

The XYREM® Drug Product

9. Roxane admits that New Drug Application ("NDA") No. 21-196 was approved by the FDA and that Jazz Pharmaceuticals is listed as the applicant for that NDA. Roxane denies all other allegations contained in paragraph 9 of the Complaint.

10. Roxane admits that the '275 patent is listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to XYREM®, but denies that the '275 patent appeared in the Orange Book at the time the present complaint was filed. Roxane denies all other allegations contained in paragraph 10 of the Complaint.

Acts Giving Rise to this Suit

11. Roxane admits that it filed ANDA No. 202090. Roxane's ANDA speaks for itself as to its contents. Roxane denies all other allegations contained in paragraph 11 of the Complaint.

12. Roxane admits that in connection with its ANDA, it provided written certifications to the FDA pursuant to Section 505 of the Federal Food Drug and Cosmetics Act

("FFDCA"). Roxane's certifications speak for themselves as to the contents of each. Roxane has not certified as to the '275 patent. Roxane denies all other allegations contained in paragraph 12 of the Complaint.

13. Roxane's ANDA speaks for itself as to its contents. Roxane denies all other allegations contained in paragraph 13 of the Complaint.

Count for Infringement of the '275 Patent

14. Roxane repeats, reasserts, and incorporates by reference its answers to paragraphs 1-13 of the Complaint above, as if fully set forth herein.

15. Roxane denies the allegations contained in paragraph 15 of the Complaint.

16. Roxane admits the allegations contained in paragraph 16 of the Complaint.

17. Roxane denies the allegations contained in paragraph 17 of the Complaint.

18. Roxane denies the allegations contained in paragraph 18 of the Complaint.

19. Roxane denies the allegations contained in paragraph 19 of the Complaint.

20. Roxane denies the allegations contained in paragraph 20 of the Complaint.

21. Roxane denies the allegations contained in paragraph 21 of the Complaint.

22. Roxane denies the allegations contained in paragraph 22 of the Complaint.

23. Roxane denies the allegations contained in paragraph 23 of the Complaint.

PRAYER FOR RELIEF

Roxane specifically denies that Jazz Pharmaceuticals is entitled to the general or specific relief requested against Roxane, or to any relief whatsoever, and prays for judgment in favor of Roxane dismissing this action with prejudice, and awarding Roxane its reasonable attorneys' fees pursuant to 35 U.S.C. § 285, interest, and costs of this action, and such other or further relief as this Court may deem just and proper.

AFFIRMATIVE DEFENSES

Without prejudice to the denials set forth in its Answer and without admitting any allegations of the Complaint not otherwise admitted, Roxane avers and asserts the following Affirmative Defenses to the Complaint of Plaintiff Jazz Pharmaceuticals.

FIRST AFFIRMATIVE DEFENSE
(Noninfringement of U.S. Patent No. 8,324,275)

The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that is the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 8,324,275 ("the '275 patent") either literally or under the doctrine of equivalents.

SECOND AFFIRMATIVE DEFENSE
(Invalidity of U.S. Patent No. 8,324,275)

Upon information and belief, the claims of the '275 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

THIRD AFFIRMATIVE DEFENSE
(Failure to State a Claim)

Jazz Pharmaceuticals has failed to state a claim upon which relief can be granted.

FOURTH AFFIRMATIVE DEFENSE
(Lack of Subject Matter Jurisdiction)

Jazz Pharmaceuticals has failed to state a claim under 35 U.S.C. § 271(e)(2) and therefore the Court lacks subject matter jurisdiction over this matter.

Dated: January 4, 2013

Respectfully Submitted,

/s/ Theodora McCormick
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CERTIFICATION PURSUANT TO L. CIV. R. 11.2

Pursuant to L. Civ. R. 11.2, I hereby certify that to the best of my knowledge, information, and belief, aside from this action, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: January 4, 2013

/s/ Theodora McCormick
THEODORA MCCORMICK

CERTIFICATION OF SERVICE

I hereby certify that, on January 4, 2013, I electronically filed the attached Answer and Affirmative Defenses to Plaintiff's Complaint with the clerk of the Court by using the Court's CM/ECF system, and accordingly served all parties who receive notice of the filing via the Court's CM/ECF system.

Dated: January 4, 2013

/s/ Theodora McCormick
THEODORA MCCORMICK

NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC,	:	
	:	**Civil Action No. 10-6108 (ES)**
Plaintiff,	:	
	:	
v.	:	
	:	
ROXANE LABORATORIES, INC.,	:	**OPINION**
	:	
Defendant.	:	

SALAS, DISTRICT JUDGE

Presently before the Court is the parties' request for claim construction. The Court held a *Markman* hearing on April 26, 2012. This Opinion addresses the proper construction of the disputed claim terms.

I. Background

Plaintiff Jazz Pharmaceuticals, Inc. ("Plaintiff" or "Jazz") brings this action against Roxane Laboratories, Inc. ("Defendant" or "Roxane") for patent infringement under 35 U.S.C. § 100, *et seq.* The action arises from Roxane's filing of an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market a generic version of Jazz's drug XYREM®. Under § 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), Roxane filed ANDA No. 202-090 ("Roxane's ANDA") seeking approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of 500 mg/ml sodium oxybate oral solution. (Complaint, D.E. 1, "Compl." ¶ 15). Roxane's ANDA filing resulted in this five-count infringement Complaint regarding the patents-in-suit, for which the parties have requested claim construction.

Generally, Jazz alleges, among other things, that Roxane's ANDA constitutes infringement of certain claims of United States Patent Nos. 6,472,431 (the "'431 patent"), 6,780,889 (the "'889 patent"), 7,262,219 (the "'219 patent"), and 7,851,506 (the "'506 patent"), (collectively, the "'431 patent family" or the "'431 family"), and 7,668,730 (the "'730 patent"), 7,765,106 (the "'106 patent"), 7,765,107 (the "'107 patent") and 7,895,059 (the "'059 patent"), (collectively, the "'730 patent family" or "'730 family"), owned by Jazz Pharmaceuticals (collectively, "the patents-in-suit") under 35 U.S.C. § 271(e)(2). The '431 family covers pharmaceutical compositions of sodium oxybate, which is the salt form of gamma-hydroxybutyrate ("GHB"), the active ingredient in Xyrem®. The parties dispute eight claim terms from the '431 patent family.[1] The '730 family covers methods of safely distributing and treating patients with sodium oxybate. Safe distribution of the drug is critical because GHB has been listed as a controlled substance for its illicit uses, including as a "date rape" drug. The parties dispute nineteen claim terms from this family.[2]

Pursuant to Local Patent Rules 4.2(a)-(b), on September 21, 2011, the parties exchanged preliminary claim constructions and identified intrinsic as well as extrinsic evidence in support of their proposed preliminary constructions. On December 2, 2011, the parties submitted their revised joint claim construction and prehearing statement. (D.E. 76, "Joint Claim Construction Br."). On December 5, 2011, the parties filed their opening *Markman* briefs and related declarations and attachments. (D.E. 80, "Jazz Opening Br."; D.E. 77 "Roxane Opening Br.").

[1] By letter dated Apr. 20, 2012, (D.E. 119), the parties agreed that, pursuant to a telephone conference with the Court on April 10, 2012, claim term "wherein . . . is" from the '431 family need not be construed, and that the term should be given its plain and ordinary meaning as understood by a person of ordinary skill in the art. Accordingly, the Court will do so.

[2] In the April 2012 letter, the parties agreed that the following terms from the '730 family need not be construed, and that the terms should be given their plain and ordinary meaning as understood by a person of ordinary skill in the art: "prescription requests"; "prescriptions . . . are processed"; "prescriptions . . . processed for authorization"; "verifying"; "therapeutic"; and "making sure the database available to the DEA . . ." (D.E. 119). Accordingly, the Court will do so.

On February 21, 2012, the parties filed their responsive briefs. (D.E. 100, "Jazz Response Br."; D.E. 98, "Roxane Response Br."). On April 26, 2012, the Court held oral argument for purposes of claim construction.

II. Legal Standard

Claim construction is a matter of law to be determined solely by the court. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312, 1330 (Fed. Cir. 2005). "It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Id.* (quotations omitted). In construing the terms of a patent, a court should look first to the language of the claim itself. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The terms in the claim "are generally given their ordinary and customary meaning." *Id.* at 1582. "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, *i.e.*, as of the effective filing date of the patent application." *Phillips*, 415 F.3d at 1313. A court "must look at the ordinary meaning in the context of the written description and the prosecution history." *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005). The court should turn to "those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean." *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004).

To this end, the court should first examine the intrinsic record—the patent itself, including the claims, the specification, and the prosecution history. *Vitronics*, 90 F.3d at 1582 (citing *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995)). The specification "acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication." *Id.* Indeed, the Federal Circuit explains that the specification is

"'usually . . . dispositive . . . [and] the single best guide [for] the meaning of a disputed term.'" *Phillips*, 415 F.3d at 1315 (quoting *Vitronics*, 90 F.3d at 1582). It is "entirely appropriate for a court, when conducting claim construction, to rely heavily on the written description for guidance as to the meaning of the claims." *Id.* at 1317. The specification is also an important guide in claim construction because it may contain "an intentional disclaimer, or disavowal, of claim scope by the inventor." *Id.* at 1316.

Additionally, the court should consult the patent's prosecution history because it "provides evidence of how the [Patent and Trademark Office, ("PTO")] and the inventor understood the patent." *Id.* The prosecution history is the complete record of the proceedings before the PTO and includes the prior art cited by the patentee during examination of the patent. *Id.* at 1317. Moreover, the prosecution history "can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id.* Indeed, the Federal Circuit has repeatedly emphasized the need to consult the prosecution history to "exclude any interpretation that was disclaimed during prosecution." *Chimie v. PPG Indus.*, 402 F.3d 1371, 1384 (Fed. Cir. 2005) (quotation omitted).

A district court may also examine extrinsic evidence—*i.e.*, "all evidence external to the patent and prosecution history." *Markman*, 52 F.3d at 980; *Phillips*, 415 F.3d at 1317-18 ("[The Federal Circuit] ha[s] authorized district courts to rely on extrinsic evidence . . . ."). Extrinsic evidence consists of testimony by the inventor or by experts, dictionaries, and treatises. *Markman*, 52 F.3d at 980. In particular, a court may find reference to technical dictionaries useful "in determining the meaning of particular terminology . . . ." *Phillips*, 415 F.3d at 1318. However, extrinsic evidence is "less significant than the intrinsic record in determining the

legally operative meaning of disputed claim language." *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004) (quotation omitted).

III. The Disputed Claim Terms

A. The '431 Patent Family

The '431, '889, '219, and '506 patents claim pharmaceutical compositions containing sodium oxybate and methods of making and using the compositions. The parties dispute 8 terms in those patents. The primary location of these terms is claim 1 of the '431 patent.[3] The Court will address each of the disputed terms below.

1. "resistant to microbial growth"[4]

The Court construes this phrase—"resistant to microbial growth"—to mean: "the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days."

Jazz proposes the following construction: "the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles." (Jazz Opening Br. at 5). Roxane proposes: "the formulations meet the

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[3] Claim 1 of the '431 patent states:

> A method of rendering an aqueous medium resistant to microbial growth, comprising adding the gamma-hydroxybutyrate salt to the aqueous medium, adjusting the concentration of the gamma-hydroxybutyrate salt in the aqueous medium to a final concentration of at least about 250 mg/ml, and adjusting the pH of the medium to a final pH of about 6 to about 10, so that the medium is chemically stable and resistant to microbial growth.

'431 Patent at 3:22-26.

[4] The term "resistant to microbial growth" appears claim 1 of the '431 patent, claim 1 of the '889 patent, and claims 1 and 4 of the '219 patent.

criteria set by the Food and Drug Administration and the U.S. Pharmacopeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days, including but not limited to formulations containing greater than about 150 mg/ml GHB to GHB's maximal solubility in an aqueous medium." The '431 patent defines the claim term as follows: "'Resistant to microbial growth' . . . means that the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days." ('431 Patent at 3:23-32). The Court will define the term as the patent does. *See Phillips*, 415 F.3d at 1315.

Essentially, the parties split the proposed construction into three clauses, agreeing that the first clause should be included in the construction, but disagreeing as to whether the second and third clauses should be included. Jazz argues that the definition should be truncated after "bases and vehicles," because the clauses that follow that language—"which for bacteria . . ." and "which for yeast and molds"—are merely definitions of the U.S. Pharmacopoeia criteria, and not part of the definition of "resistant to microbial growth," and therefore the "which" clauses add nothing to the definition and should be excluded for claim construction purposes. (Jazz's Opening Br. at 5-6). The Court rejects this argument and agrees with Roxane, who argues that the definition should not "stop midsentence and lop off much of applicants' explicit definition . . . ." (Roxane's Opening Br. at 4). The "as used herein" language leading into the definition, ('431 Patent at 32:22-23), indicates that the patentee became his own lexicographer, and

therefore the full definition, including the "which" clauses should be used. Additionally, the "which" clauses should be included because the U.S. Pharmacopoeia's definitions and requirements for microbial resistance change over time, and this language fixes the meaning at the time the patent was sought. Accordingly, the Court construes the definition as containing the "which" clauses.

However, the Court excludes the clause "including but not limited to formulations containing greater than about 150 mg/ml GHB to GHB's maximal solubility in an aqueous medium"—which Roxane proposes should be included in the definition for claim construction purposes. (Roxane Opening Br. at 3). Roxane argues that this clause should be included because claim construction should take into account definitional examples, and without this clause, the definition would lack sufficient specificity. (Roxane's Responsive Br. at 4 (citing *MSM Investments Co. v. Carolwood Corp.*, 259 F.3d 1335, 1339-40 (Fed. Cir. 2001))).

First, Roxane's clause is not found in the definition of the term. Instead, the language merely paraphrases an example from elsewhere in the patent. (*See* '431 Patent at 11:15-26). Second, the language "including but not limited to," followed by an example of one embodiment, ("150 mg/ml . . ."), impermissibly imports an example into the definition. *See Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 805 F.2d 1558, 1563 (Fed. Cir. 1986). The "but not limited to" language clearly indicates that the example is *non-limiting*. Third, Roxane's supporting decision is distinguishable. Roxane cites *MSM Investments Co., LLC v. Carolwood Corp.*, in which the Federal Circuit found that "the fact that other related patents have claims that are limited to certain pharmacological uses . . . does not compel the conclusion that the claims of the [patent at issue] must be limited to nutritional uses." 259 F.3d at 1340. In *MSM*, examples expanded rather than narrowed the meaning. *See id.* ("[T]he term 'feeding' in claim 1 of the

'878 patent covers *both* nutritional *and* pharmacological uses of MSM® . . . .") (emphasis added). The Court therefore rejects Roxane's proposal to include the third portion of language.

2. "adding the gamma-hydroxybutyrate salt to the aqueous medium"[5]

Within this phrase, the parties primarily dispute the terms "adding" and "aqueous medium." The Court will not construe the terms "adding" or "aqueous medium," because the parties' proposed constructions either do not improve over the "readily apparent" meaning of the terms or the proposals impermissibly import limitations solely for the purpose of improving their infringement and non-infringement positions. *Phillips*, 415 F.3d at 1314 ("In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words.") (citation omitted). The parties' underlying dispute regarding these terms (and, as the Court will explain below, many others), is whether "adding" means that a pre-made GHB salt is to be taken from *outside* the aqueous solution (*e.g.*, water) and added into it (Roxane's position) or whether "adding GHB" can also mean that the GBH salt forms *in* the water (Jazz's position).

As to "adding," Jazz proposes the construction of "including," which derives from Merriam-Webster's Collegiate Dictionary, 10th ed. (1997) at 13. At the *Markman* hearing, Jazz clarified that it considered "adding" and "including" to be equivalent, and that Jazz's primary position was that the Court should not import the claim limitations that Roxanne proposes (discussed below). (Tr. at 60:7-16 ("Court: Do you think adding [needs] construction?; Jazz: I don't. . . . You can add [the salt], you include it. *Adding means include the member of a group.* We included the salt as a member of the group. [Roxanne] want to say no, [the salt] has to come from . . . a pre-made batch. [Roxane has] all kinds of restrictions that don't appear anywhere in

[5] The term "adding the gamma-hydroxybutyrate salt to the aqueous medium" is in claim 1 of the '431 patent.

the claims.") (emphasis added)). The Court finds that construing "adding" as "including" adds little to the "ordinary meaning of claim language as understood by a person of skill in the art" and that claim construction in this case "involves little more than the application of the widely accepted meaning of commonly understood words." *Phillips*, 415 F.3d at 1314. Accordingly, the Court does not construe "adding" to mean "including."

The Court also rejects Roxane's proposal, construing "adding" to mean "externally adding," limiting the term with the word "externally." Roxane bases its proposal on two separate arguments. First, Roxane argues, "[t]he specification repeatedly describes 'dissolving or mixing' *already existing* NaGHB salt into an aqueous medium." (Roxane's Opening Br. at 5 (citing, *e.g.*, '431 Patent at 3:46-48 ("The amount of GHB that may be mixed or dissolved into an aqueous medium and still be resistant to microbial growth depends upon the pH of the aqueous medium."), *id.* at 4:25-28 ("At the medium to high end of the concentration or content of GHB that may be dissolved or mixed in the aqueous medium . . . .") (emphasis added)). The Court rejects this argument because Roxane points to nothing in the intrinsic evidence that requires the salt to be pre-formed and added from an external location. The fact that the patent describes the salt being "mixed or dissolved" does not mean the salt has to come from outside the aqueous solution. Additionally, the patent's use of the word "in" within the phrase "may be dissolved or mixed *in* the aqueous medium," *id.* at 4:25-28 (emphasis added), demonstrates that the "adding" is not limited in the way Roxane proposes. For example, NaGHB could form *in situ* in the aqueous solution and dissolve from there. Nothing in the patent requires Roxane's limitation.

Second, Roxane supports its position with the prosecution history, arguing "Applicants inserted the 'adding' limitation to overcome a patentability rejection." (Roxane's Opening Br. at 5-6 (citing Ex. I, '431 Patent History, 4/6/02 Notice of Allowability at 2, ROXGBH02926

("Claims 70-78 are allowed over the prior reference[s] . . . [which] fail[] to teach the use of gamma-hydroxybutyrate salt, at the claimed concentration (at last [sic] 250 mg/ml), as an agent that renders 'an aqueous medium' resistant to microbial growth.")); Roxane's Responsive Br. at 7 (citing Ex. Y, '431 Patent History, JPI-00000668-671 (demonstrating that "adding the gamma-hydroxybutyrate salt to the aqueous medium" was added to the claim to satisfy the Examiner)); Tr. at 65:17-21). Therefore, according to Roxane, Jazz's omission of the "adding" step in its proposal violates the claim construction principle that claim terms should not be read out of a patent in the context of a method claim. (Roxane Opening Br. at 6 (citing *Gen. Am. Transp. Corp. v. Cryo-Trans, Inc.*, 93 F.3d 776, 770 (Fed. Cir. 1996))).

The Court rejects Roxane's prosecution history argument. The examiner found the claims distinguished the prior art because the claims "render[ed] 'an aqueous medium' resistant to microbial growth" with particular concentrations of GHB; not, as Roxanne contends, that those concentrations were generated by pre-forming the salt outside the aqueous medium and then putting it inside the medium to achieve resistance. (*See* Ex. I, '431 Patent History, 4/6/02 Notice of Allowability at 2, ROXGBH02926). Roxane makes a leap from the patent history (which demonstrates that the language "adding the gamma-hydroxybutyrate salt to the aqueous medium" was added to satisfy the Examiner) to the inference that "adding" must mean "externally" adding a pre-formed GHB salt. Aside from this inferential leap, Roxane points to no evidence that "adding" was included for a reason related to patentability.

As to construing "aqueous medium," Jazz proposes "more than 50% water," while Roxane proposes, "*pre-existing* aqueous medium." The Court rejects both proposals.

The patent's specification contains the following discussion of "aqueous medium": "As used herein in certain embodiments, an 'aqueous medium' may mean a liquid comprising more

than about 50% water. In certain preferred embodiments, an 'aqueous medium' may be a solution suspension, gel or emulsion of GHB . . . ." ('431 Patent at 3:31-36). Accordingly, Jazz's proposal attempts to turn what an aqueous medium "may" be into what it must be, which would exclude other examples in the specification—such as gels or emulsions—that do not necessarily contain more than 50% water. The Court declines to import a limitation that would exclude examples of aqueous media that "may" be preferred embodiments, and the Court finds that Jazz's context-specific citations to the specification do not support its proposed construction. (*Id.* at 3:37-48 ("Compositions that are resistant to microbial growth are created by dissolving or mixing GHB in an aqueous medium to a concentration or content of greater than of [sic] about 150 mg/ml GHB to the maximal solubility of GHB."), 4:10-13 (same), 4:10-28 (listing various mg/ml amounts)).

The Court also rejects Roxane's proposals to construe "aqueous medium" as "pre-existing aqueous medium" for the same reasons that the Court rejected Roxane's request to add the words "externally" and "pre-made" to the construction: because, as outlined more fully above, nothing in the intrinsic evidence supports a construction of "adding the gamma-hydroxybutyrate salt to the aqueous medium" to be limited to situations where GHB is taken from *outside* an aqueous mixture and placed *into* it. The Court agrees with Jazz's representation at oral argument: "[W]e don't care how [the salt] gets there. Just get there. There is no limitation how it gets there." (Tr. at 59:5-7).

3. "salt"[6]

[6] The term "salt" appears in claims 1 and 2 of the '431 patent. Its use in claim 1 is as follows:

> In certain embodiments, the composition may contain one or more salts. A "**salt**" is understood herein to mean certain embodiments to mean [sic] a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base. Various salts, including salts of GHB, are also encompassed by the invention, particularly as pH adjusting or buffering agents. Pharmaceutically acceptable salts, include inorganic acids such as,

The Court construes the claim term "salt" as Roxane proposes, to mean: "a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base."[7] (Roxane Opening Br. at 4). The specification provides: "A 'salt' is understood herein to mean certain embodiments to mean [sic] a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base." ('431 Patent at 7:1-5). Despite the words "certain embodiments," the parties do not dispute that the patent itself defines salt, and that the Court's construction should therefore include the specification's first clause, "a compound formed by the interaction of an acid and a base." (*See* Tr. at 70:16-20, 73:7-8; Roxane Opening Br. at 4; Jazz Opening Br at 9). However, the parties do dispute whether the second clause, "the hydrogen atoms of the acid being replaced by the positive ion of the base," is merely an example that should not be included in the "definition" (Jazz's position) or part of the "definition" itself (Roxane's position).

Jazz argues that including the second clause into the construction would inappropriately read a limiting example into the claim, violating *Philips*, 415 F.3d at 1323. (Jazz's Opening Br. at 9-10). Jazz argues that reading this limiting example into the claim term's definition would exclude other examples of "salts" mentioned elsewhere in the specification. Salt is not limited to any of the preferred embodiments listed in lines 1-30 of column 7, defining salt. (Jazz's

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> for example, hydrochloric or phosphoric acids, or such organic acids as malic, acetic, oxalic, tartaric, mandelic, and the like. Salts formed can also be derived from inorganic bases such as, for example, sodium, potassium, silicates, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Alkali metal salts, such as lithium, potassium, sodium, and the like may be used, preferably with an acid to form a pH adjusting agent. Other salts may comprise ammonium, calcium, magnesium and the like.

'431 Patent at 7:1-30.

[7] The Court has trouble accepting Jazz's argument—that the Court should reject Roxane's proposal because it reads examples out of the definition despite their presence elsewhere in the specification—because, for other terms, Jazz has argued that the patent need not cover every example in the specification. (*Compare* Tr. at 71:24-72:5 (Jazz's argument that the Court should not adopt language that would read examples out of the definition), *with* Jazz's Opening Br. at 7-8 (citing 3:31-33 (Jazz's argument that the Court should adopt language that would read examples out of the definition)).

Responsive Br. at 4 (citing *Tex. Instruments*, 805 F.2d at 1563)). In opposition, Roxane argues that the claim construction should include the first *and* second portions of the definition in the specification because "artificially truncating" the definition at the comma is inappropriate because the portion of language after the comma ("the hydrogen atoms . . .") is not merely an example, it is part of the actual definition. (Roxane's Opening Br. at 4, 6). Roxane also argues that truncating the construction as Jazz proposes would create anomalous scientific results, because one common interaction of an acid and a base is adding HCl (acid) to NaOH (base) to yield NaCL (table salt) and H20 (water). Roxane argues that water would fall into Jazz's construction, but obviously H20 is not a salt. (Roxane's Opening Br. at 4). Jazz counters that, "no one of skill in the art would be misled into thinking that water is a 'salt' based on Jazz's construction." (Jazz's Responsive Br. at 4-5).

The Court finds that including the second clause in the construction is more faithful to the portion of the specification that the parties agree is a definition. First, if this portion of the specification is a definition, it *includes* the second clause. Second, the word "herein" is used once at the beginning of the full sentence and therefore applies to the first and second clauses equally. Third, the sentence immediately *following* the two-clause definition for salt indicates the beginning of the specification's discussion of examples. ('431 Patent at 7:5-28 ("Various salts, including salts of GHB . . . . Pharmaceutically acceptable salts, include inorganic acids such as, for example, hydrochloric or phosphoric acids . . . ."). The existence of the "Various salts" sentence *following* the two-clause definition sentence further reinforces the fact that the language in the two-clause sentence contains a unit of text defining the term, not merely a definition (clause one) with an example tacked on (clause two).

4. "about"[8]

The Court finds that no construction of this claim term is necessary. Jazz proposes a definition of "reasonably close to" and Roxane proposes "20% of the number modified in the appropriate direction(s)." The patent states: "As used herein, the term 'about' generally means within about 10-20%." ('431 Patent at 4:8-9).

Roxane argues that the applicants acted as their own lexicographers, so the plain meaning of "about" is not appropriate in this case, and the term "about" must be construed in the context of the intrinsic evidence. Essentially, Roxane argues that the patent's "general[]" definition is *the* definition. Jazz argues that the patent's use of the word "generally" in its definition of "about" means the suggested percentages are purposefully imprecise, and that Jazz's construction—"reasonably close to"—reflects this general approach, and is supported by the extrinsic dictionary definition of the word. (Jazz's Opening Br. at 11; Jazz's Responsive Br. at 7 (citing *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1369 (Fed. Cir. 2005) (construing "about" to mean "approximately" without including some specific numeric range))).

The Court rejects both proposals. The Federal Circuit has held that the term "about" does not have a universal meaning in patents and that it depends on the context of the content. *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995) ("[T]he use of the word 'about,' avoids a strict numerical boundary to the specified parameter. Its range must be interpreted in its technologic and stylistic context."); *Astrazeneca Pharm. LP v. Handa Pharm., LLC*, No. 08-3773, 2010 WL 4941431, at *4-5 (D.N.J. Nov. 30, 2010) (rejecting proposed definitions for "about" that "limit[ed] the ranges to exact numbers" where nothing in the claim language compelled such an interpretation, and accepting the construction of "approximately").

[8] The term "about" appears in claims 1, 3, and 5 of the '431 patent, claim 1 of the '889 patent, claims 1, 2, and 4 of the '219 patent, and claim 1 of the '506 patent.

In the context of the '431 patent family, "about" modifies pH values and salt concentrations. (*See* '431 Patent Claim 1 at 70:5-12 ("A method of rendering an aqueous medium resistant to microbial growth, comprising adding the gamma-hydroxybutyrate salt to the aqueous medium, adjusting the concentration of the gamma-hydroxybutyrate salt in the aqueous medium to a final concentration of a least about 250 mg/ml, and adjusting the pH of the medium to a final pH of about 6 to about 10, so that the medium is chemically stable and resistant to microbial growth.")). Throughout the specification, the patent repeatedly demonstrates an upper pH limit of 10.3. (*See* '431 Patent at 3:57-58 ("In a preferred embodiment, the pH of said aqueous medium is about 6 to about 7.5. The pH may be from about 3.0 to about 10.3 . . . ."), 4:30-36 ("[T]he pH may be of about 3.9 to about 10.3."), 20:5-9 ("The inventors contemplate that a concentration of greater than about 150 mg/ml of GHB, up to the maximal solubility in aqueous solutions of GHB will be suitably resistant to microbial challenge from about pH 3 to pH 10.3.")). Applying Roxane's proposed definition—importing a 20% limitation, and leaving out the 10% language in the general definition—would consistently lead to pH values in column 3 of the '431 patent well above the apparent upper limit of pH 10.3, and as Jazz argued at the *Markman* hearing, the salt concentration numbers in column 4 of the '431 Patent "would be all over each other and it makes no sense." (Tr. at 78:19-22). The Court agrees that Roxane's proposal does not fit into either context.

Additionally, Roxane's argument that its proposal is supported by an explicit definition in the specification is undercut for two reasons. First, the portion of language to which Roxane points comes after the word "generally," which indicates that the following "definition" is not precise. Second, Roxane's proposal is not faithful to the language following "generally" because Roxane omits the 10% figure from its proposal. Arguing that 20% subsumes 10%, (Tr. at

79:22), is unpersuasive, because if Roxane purports to remain faithful to a particular definition, it should remain faithful to the full definition.

The Court also rejects Jazz's proposal because "reasonably close to" is merely the dictionary definition of a word that would be easy for a person of ordinary skill in the art to understand in the context of the '431 family of patents. Jazz's definition relying on extrinsic evidence, adds no additional understanding. For example, in the context of pH, the patent states that "[t]he pH may be from about 3.0 to about 10.3, namely of about 3.0, about 3.1, about 3.2, about 3.3, about 3.4 . . . or about 10.3," listing every tenth. ('431 Patent at 3:55-4:4; *see also id.* at 4:10-24 (listing concentrations for every ten ml/mg, *e.g.*, "about 230 mg/ml, about 240 mg/ml . . . .")). Because of the patent's extensive list of each one-tenth of a pH value, the definitions for "about 3.1," "about 3.2," and "about 3.3," are clear.

5. "does not contain a preservative"; "free of preservatives"[9]

Within this phrase, the parties dispute the term, "preservative." Jazz proposes, "conventional exogenous substances that are added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action," and Roxane proposes, "any substance added to inhibit chemical change or microbial action." The patent provides: "A 'preservative' is understood herein to mean certain embodiments which are substances added to inhibit chemical change or microbial action. Such preservatives may include, but are not limited to, xylitol, sodium benzoate . . . ." ('431 Patent at 7:42-46). The Court construes the term "preservative(s)" to mean: "a substance or substances added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action."

[9] The term "does not contain a preservative" appears in claim 4 of the '431 patent, which states, "[t]he method of claim 1, 2, or 3 wherein the medium does not contain a preservative." (70:18-19). The term "free of preservatives" appears in claim 1 of the '889 patent and claims 1 and 4 of the '219 patent. The parties have agreed that the construction of the term "does not contain a preservative" will also apply to the term "free of preservatives." (*See* Ex. A to the Revised Joint Claim Construction and Prehearing Statement, D.E. 76 at 2).

The parties agree that the construction should include the following portion from the specification: "substance[] added to inhibit chemical change or microbial action." The real dispute is what, if anything, to add to that language. Jazz proposes the inclusion of the words "conventional exogenous" to modify "substances" and the phrase "in addition to the [GHB] salt." Roxane proposes the inclusion of the word "any" to modify "substances."

The Court accepts Jazz's proposal to include "in addition to the gamma-hydroxybutyrate salt," because self-preserving GHB formulations are themselves preferred embodiments within the specification, (*see* '431 Patent at 18:1-6, 19:36-20:10), and preferred embodiments should not be excluded from a term's construction. *See Chimie v. PPG Indus.*, 402 F.3d 1371, 1377 (Fed. Cir. 2005) ("[A] construction that would not read on the preferred embodiment . . . would rarely if ever [be] correct . . . ."). Additionally, at the *Markman* hearing, Roxane conceded, "I would be happy to say not including GHB. I mean GHB can be in there." (Tr. at 90:22-23; 97:6-12).

Similarly, the Court rejects Roxane's proposal to include the word "any" to modify "substances," because "any" would include GHB as a "preservative," and therefore the phrase at issue—"free of preservatives"—would *exclude* GHB, a preferred embodiment. The Court agrees with Jazz's argument during the *Markman* hearing that, if you included "any" into the definition, "you have to have a GHB formulation free of GHB. That makes no sense. Cannot be." (Tr. at 86:10-12). Including the word "any" in the construction would inject confusion on an issue on which the parties agree.

The Court also rejects Jazz's proposal to modify the term "substances" with "conventional exogenous." In support of this addition, Jazz argues that the patent prosecution history demonstrates the applicant's clear disavowal of using conventional exogenous substances

for stabilization. Although the Court agrees that the prosecution history does provide support for the proposition that the preferred embodiments do not contemplate the use of conventional exogenous substances for stabilization, the Court finds that the prosecution history statements on which Jazz relies do not rise to the "exacting" level of being a clear disavowal of claim scope, warranting the inclusion of the "conventional exogenous" limitation into the construction. *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1366 (Fed. Cir. 2012) ("The patentee may demonstrate intent to deviate from the ordinary and accustomed meaning of a claim term by including in the specification expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope.") (citing *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002)). Some of Jazz's references demonstrate that self-stabilization—instead of conventional preservatives—distinguished the prior art. (*See*, *e.g.*, Ex. 10, August 10, 2001 response to an Office Action, at JPI-00000627 ("None of the [prior art] references, including the admitted prior art, teaches or suggests any method of making a solution of GHB salt resistant to microbial growth other than by adding conventional preservatives.")). Other references demonstrate that conventional exogenous preservatives, (*e.g.*, xylitol), are not used in the patent's preferred embodiments. (*See* Ex. 10 at 627-28 ("[The prior art references] provide no suggestion or motivation that this could be done by adjusting the final concentration of GHB salt to at least about 250 mg/ml and adjusting the pH to the range of about 6 to 10, as recited in claims 66-69. Instead, one would simply add the preservatives disclosed by the references or otherwise conventional in the art, and hope for the best."); Ex. 12, April 1, 2002 Amendment and Response to an Office Action, at JP-00000663 ("[I]t is clearly set forth throughout the present specification that the preferred embodiment is a solution of GHB salt that is resistant to microbial growth without the need to add exogenous preservatives.")).

Accordingly, the Court adopts the patent's definition, adding only "in addition to the gamma-hydroxybutyrate salt" to avoid reading preferred embodiments out of the definition.

6. "pH-adjusting agent"[10]

Jazz proposes that no construction is necessary. Roxanne proposes, "an agent, which is an acid or base, directly added primarily to alter the pH." The Court rejects both proposals and construes the term to be, "compositions that achieve a desired pH," which is consistent with the specification language.

The Court rejects Jazz's proposal not to construe the term because in the context of this patent family, "pH-adjusting agent" is not the sort of non-technical phrase whose meaning is obvious. Additionally, the parties' proposals represent a true conflict, because Roxane's proposal to include "directly added primarily," echoes its other proposed constructions seeking to limit the patent's scope so "that the listed pH-adjusting agents are agents that are added to aqueous media *without any additional step* (*i.e.*, directly) for the principal purpose (*i.e.*, primarily) of adjusting the pH of the aqueous media." (Roxane's Responsive Br. at 14) (emphasis added). Jazz rejects the inclusion of such a limitation.

The Court rejects Roxane's proposal to include "directly added primarily," finding that the portions of the specification cited by Roxane do not support its position. (*See* '431 Patent at 6:36-39 ("In certain other embodiments of the present invention, the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids, bases, or combinations thereof."), 8:54-59 ("comprising admixing GHB and a pH-adjusting or buffering agent in an aqueous medium. In certain embodiments, the method of preparing the

[10] The term "pH-adjusting agent" appears in claim 6 of the '431 patent: "The method of claim 1, wherein said pH-adjusting agent is an organic acid." ('431 Patent at 70:23-24). The term also appears in claim 1 of the '889 patent and claims 1, 3, and 4 of the '219 patent.

pharmaceutical composition further comprises admixing a preservative with the pharmaceutical composition."), 12:50-63 ("[A] pH-adjusting agent may be added to the composition. . . . Compositions of GHB, pH adjusted with malic acid are resistant to both microbial growth and chemical degradation of GHB, and are preferred.")). Similarly, the Court rejects Roxane's prosecution history disclaimer argument because nothing in the prosecution history supports a disclaimer of claim scope warranting the inclusion of "directly added primarily." (*See* Ex. J, '889 Patent History, March 18, 2004 Notice of Allowability at 2, ROXGHB002942).

Because the Court does find that the term should be construed, the Court looks to the specification, which provides: "In certain other embodiments of the present invention, the pharmaceutical composition may compromise a pH adjusting or buffering agent. Such agents may be acids, bases, or combinations thereof." ('431 Patent at 6:36-39). Additionally, the specification provides: "In certain embodiments, the acid may be an organic acid," (6:39-40); "In a preferred embodiment, the acid is malic or hydrochloric acid," (6:52-53); "In certain other embodiments, the pH adjusting agent may be a base," (6:53-54); "In certain other embodiments, the pH adjusting agent may be a mixture of more than one acid and/or more than one base. In other preferred embodiments, a weak acid and its conjugate base are used to form a buffering agent to help stabilize the composition's pH," (6:63-67); "In one embodiment, a salt of GHB comprising an alkali metal may be combined with an acid to create a composition that achieves the desired pH when admixed with an aqueous medium . . . ." (7:18-24). The Court's construction, "compositions that achieve a desired pH," includes all of the examples explicitly listed in the specification, in addition to compositions with a pH of 7.0 that have not been disclaimed. Accordingly, the Court's construction does not read limitations from particular examples into the construction.

The Court rejects Roxane's proposal to include the limitation, "acid or base," because the specification's use of the words "may," "certain embodiments," and "preferred embodiment" demonstrate that the lists of acids and bases are a non-exhaustive group of examples of compositions that act as pH-adjusting agents. (*See* Tr. at 107:22-25). Additionally, nothing in the prosecution history demonstrates a clear disavowal of claim scope, and including "acid or base" in the construction would preclude the use of a composition with a pH of exactly 7.0. (*See* Tr. at 107:9-14). Without a clear disavowal, Jazz is entitled to the full scope of the term, which the Court finds is reflected in the word "composition," which itself appears in the specification, and non-exclusively encapsulates acids, bases, and combinations thereof. ('431 Patent at 7:19-24); *see Elbex Video, Ltd. v. Sensormatic Elecs. Corp.*, 508 F.3d 1366, 1371 (Fed. Cir. 2007) ("Claim terms are entitled to a heavy presumption that they carry their ordinary and customary meaning to those skilled in the art in light of the claim term's usage in the patent specification.") (quotations omitted).[11]

The Court's construction reflects the plain meaning of the term in the context of the '431 patent family.

7. "organic acid"[12]

Jazz proposes, "a substance containing one or more carbon atoms that is capable of yielding a proton (hydrogen ion) in aqueous solution, turning blue litmus paper red in aqueous solutions, ionizing in solution to yield the positive ion of the solvent, reacting with bases to form salts, or accepting electrons in an acid-base reaction," and Roxane proposes "an acid containing

[11] Finally, the Court rejects Roxane's argument under 35 U.S.C. § 112 ¶ 4—that limiting a dependent claim limits the independent claim—because the phrase "pH-adjusting agent" does not appear in claim 1 of the '431 Patent.

[12] The term "organic acid" appears in claim 6 of the '431 patent.

at least one carbon atom that directly acidifies a solution." The Court construes the term to mean, "a substance containing at least one carbon atom that lowers pH."

The parties agree on the definition of "organic," (Tr. at 111:2), and during the *Markman* hearing, the parties agreed on a construction that includes, "a substance containing at least one carbon atom that lowers pH," (Tr. at 114:3-7), so the only question left for the Court is whether to include the word "directly," as Roxane proposes. Roxane summarized the significance of the proposal at the hearing: "What [acids] do is what they directly do, not that they convert three times in a reaction and then finally lower the pH. They do it immediately. That is what I mean by directly. There is no intermediate reaction . . . ." (114:21-25).

The Court rejects Roxane's proposal. The word "directly" does not appear to be in the passages cited by Roxane. (*See* '431 Patent at 20:27-32 ("The feasibility of preparing formulations containing 150 mg/mL of GHB at pH 3, 5 and 7 was established. Solutions containing 150 mg/mL GHB were prepared. The initial pH was greater than pH 7.5 and the final pH was adjusted to 3, 5 or 7 with hydrochloric acid."), 32:58-60 ("Acidulent was added to water and cooled to room temperature. The sodium oxybate was dissolved in the diluted acidulent solution.")). These passages demonstrate methods in which sodium oxybate is added to acidic solutions, without providing clear support for the limitation "directly." Without clear support in the specification or disavowal of the claim's scope in the prosecution history, the Court finds that it would be inappropriate to import the limitation "directly."

8. "dose"[13]

Jazz proposes that no construction is necessary, and Roxanne proposes, "a therapeutic amount of a pharmaceutical composition comprising chemically stable gamma-hydroxybutyrate

[13] The term "dose" appears in claim 1 of the '506 patent.

in an aqueous medium resistant to microbial growth taken by a patient." The Court accepts Jazz's proposal, does not construe the term, and gives "dose" the ordinary and customary meaning the term would have to a person of ordinary skill in the art.

The patent does not define "dose," and the parties' dispute is as follows. Roxane's proposal is rooted in its desire to construe "dose" to refer to the liquid a patient actually ingests. Jazz's proposal is rooted in its desire to include the concentrated liquid in the bottle a patient receives from the pharmacy and then dilutes in water before ingesting. Because this is the real issue, the key portion of Roxane's proposal is "by a patient."

Although Roxane's construction does find support in the specification, its proposal also imports limitations and redundancies unnecessary to the fact-finder's understanding of what dosage means in the context of this claim. (*See* '506 Patent at 8:60-65 ("The invention also provides a method of treating any *therapeutic* category of disorder responsive to GHB, comprising administering to a patient suspected of having such a condition a therapeutic amount of a pharmaceutical composition comprising chemically stable GHB (*e.g.*, 1-10 gms.) in an aqueous medium resistant to microbial growth. *In certain embodiments*, the method of treating a condition responsive to GHB comprises *a patient taking* a first dosage of from about 0.1 g to about 10g . . . .") (emphases added), 72:20-22: ("comprising orally administering *to a patient* afflicted with the condition an aqueous composition comprising a first dose of about . . . ."). The language "certain embodiments" demonstrates that Roxane seeks to read the limitation found in some examples into the construction itself. Additionally, claim 1 of the '506 Patent itself specifies the amount of GHB to be administered, ("comprising a first dose of about 4.5 to about 10 grams of [NaGHB] . . . comprising a second dose of about 4.5 to about 10 grams within

2 to 5 hours . . . "), and therefore construing "dose" would become an "obligatory exercise in redundancy." *U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997).

B. '730 Patent Family

The '730, '106, '107, and '059 patents claim methods of using drugs such as sodium oxybate under a restricted distribution system based on the drug's Schedule I status. Jazz argues that no construction is necessary for many of the disputed terms in this patent family, and Roxane argues that construction is necessary based on Jazz's clear disclaimers and disavowals in the patent history, and based on limitations derived from inferences from examples in the specification. Because the patent prosecution history forms the basis of Roxane's core arguments for its proposed constructions of the claim terms in the '730 family, the Court summarizes it here.

First, on October 18, 2006 (Final Office Action) and on Feb. 5, 2007 (Advisory Action), the Examiner rejected the patents in the '730 family as obvious. Second, applicants appealed the rejection, but the Board of Patent Appeals ("the Board") affirmed the rejection on August 31, 2009. (Ex. L '730 Patent History ROXGHB004771). Third, on Nov. 2, 2009, applicants amended the claims and made further representations to the Examiner, distinguishing the prior art. It is on these representations that Roxane bases most of its claim construction arguments with respect to the '730 patent family. With this patent prosecution history in mind, Roxane's three main disclaimer arguments for its claim construction positions in the '730 patent family are as follows:

(1) ***Single*** **or** ***Exclusive*** **Pharmacy and Central Database:** To obtain their patents and to avoid obviousness over the prior art, Roxane argues that the applicants represented that the prior art did not require a "single" pharmacy with a "single" central database for distribution of

all of the prescription drugs, whereas the '730 patent would require a single pharmacy and a single central database. (Roxane's Opening Br. at 11-12). In support, Roxane cites the following patent history:

- Ex. L '730 Patent History
    - July 31, 2006 Interview Agenda at 6, ROXGHB004563: The applicants' agenda with the USPTO included the following "additional limitation" for discussion: "*only way to distribute sensitive drug is through use of the central database*." (emphasis added) The applicants explained that the prior art references, Maradi and Lilly, "alone or combined, suggest that a sensitive drug can only be distributed under control of a single source, or required to be tracked through the use of a single central database. [The '730 patent] provides the ability to track potential abuse patterns with much greater accuracy, and may have been the basis for allowing the life improving drug XYREM®, to make it onto the market."
    - Jan. 17, 2007 Amdt. at 9-10 ROXGHB 004611-12: In their attempts to oppose the obviousness challenge to '730 over the prior art of Ukens, Moradi, Lilly, and Califano, applicants stated: "[The prior art] advocates *away from the use of a single pharmacy*. . . . Ukens does not describe the use of an exclusive computer database. This combination of four references does not provide or suggest a solution to one of skill in the art allowing distribution of a sensitive drug as claimed." (emphasis added)
    - July 18, 2007 Substitute Appeal Br. at 16-23 ROXGHB004689-96: Applicants' appeal brief distinguishes relevant prior art over an obviousness challenge by arguing that the prior art fails "to teach or suggest an exclusive computer database," (4689), "Ukens teaches away from the proposed combination of references," (4692), "independent claim 33 must be read as including a sensitive drug under exclusive control of a central pharmacy. This control is through the exclusive computer database of the central pharmacy. . . . This is different from . . . Moradi which merely provides a pharmacy including a central server without any limitation as to the prescriptions which may be filled." (4695).
    - Dec. 3, 2007 Reply Brief at 2-4, ROXGHB004733-35: Finding fault with the Examiner, applicants argue, "The Examiner gave the claim language 'exclusive computer database' the broadest reasonable interpretation. . . . [T]he broadest reasonable interpretation must be limited by the ordinary meaning of the word at issue. The term 'exclusive' means 'single' or 'sole,' and as pointed out above, [prior art reference] Lilly et al. discloses that each entity typically maintains its own database. That is, there is not an exclusive, single, or sole database disclosed in Lilly et al." (4733).

- Nov. 2, 2009 Amdt. at 9-14 ROXGHB004779-84: In the applicants' amendments to overcome Examiner Najarian's finding of obviousness, they argued, "none of the references, either alone or in combination, discloses 'all prescriptions for [a] sensitive drug are processed only by [an] exclusive central pharmacy using only [an] exclusive computer database' and 'mailing the sensitive drug to the patients only if no potential abuse is found by the patient to whom the sensitive drug is prescribed and the doctor prescribing the sensitive drug . . . ." (4782).

- Ex. M '106 Patent History

  - Mar. 11, 2010 Amdt. at 11-12, ROX GHB005046-47: In response to the Office Action mailed Nov. 17, 2009, denying the application because it was not patentable over Moradi, Ukens, and Melker, applicants filed their Amendment & Response, amending the claims and arguing, "none of the cited references discloses the features of receiving all prescription requests only into an exclusive central computer system or an exclusive computer database, requiring entry of information into the exclusive computer database, and noting, based on the analysis of the potential abuse, misuse, or diversion of the prescription drug and/or the periodic reports, that there is a potential for abuse, misuse or diversion by the patient to whom the prescription drug is prescribed." (5046-47).

- Ex. N '107 Patent History

  - Nov. 3, 2009 Amdt. At 8-12, ROXGHB005271-75: In response to the Office Action mailed on September 14, 2009, in which the Examiner rejected the claims, applicants argued that their proposed amendments distinguished Moradi, Ukens, and Lilly because "these references simply do not relate to the tracking of a particular sensitive drug using an exclusive central pharmacy and an exclusive central database to determine potential abuse by a particular doctor who is permitted to prescribe such sensitive drugs and a particular patient to whom prescriptions are written." (5275).

(2) ***Only*** **the Central Pharmacy:** Second, Roxane uses the patent history to argue that applicants amended the claims to require that all prescriptions be "received *only* at the central pharmacy and that *all* prescriptions [be] processed *only* by the exclusive pharmacy and using *only* the exclusive computer database." (Roxane's Opening Br. at 11-12). In support, Roxane cites the following patent history:

- Ex. L '730 Patent History Nov. 2, 2009 Amdt. at 9 ROXGHB004779: Applicants represented that they "ha[ve] amended the claims so that the prescriptions are received *only* at the central pharmacy and that all prescriptions are processed *only by the exclusive pharmacy and using only the exclusive computer database*." (emphasis added).

- Ex. N. '107 Patent History Nov. 3, 2009 Amdt. at 6 ROXGHB005269: (Same)

(3) Drug Dispensed in a Form Ready for Receipt, not Inventoried for Later: Third, Roxane argues, "[w]hen the exclusive central pharmacy dispenses the drug product, it must be in a form ready for receipt and use by the patient. It would be contrary to the patent's teachings and applicants' representations to the Patent Office to construe the claims to include a situation where the exclusive central pharmacy sends a bulk stock to another pharmacy to keep as inventory for later dispensing to a patient." (Roxane Opening Br. at 12). Roxane's support is as follows:

- Ex. E '730 Patent at 3:34-35: "In a further embodiment, bulk sodium oxybate is manufactured at a single site, as is the finished drug product. Following manufacture of the drug product, it is stored at a facility compliant with FDA Schedule III regulations, where a consignment inventory is maintained."

- Ex. L '730 Patent History Nov. 2, 2009 Amdt. at 10-11, ROXGHB 004780-81: Applicants argued that their amendments distinguished Maradi, which does not require prescriptions for a sensitive drug to be "processed only by the central service station . . . [or] requiring that a drug be distributed only through its disclosed system." (4781). Lilly "does not disclose that all drugs are processed by its system or method using its data storage . . . . [In Lilly] "each user (such as a doctor, hospital, or pharmacy) may maintain its own database . . . ." (4781).

Jazz argues, generally, that "Roxane seeks to wield the prosecution history as a magic wand that it can wave over all of the disputed claim terms to convert their plain and ordinary meanings into Roxane's proposed constructions. Of course, Roxane ignores that '[a]bsent a clear disavowal or contrary definition in the specification or the prosecution history, the patentee is entitled to the full scope of its claim language." (Jazz's Responsive Br. at 14 (citing *Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1358 (Fed. Cir. 2004))). Jazz argues that the

majority of the disputed terms (*e.g.*, "pharmacy," "only," "at," "all," and "dispensed") have ordinary meanings that do not require construction. (*Id.*).

1. "prescription drug"[14]

Jazz proposes: "an FDA approved finished dosage form that may be dispensed only upon a prescription." Roxane proposes: "a product containing an active pharmaceutical ingredient available by prescription and not based on brand manufacture." The Court's construction is: "an FDA approved dosage form that may be dispensed only upon a prescription."

The intrinsic evidence supports Jazz's proposal to use the words "FDA approved," and "upon a prescription." (Ex. 5 '730 Patent at 1:10-15 ("Sensitive drugs are controlled to minimize risk and ensure that they are not abused, or cause adverse reactions. Such sensitive drugs are *approved* for specific uses *by the Food and Drug Administration*, and *must be prescribed by a licensed physician* in order to be purchased by consumers.") (emphasis added)). However, the Court rejects Jazz's proposal to include the limitation "finished," because its support in the FDA guidelines provides a definition for "drug product" and not "drug" alone. (*See* Ex. 17, 21 C.F.R. § 314 (2002) at JPE-00358852 ("Drug product means a finished dosage form, for example, tablet, capsule, or solution . . . .")). The Court finds no need to import an external definition for a term that does not appear within the claim phrase at issue.

Additionally, the Court rejects Roxane's proposal to add "not based on brand manufacture" into the construction because it is unsupported by the specification, the prosecution history, or the doctrine of claim differentiation, as Roxane argues. "Under the doctrine of claim differentiation, two claims of a patent are presumptively of different scope." *Kraft Foods, Inc. v. Int'l Trading Co.*, 203 F.3d 1362, 1366 (Fed. Cir. 2000).

[14] The term "prescription drug" appears in claims 1, 2, 4, 6, 7, and 11 of the '730 patent, claims 1, 3, 5, and 7 of the '106 patent, claims 1, 2, and 3 of the '107 patent, and claims 1, 3, 5-8, 10, and 14-16 of the '059 patent.

Roxane's citations to the specification do not support its contention that prescription drugs are identified by active ingredient, not the brand manufacturer. (*See* '730 Patent at 1:38-41 ("A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug."), 3:14-24 ("A sensitive drug is one which can be abused, or has addiction properties or other properties that render the drug sensitive. One example of such a drug is sodium oxybate, also known as [GHB] . . . which is useful for treatment of cataplexy in patients with narcolepsy. GHB is *marketed under the trademark of Xyrem®* . . . which trademark can be used interchangeably with GHB herein.") (emphasis added)). In fact, the emphasized language referring to "Xyrem®" directly contradicts Roxane's proposal.

Additionally, Roxane's proposal is not supported by the doctrine of claim differentiation. "Under the doctrine of claim differentiation, two claims *of a patent* are presumptively of different scope." *Kraft Foods*, 203 F.3d at 1366 (emphasis added). Roxane argues that the doctrine supports its proposal to include "not based on brand manufacture" in the construction, because, in a later-filed continuation application, Jazz wanted to limit "prescription drug" to a particular brand, and it clearly did so. (Roxane's Responsive Br. at 19 (citing Ex. P, U.S. Pat. Appl. No. 2011/01119085, claim 1 ("*company's* prescription drug"), claim 30 ("prescription drug . . . sold or distributed under a *single trademark*") (emphases added)). The applicant's later intention to limit the claim to a particular brand, Roxane argues, evinces the applicant's intent that the actual language in claim 1 of the '730 Patent at issue for purposes of the instant construction must *not* be limited to brand. (Roxane's Responsive Br. at 19 (citing *Precise Exercise Equip. Inc. v. Chi HsinImpex Inc.*, No. 96-6418, 1998 WL 798163 (C.D. Cal. 1998) (applying the doctrine of claim differentiation to related patents in the same family))). The Court rejects this argument because claims contained in a different patent application are not part of the

intrinsic record and Roxane provides no binding authority to extend the doctrine of claim differentiation in this manner.

2. "selecting . . . multiple controls"; "places controls"[15]

These terms (in addition to the following two terms, "controls selected from the group consisting of" and "the controls comprising") are related to whether the '731 patent family contains an open-ended list of optional controls (Jazz's position) or a mandatory list of controls that must *all* be used (Roxane's position) to prevent the misuse of GHB. As to each term, Jazz proposes that no construction is necessary, and the Court accepts Jazz's proposals.

As to the term "selecting . . . multiple controls"; "places controls," Roxane proposes, "deciding to select more than one control." The Court rejects Roxane's proposal because the term consists of uncomplicated, non-technical language that does not require further construction. Defining "multiple" with "more than one" becomes an unnecessary task in redundancy, and importing the word "deciding" as the definition for "selecting" is circular. Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the

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[15] The terms "selecting . . . multiple controls" and "places controls" appear in claims 1, 3, 5, and 7 of the '106 patent, claims 1, 2, 4, and 5 of the '107 patent, and claims 8, 11, and 16 of the '059 patent. Claim 1 of the '107 patent is as follows:

> A computerized method to control abuse of a prescription drug comprising: selecting with the computer processor multiple controls for distribution by said exclusive central pharmacy, the controls comprising communicating prescriptions from a physician to the central pharmacy; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial 10 shipping service . . . .

('107 Patent at 8:35-9:25) (emphasis added).

plain meaning of the term as understood by someone of ordinary skill shall apply. The Court discusses its rejection of Roxane's related patent prosecution history arguments below.

3. "controls selected from the group consisting of"[16]

Jazz proposes that no construction is necessary and Roxane proposes, "selected from the group consisting of the listed controls and no others." The Court accepts Jazz's proposal and rejects Roxane's.

Roxane supports its proposal for the inclusion of "and no others," by arguing that the language "consisting of" has special meaning in the patent context, and that that the language requires a closed or Markush group. *See Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 212 F.3d 1377, 1382 (Fed. Cir. 2000) ("The phrase 'consisting of' is a term of art in patent law signifying restriction and exclusion, while, in contrast, the term 'comprising' indicates an open-ended construction."). In this case, Roxane argues, "consisting of" means "[y]ou can't have other controls. You can have any one of the controls . . . three, four, five, you could have all 23 . . . [but] you couldn't have 24." At oral argument, Jazz conceded that, as a matter of law "consisting of" means a closed group. (Tr. at 154:5-20). The Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning, viewed through the lens of black letter patent law, would be clear to one skilled in the art. The Court attributes to the term its plain meaning as understood by someone of ordinary skill in the art.

4. "the controls comprising"[17]

Jazz proposes that no construction is necessary and Roxane proposes, "including all of the recited controls but open to additional controls." The Court accepts Jazz's proposal and

[16] The term "controls selected from the group consisting of" appears in claims 1, 3, 5, and 7 of the '106 patent and claims 8, 11, and 16 of the '059 patent.

[17] The term "the controls comprising" appears in claims 1 and 4 of the '107 patent.

rejects Roxane's. The key dispute—indeed, the key dispute with all of the terms including the word "controls"—is whether (as Jazz argues) the terms indicate an open-ended list of optional controls, or whether (as Roxane argues) "all" of the controls necessarily must be chosen.

The Court finds that the context provided by the specification clearly demonstrates that not "all" of the controls must be selected, otherwise the word "selecting," (which comes before the term at issue, "the controls comprising") would be read out of the claim. For example, claim 1 of the '107 patent provides: "A computerized method to control abuse of a prescription drug comprising: selecting with the computer processor multiple controls for distribution by said exclusive central pharmacy, the controls comprising communicating prescriptions . . . ." Accordingly, as Jazz argues, and as the Court agrees, in the context of the specification, if "all" of the controls needed to be included, there would be nothing to "select." *See Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 951 (Fed. Cir. 2006) ("[T]he effect of adopting [the party's] proposed claim construction would be to read limitations . . . out of the claim."). Roxane's construction would not permit decision, which would read the contextual terms "selecting" and "multiple" out of the claim. Accordingly, the Court rejects Roxane's proposal. Notably, Roxane's proposal for this claim phrase (requiring the selection of "all" controls) conflicts with its proposal for "controls selected from the group consisting of" for which Roxane proposed to include "selected." The Court construes the terms consistently to include the concept of selection, in accordance with the patent's specification.

Additionally, Roxane's citations to the patent history do not support a clear disavowal. Roxane argues that the patent history demonstrates that the applicant amended the claim from "selected from the group consisting of" to "comprising," thereby clearly disavowing "selected" in favor of a terms that mean "all" controls must be selected. The applicant made this change to

overcome an Examiner's finding that at least two of the controls, but not all of them, were in the prior art. (Ex. N Sept. 14, 2009 Office Action at 6-7, ROXGHB005239-40 ("At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned features [identifying the patient, the drug prescribed, credentials of the doctor, verifying the prescription, and obtaining patient information] of Lilly and Ukens within Moradi."), Nov. 3, 2009 Amdt. at 2, ROXHB005265 (amending from "selected from the group . . ." to "comprising"))). However, Roxane's patent history argument mistakenly suggests that applicants changed "consisting of" to "comprising" in order to overcome a rejection. Indeed, as Jazz points out, "the applicants submitted more than eight pages of 'Remarks' with their amendments, but they did not mention the amendment from "consisting of" to "comprising" at all, let alone in a way that supports Roxane's assertion that the amendment was made to overcome a rejection. (Jazz's Responsive Br. at 33 (citing Ex. N. at ROXGHB005269-77)).

Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the plain meaning of the term as understood by someone of ordinary skill shall apply.

5. "exclusive"[18]

Jazz proposes that no construction is necessary, and Roxane proposes, "sole." The Court's construction is "single or sole," which is consistent with the intrinsic evidence.

The Court construes the term because the patent prosecution history and the parties' representations at oral argument make clear that confusion has surrounded the term. For example, in the applicant's reply brief on appeal, applicants explicitly narrowed the definition of "exclusive" in an effort to distinguish the prior art. Finding fault with the Examiner, applicants

[18] The term "exclusive" appears in claims 1-3 and 7-11 of the '730 patent, claims 1-8 of the '106 patent, claims 1 and 4 of the '107 patent, and claims 1, 2, 6, 7, 9, 10, and 12-15 of the '059 patent.

argued, "[t]he Examiner gave the claim language 'exclusive computer database' the broadest reasonable interpretation. . . . [T]he broadest reasonable interpretation must be limited by the ordinary meaning of the word at issue. *The term 'exclusive' means 'single' or 'sole,'* and as pointed out above, [prior art reference] Lilly et al. discloses that each entity typically maintains its own database. That is, there is not an exclusive, single, or sole database disclose in Lilly et al." (Ex. L Dec. 3, 2007 Reply Br. at 2, ROXGHB004733; Tr. at 174:9-14 ("If you remember, after the examiner rejected all the claims as obvious, [on] the applicant's appeal, and the Board tried to determine what was meant by the term exclusive in the context of the phrase 'exclusive central database.' And . . . the Board, says well, the applicants are telling us it means *single or sole.*") (emphases added)). In contrast to Roxane's other disavowal arguments, the patent prosecution for "exclusive" clearly sets forth the applicant's position.

Accordingly, rather than perpetuating the confusion that has persisted, the Court construes the term as it was clearly set forth in the patent prosecution history, as "single or sole."

6. "pharmacy"[19]

Jazz proposes that no construction is necessary, and Roxane proposes, "a place where drugs are compounded or dispensed from a supply stock." The Court accepts Jazz's proposal.

The Court rejects Roxane's proposal because it is rooted in an unsupportive portion of the specification. Roxane cites the following: "The inventory is owned by a company, and is managed by a central pharmacy, which maintains the consignment inventory. Xyrem® is distributed and dispensed through a primary and exclusive central pharmacy, and is not stocked in retail pharmacy outlets.")). ('730 Patent at 3:38-42). The Court finds that the portion of the specification Roxane cites is not a definition, and even if it were a definition, it does not contain

[19] The term "pharmacy" appears in claims 1-3 and 7-11 of the '730 patent, claims 1, 3, 5, and 7 of the '106 patent, claims 1, 2, 4, and 5 of the '107 patent, and claims 1, 2, and 6-16 of the '059 patent.

"supply stock" or "compounding," words which do not add understanding to the plain and ordinary meaning of "pharmacy." Additionally, because there is no confusion as to the meaning of the term, it is not necessary to address the extrinsic dictionary meaning set forth by Roxane.

Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the plain meaning of the term as understood by someone of ordinary skill shall apply.

7. "only"[20]

Jazz proposes that no construction is necessary, and Roxane proposes, "and no other." The Court finds that no construction is necessary.

Roxane's proposal is rooted in its desire to limit pharmacy to being one exclusive pharmacy, but the Court finds nothing in the patent prosecution history, (*e.g.*, Ex. L Aug. 31, 2009 Board Decision at 12, ROXGHB4762), or the specification, (*e.g.*, '730 Patent Figs. 2A-2C, 3:62-4:1, 3:35-45), that requires an explicit limitation in the construction. Although certain embodiments describe such a pharmacy, nothing in the patent requires the inclusion of Roxane's proposed language, and the Court declines to read particular embodiments into the construction.

Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the plain meaning of the term as understood by someone of ordinary skill shall apply.

8. "at"[21]

Jazz proposes no construction is necessary, and Roxane proposes, "located at." At oral argument, the parties agreed that the dispute in numerous terms, including "at" related to the

[20] The term "only" appears in claims 1, 2, and 7-11 of the '730 patent, claims 1, 3, 5, and 7 of the '106 patent, claims 1 and 4 of the '107 patent, and claims 1, 6, 9 and 12-14 of the '059 patent.

[21] The term "at" appears in claims 1, 2, and 7-11 of the '730 patent, claims 1 and 4 of the '107 patent and claims 1, 6, 9, and 12-14 of the '059 patent.

concept of exclusivity. Essentially, the undercurrent of Roxane's argument is that, "[t]here can really be just the one database, the one pharmacy. Any and all, this is the same thing. It really comes back to the same thing." (208:1-3). Jazz argues that the terms do not require such a limitation. The Court agrees.

Roxane argues that it construction conveys that the location of the computer processor that receives all prescription requests is "only at the exclusive pharmacy," ('731 Patent Claim 1), and therefore the computer processor must be located at the pharmacy. The Court finds that adding the word "located" to add meaning to "at" injects redundancy. Additionally, "located at," is not clearly supported by the prosecution history, (Ex. L Nov. 2, 2009 Amdt at 9, ROXGHB004779-84), and accordingly, the Court attributes to "at" its plain and ordinary meaning to one skilled in the art.

9. "associated"[22]

Jazz proposes no construction is necessary, and Roxane proposes, "located either at or remote from, but not both." The Court accepts Jazz's proposal.

In support of its position, Roxane cites embodiments where the external database is "used in place of" the internal database. ('730 Patent Figure 1 & 3:67). However, this portion of the specification makes clear that it is only "one embodiment," which would be inappropriate to read into the construction. Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the plain meaning of the term as understood by someone of ordinary skill shall apply.

10. "all"[23]

[22] The term "associated" appears in claims 1 and 2 of the '730 patent, claims 1, 3, and 7 of the '106 patent, and claim 1 of the '059 patent.

Jazz proposes that no construction is necessary, and Roxane proposes, "every single one, no exceptions." Roxane's construction reflects its position that the applicant included a limitation to distinguish a situation where, before including the words "any and all," "there could be a patient or doctor sending [or] . . . having their own little database, or a pharmacy having it." (Tr. at 208:5-10). Again, Roxane's proposal reflects its view on the concept of exclusivity.

Although the Court's review of Roxane's citations to the patent history does show that the claims were amended to include the word "all," the record does not provide support for Roxane's proposal of "every single one, no exceptions." (*See* Ex. L Dec. 31, 2009 Notice of Allowability at 10-11, ROXGHB004805-06 (demonstrating that the patent claims would be allowed over the prior art because "the closest prior art of record does not teach or fairly suggest that *all* prescriptions for the prescription drug [GHB] are processed *only by the exclusive central pharmacy using only the exclusive computer database*") (emphasis in the original record). The prosecution history ascribes no special meaning to the word "all" over its common understanding. Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the plain meaning of the term as understood by someone of ordinary skill shall apply.

11. "database"[24]

Jazz proposes that no construction is necessary, and Roxane proposes, "database containing all relevant data related to the distribution of the drug and the process of distributing it, including patient, physician and prescription information." The Court accepts Jazz's proposal.

[23] The term "all" appears in claims 1, 2, and 7-11 of the '730 patent, claims 1, 3, and 5-7 of the '106 patent, claims 1 and 4 of the '107 patent, and claims 1, 6, 9, and 12-14 of the '059 patent.

[24] The term "database" appears in claims 1-3 and 7-11 of the '730 patent, claims 1, 3, and 5-7 of the '106 patent, claims 1 and 4 of the '107 patent, and claims 1, 2, 6, 9, and 12-14 of the '059 patent.

Although the patent history does contain the language Roxane proposes, the language defines, "exclusive computer database," and not "database," the Court's focus of construction here. (*See* Ex. L Aug. 31, 2009 Board Decision at 9, ROXGHB004759 ("[A]s used in the claims in light of the Specification as it would be interpreted by one of ordinary skill in the art is that [the claim term '*exclusive* computer database'] is a central computer database exclusive of other databases that 'contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information.'") (emphasis added) (citing '730 Patent at 2:10-12); *see also* Tr. at 213:8-14)). Because the patent history's focus was "exclusive computer database," the citation is off-point, and Roxane's proposal merely reflects its recurring position on exclusivity.

Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the plain meaning of the term as understood by someone of ordinary skill shall apply.

12. "control"[25] and "maintains"[26]

The parties' dispute as to both of these terms relates to Roxane's contention that, "both of these [terms] talk about whether the pharmacy is the only one that has the right to write on to the database. . . . Requiring entering of the information, into an exclusive computer database under exclusive control of the central pharmacy." (Tr. at 215:25-216:2). Again, therefore, Roxane's contention relates to its exclusivity contention.

As to "control," Jazz proposes that no construction is necessary, and Roxane proposes, "write accessibility." In support of its construction, Roxane cites three columns of examples

[25] The term "control" appears in claims 1, 2, and 7-11 of the '730 patent, claims 1, 6, 9, and 12-14 of the '059 patent.

[26] The term "maintains" appears in claims 1 and 4 of the '107 patent.

from the patent that Roxane synthesizes into its proposal, but nothing in the columns actually defines the term "control." (*See* Roxane's Opening Br. at 20 (citing '730 Patent at 4:7-7:25)). The Court declines to read examples into the construction where construing "control" would not increase the understanding of one skilled in the art.

As to "maintains," Jazz proposes that the term needs no construction, and Roxane proposes, "has write access to." Roxane points to nothing in the specification or the patent prosecution history that supports its construction, and Roxane has not convinced the Court that the term requires construction.[27]

Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the plain meaning of the term as understood by someone of ordinary skill shall apply.

13. "confirming . . . patient"[28]

Jazz proposes that no construction is necessary, and Roxane proposes, "contacting the patient and the patient responding." Roxane's position reflects its view that the specification "requires both an action by the pharmacy, and the patient." (Tr. at 220:4-5). Although the specification contains examples that support this concept, ('730 Patent at 1:53-56, 5:27-41, 61-63), the Court declines to read limitations from examples into the construction. Additionally, Jazz pointed out during the *Markman* hearing that logic does not require confirmation by a patient: "If I hand something to you, I don't have to confirm with you that you received it. I

[27] Additionally, Jazz convincingly argues that Roxane's attempts to read embodiments into the claims would support Roxane's proposed distribution system for its ANDA drug, which "employ[s] multiple pharmacies, and not a single exclusive pharmacy, having write access to the central database." (Jazz's Responsive Br. at 23 (citing Ex. 18 at 31199 (Roxane's proposed distribution strategy), Ex. 19 at ROXGBH031204-06, 08 (Roxane's proposed ANDA drug), and Ex. 20 at ROXGHB031314-19, 21, 27, 30, 32) (Roxane's proposed Risk Evaluation and Mitigation Strategy ("REMS")))).

[28] The term "confirming . . . patient" appears in claims 1, 2, and 7-19 of the '730 patent, claims 1, 3, 5, and 7 of the '106 patent, claims 1, 2, 4, and 5 of the '107 patent, and claims 1, 6, 8-14, and 16 of the '059 patent.

know you received it. There is no confirmation necessary. And this system as well. If the pharmacist hands it to you and says, 'here,' you don't need to shake your hand or wave, I got it." (Tr. at 220:17-23). The Court agrees that no such limitation is appropriate based on the intrinsic evidence.

Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the plain meaning of the term as understood by someone of ordinary skill shall apply.

14. ". . . to . . . patient"[29]

As to ". . . to . . . patient," Jazz proposes that the term needs no construction, and Roxane proposes, "to the patient in a dispensed form." The parties agreed that this term relates to "confirming . . . patient," and that both terms relate to Roxane's argument for exclusivity. (*See* Tr. at 223:12-13). Although Roxane cites to portions of the specification in support of the limitation "in a dispensed form," nothing in those citations contains that limitation, (Tr. at 224:7-8), and the Court declines to import limitations from examples into the construction.

Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the plain meaning of the term as understood by someone of ordinary skill shall apply.

15. "dispensed"[30]

Jazz proposes that no construction is necessary, and Roxane proposes, "prepared in a form suitable for providing to an individual patient." The Court accepts Jazz's proposal.

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[29] The term ". . . to . . . patient" appears in claims 1, 2, and 7-11 of the '730 patent, claims 1 and 4 of the '107 patent, claims 1, 3, 5, and 7 of the '106 patent, and claims 1, 6, 7, 9, 10, and 12-15 of the '059 patent.

[30] The term "dispensed" appears in claims 7, 10, and 15 of the '059 patent.

Roxane's proposal "means [the pharmaceutical] . . . . [c]an't be a stock supply. . . . We are trying to distinguish when the exclusive central pharmacy sends it to the patient, it is in a form suitable for providing to an individual patient." (Tr. at 225:20-226:1). In support of its position, Roxane cites claim context, ('059 Patent claim 7 at 9:53-55 ("The computerized method of claim 6, wherein providing the prescription drug to the patient comprises the central pharmacy authorizing the prescription drug to be dispensed to the patient by another pharmacy.")), and an extrinsic dictionary definition. The Court finds no direct support for the limitations set forth by Roxane, and it finds that the limitation "to an individual patient" injects redundancy. *See U.S. Surgical Corp.,* 103 F.3d at 1568 (holding that claim construction is not an "exercise in redundancy").

Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the plain meaning of the term as understood by someone of ordinary skill shall apply.

16. "computer system"[31]

Jazz proposes that the term needs no construction, and Roxane proposes, "a computer system that is located at the exclusive central pharmacy," further linking its proposal to its argument of exclusivity. The Court accepts Jazz's proposal.

Roxane seeks to import the limitation that the computer system (such as the one in the '106 Patent in Figure 1) is located at the exclusive central pharmacy. (*See* '106 Patent Figure 1 & 2:19-37 ("The exclusive central database contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information . . . Fig. 1 is a block diagram of a computer system for use in implementing the

[31] The term "computer system" appears in claims 1-5, 7, and 8 of the '106 patent.

system and method of the present invention.")). Roxane uses this example to import the limitation that because all the requests are received at the exclusive central pharmacy, then the exclusive central computer system must be located at the exclusive central pharmacy. The Court finds that no such limitation—whether the computer system can be remote or has to be located at a certain place—flows from the specification, and that, in defining "computer system" with a construction that begins with "computer system . . . ," Roxane admits the self-evident nature of the term.

Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the plain meaning of the term as understood by someone of ordinary skill shall apply.

17. "shipping"; "shipment"[32]

Jazz proposes that no construction is necessary, and Roxane proposes, "sending of the prescription drug in dispensed form by carrier." The Court accepts Jazz's proposal.

Roxane's points to examples in the specification to support its construction, relying on examples, in which, after preparation, the drugs are shipped via courier or by mail. (*See*, *e.g.*, '730 Patent at 1:61-62 ("courier service's tracking system is used to confirm delivery"), 3:43-45 ("US Mail"), and 5:57-58 ("USPS"))). However, as with related terms, the Court will not read limitations from examples into the construction.

Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the plain meaning of the term as understood by someone of ordinary skill shall apply.

18. "a separate database"[33]

[32] The terms "shipping" and "shipment" appear in claims 1, 3, 5, and 7 of the '106 patent and claims 1, 2, 4 and 5 of the '107 patent.

Jazz proposes that no construction is necessary, and Roxane proposes, "a database other than the exclusive central database." The Court accepts Jazz's proposal.

Roxane argues that the term appears in claim 3 of the '107 Patent, which depends from claim 1. Claim 3 is: "The method of claim 1 which further comprises consulting a separate database to verify that the medical doctor is eligible to prescribe the drug." Claim 1 refers to the exclusive central pharmacy that maintains a central database, and therefore when claim 3 refers to a "separate" database, it must be referring to a database other than the exclusive central database. (Roxane's Opening Br. at 29). The Court finds that the language of the claim term is clear on its face. Accordingly, the Court agrees with Jazz that no construction of this term is necessary and finds that its ordinary and customary meaning would be clear to one skilled in the art. Therefore, the plain meaning of the term as understood by someone of ordinary skill shall apply.

IV. Conclusion

For the reasons set forth above, the disputed terms at issue will be construed as indicated. An appropriate Order shall accompany this Opinion.

/s/ Esther Salas
Dated: September 14, 2012 **Esther Salas, U.S.D.J.**

[33] The term "a separate database" appears in claims 3 and 6 of the '107 patent.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/595,757	08/27/2012	Dayton T. Reardan	101.031US11	5359

21186 7590 01/17/2013

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

NOTIFICATION DATE	DELIVERY MODE
01/17/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@slwip.com
SLW@blackhillsip.com

Office Action Summary	Application No.	Applicant(s)	
	13/595,757	REARDAN ET AL.	
	Examiner	Art Unit	
	LENA NAJARIAN	3686	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-15* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-15* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20121002*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-15 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 7,668,730 and claims 1-16 of U.S. Patent No. 7,895,059. Although the conflicting claims are not identical, they are not patentably distinct from each other because they contain substantially the same limitations that are in the aforementioned claims of U.S. Patent 7,668,730 and U.S. Patent No. 7,895,059.

Claim Rejections - 35 USC § 112

2. The following is a quotation of 35 U.S.C. 112(b):

(B) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-15 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

The term "various credentials" in claims 1 and 9 is a relative term which renders the claims indefinite. The term "various credentials" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear which credentials are included.

The terms "unique" and “uniqueness” in claims 1 and 9 are relative terms which render the claims indefinite. The terms are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Examiner suggests Applicant remove the aforementioned terms from the claims.

The term "controls" in claims 5 and 13 is a relative term which renders the claims indefinite. The term "controls" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how the pharmacy is controlling the database.

Claims 2-4, 6-8, 10-12, 14, and 15 incorporate the deficiencies of claims 1 and 9, through dependency, and are also rejected.

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LENA NAJARIAN whose telephone number is

(571)272-7072. The examiner can normally be reached on Monday - Friday, 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jerry O'Connor can be reached on (571) 272-6787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LENA NAJARIAN/
Primary Examiner, Art Unit 3686
1/11/13

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Dayton T. Reardan Ph.D et al.	Examiner: Lena Najarian
Serial No.:	13/592,202	Group Art Unit: 3686
Filed:	August 22, 2012	Docket: 101.031US9
Customer No.:	21186	Confirmation No.: 5805
Title:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD	

RESPONSE TO RESTRICTION REQUIREMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In response to the Restriction Requirement mailed January 16, 2013, Applicants submit the following.

Electronic Acknowledgement Receipt

EFS ID:	14970068
Application Number:	13592202
International Application Number:	
Confirmation Number:	5805
Title of Invention:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
First Named Inventor/Applicant Name:	Dayton T. Reardan
Customer Number:	21186
Filer:	Gregory M. Stark/John Gustav-Wrathall
Filer Authorized By:	Gregory M. Stark
Attorney Docket Number:	101.031US9
Receipt Date:	15-FEB-2013
Filing Date:	22-AUG-2012
Time Stamp:	13:00:02
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		101031us9_resp_021513.pdf	99835 085dbde30b93ad1be771e2f12d837867610b957c	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Miscellaneous Incoming Letter	1	1
	Response to Election / Restriction Filed	2	2
	Claims	3	7
	Applicant Arguments/Remarks Made in an Amendment	8	9
Warnings:			
Information:			
	Total Files Size (in bytes):	99835	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Dayton T. Reardan Ph.D et al.

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

Docket No.:	101.031US9	Serial No.:	13/592,202
Filed:	August 22, 2012	Due Date:	February 16, 2013
Examiner:	Lena Najarian	Group Art Unit:	3686
Customer No.:	21186	Confirmation No.:	5805

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We are transmitting herewith the following attached items (as indicated with an "X"):

X Response to Restriction Requirement (8 pgs.)

If not provided for in a separate paper filed herewith, please consider this a PETITION FOR EXTENSION OF TIME for sufficient number of months to enter these papers and please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
Customer No.: 21186

By: / /
David D'Zurilla
Reg. No. 36,776

REMARKS

In the Restriction Requirement mailed January 16, 2013, the Examiner has restricted the claims to one of the following inventions under 35 U.S.C. 121:

I. Claims 1 -22, drawn to database, schema, and data structure creation and/or modification, classified in class 707, subclass 803.

II. Claim 23-26, drawn to health care management, classified in class 705, subclass 2.

Applicants elect, without traverse, Group I, claims 1-22. Applicants respectfully cancel claims 23-26 (Group II) without prejudice or disclaimer, and reserve the right to reintroduce them in one or more divisional applications at a later date.

Applicants have added claims 27 and 28, both of which are dependent on claim 1.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (612) 371-2140 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 371-2140

Date February 15, 2013 By / /

David D'Zurilla
Reg. No. 36,776

IN THE CLAIMS

1. (Original) A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising:

one or more computer memories for storing a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug;

said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

said prescriber fields, contained within the database schema, storing information sufficient to identify a physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug;

a data processor for processing a database query that operates over all data related to the prescription fields, prescriber fields, and patient fields for the prescription drug;

said database query identifying information in the prescription fields and patient fields for reconciling inventory of the prescription drug before the shipments for a day or other time period are sent.

2. (Original) The system of claim 1, wherein the data processor is configured to process a

second database query that identifies: whether the narcoleptic patient is a cash payer and a physician that is interrelated with the narcoleptic patient through the schema of the single computer database;

said identifying by said second database query being an indicator of a potential misuse, abuse or diversion by the narcoleptic patient and being used to notify the physician that is interrelated with the narcoleptic patient through the schema of the single computer database.

3. (Original) The system of claim 1, wherein the data processor is configured to process a second database query that identifies a potential misuse, abuse or diversion by the narcoleptic patient.

4. (Original) The system of claim 3, wherein the data processor selectively blocks shipment of the prescription drug to the patient based upon said identifying by the database query.

5. (Original) The system of claim 3, wherein the prescription drug is shipped to the narcoleptic patient if no potential misuse, abuse or diversion is found for the narcoleptic patient.

6. (Original) The system of claim 1, wherein the single computer database is an exclusive database that receives data associated with all patients being prescribed the prescription drug that are associated with the company.

7. (Original) The system of claim 1, wherein an exclusive central pharmacy controls the single

computer database.

8. (Original) The system of claim 1 wherein the prescription drug comprises gamma hydroxyl butyrate (GHB).

9. (Original) The system of claim 1, wherein the single computer database comprises a relational database.

10. (Original) The system of claim 1, where the single computer database is distributed among multiple computers provided the database query that operates over all data relating to said prescription fields, prescriber fields, and patient fields for the prescription drug.

11. (Original) The system of claim 1, wherein the data processor is configured to initiate an inquiry to a prescriber when one or more prescription fields, patient fields, or prescriber fields are incomplete in the computer database.

12. (Original) The system of claim 1, wherein the data processor is configured to process a second database query that identifies an expected date for a refill of the prescription drug.

13. (Original) The system of claim 12, wherein the expected date is based on a prescription for the prescription drug and a date of a previous filling of the prescription.

14. (Original) The system of claim 13, wherein the prescription identifies an amount of the prescription drug to be provided and a schedule for consumption of the prescription drug.

15. (Original) The system of claim 1, wherein the database schema further contains and interrelates insurance fields, wherein the insurance fields, contained within the database schema, store information sufficient to identify an insurer to be contacted for payment for prescription drugs of an associated patient.

16. (Original) The system of claim 1, wherein the single computer database is used to identify a current pattern or an anticipated pattern of abuse of the prescription drug; wherein the current pattern or the anticipated pattern are identified using periodic reports generated from the single computer database.

17. (Original) The system of claim 16, wherein one or more controls for distribution of the prescription drug are selected based on the identified pattern.

18. (Original) The system of claim 17, wherein the one or more controls are submitted to an approval body for approval of distribution of the prescription drug.

19. (Original) The system of claim 1, wherein additional controls for distribution are selected in a negotiation with an approval body to garner the approval of distribution.

20. (Original) The system of claim 19, wherein the data processor is used to add further controls until approval is obtained.

21. (Original) The system of claim 20, wherein the approval body is the Food and Drug Administration (FDA) or the Drug Enforcement Agency (DEA).

22. (Original) The system of claim 1, wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent.

23 - 26. (Canceled).

27. (New) The system of claim 1, wherein the single computer database comprises an exclusive computer database of the company that obtained approval for distribution of the prescription drug, wherein all prescriptions for the company's prescription drug are stored only in the exclusive computer database of the company, and wherein the company's prescription drug is sold or distributed by the company using only the exclusive computer database of the company.

28. (New) The system of claim 1, wherein the single computer database comprises a single computer database of the company that obtained approval for distribution of the prescription drug, wherein the prescription fields store all prescription requests, for all patients being prescribed the company's prescription drug, only in the single computer database of the company, from all physicians or other prescribers allowed to prescribe the company's prescription drug, such that all prescriptions for the company's prescription drug are processed using only the single computer database of the company.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/592,202	Filing Date 08/22/2012	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
AMENDMENT	02/15/2013	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 24	Minus	** 26	= 0	X $ =		OR	X $62=	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	**0**

		(Column 1)		(Column 2)	(Column 3)					
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/KIM WATSON/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

CONFIDENTIAL

NOT FOR PUBLIC DISTRIBUTION

AMNEAL PHARMACEUTICALS, LLC

DETAILED FACTUAL AND LEGAL BASIS OF

NON-INFRINGEMENT AND/OR INVALIDITY

I. Summary of the Detailed Factual and Legal Basis Memorandum

AMNEAL PHARMACEUTICALS, LLC ("AMNEAL") filed an Abbreviated New Drug Application ("ANDA") under 21 U.S.C. § 355(j) to obtain approval from the U.S. Food & Drug Administration ("FDA") to market Sodium Oxybate Oral Solution, 500 mg/mL ("AMNEAL's ANDA product"). As discussed in detail below, the manufacture, use, sale, offer for sale, and/or importation of AMNEAL's ANDA product will not directly or indirectly infringe any valid claim of U.S. Patent Nos. 6,780,889, 7,262,219, 7,668,730, 7,765,106, 7,765,107, 7,851,506, 7,895,059 and 8,263,650, listed in the Orange Book for Xyrem®, either literally or under the doctrine of equivalents.

II. Drug Description

Sodium oxybate, sodium 4-hydroxybutyrate, is the active ingredient in Jazz's commercial product, Xyrem®. According to the package insert for Xyrem®, the product contains 500 mg of sodium oxybate per milliliter of USP Purified Water, neutralized to pH 7.5 with malic acid.

III. The Orange Book Listed Patents

As of December 7, 2012, the FDA's Orange Book lists eight patents for Xyrem® with expiration dates as follows: 6,780,889 (expiring July 4, 2020), 7,262,219 (expiring July 4, 2020), 7,668,730 (expiring June 16, 2024), 7,765,106 (expiring June 16, 2024), 7,765,107 (expiring June 16, 2024), 7,851,506 (expiring December 22, 2019), 7,895,059 (expiring December 17, 2022) and 8,263,650 (expiring December 22, 2019). There is no unexpired exclusivity for this product.

IV. AMNEAL's ANDA Product

AMNEAL's ANDA product contains sodium oxybate, 500 mg/mL. AMNEAL's ANDA product will be marketed for the currently approved indication for Xyrem®, *i.e.*, treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.

V. Detailed Factual & Legal Basis of Non-Infringement

A. U.S. Patent No. 6,780,889 ("the '889 patent")

Claim 1, the sole claim of the '889 patent, requires that the sodium oxybate composition does not contain any preservatives, *i.e.*, substances that inhibit microbial action. In contrast to the claimed composition, AMNEAL's ANDA product contains 0.01% w/v sodium propylparaben, which functions as a preservative at the pH of AMNEAL's ANDA product.

Accordingly, for at least this reason, the manufacture, use, importation, sale or offer for sale of AMNEAL's ANDA product will not literally infringe claim 1 of the '889 patent.

Furthermore, the manufacture, use, importation, sale or offer for sale of AMNEAL's ANDA product will not infringe claim 1 of the '889 patent under the doctrine of equivalents. Allowing claim 1 of the '889 patent to cover AMNEAL's ANDA product by equivalence would vitiate an essential element of the claim, namely that the composition be free of preservatives. A composition lacking a preservative cannot, as a matter of law, be equivalent to a composition containing a preservative. In addition, because the '889 patent clearly discloses but does not claim sodium oxybate compositions containing a preservative, such as AMNEAL's ANDA product, the patentee has dedicated such compositions to the public and cannot recapture them under the doctrine of equivalents.

Accordingly, for at least these reasons, the manufacture, use, importation, sale or offer for sale of AMNEAL's ANDA product will not infringe claim 1 of the '889 patent under the doctrine of equivalents.

B. U.S. Patent No. 7,262,219 ("the '219 patent")

Like claim 1 of the '889 patent, each of the claims of the '219 patent requires that the sodium oxybate composition does not contain any preservatives, *i.e.*, substances that inhibit microbial action. Accordingly, for at least the reasons given above for the '889 patent, the manufacture, use, importation, sale or offer for sale of AMNEAL's ANDA product will not infringe any claim of the '219 patent, either literally or under the doctrine of equivalents.

C. U.S. Patent No. 8,263,650 ("the '650 patent")

Like claim 1 of the '889 patent, each of the claims of the '650 patent requires that the sodium oxybate composition does not contain any preservatives, *i.e.*, substances that inhibit microbial action. Accordingly, for at least the reasons given above for the '889 patent, the manufacture, use, importation, sale or offer for sale of AMNEAL's ANDA product will not infringe any claim of the '650 patent, either literally or under the doctrine of equivalents.

D. U.S. Patent No. 7,668,730 ("the '730 patent")

Each of the claims of the '730 patent requires that the prescription drug be distributed under the control of an "exclusive central pharmacy," *i.e.*, a single, sole pharmacy. In contrast to the claimed distribution method, AMNEAL's ANDA product will not be distributed by a single, sole pharmacy. Instead, AMNEAL'S ANDA product will be distributed by two or more separate pharmacies.

Accordingly, for at least this reason, the manufacture, use, importation, sale or offer for sale of AMNEAL's ANDA product will not literally infringe any claim of the '730 patent.

Furthermore, the manufacture, use, importation, sale or offer for sale of AMNEAL's ANDA product will not infringe any claim of the '730 patent under the doctrine of equivalents. Allowing the claims of the '730 patent to cover the method of distribution of AMNEAL's ANDA product by equivalence would vitiate an essential element of the claims, namely that the prescription drug be distributed by an exclusive central pharmacy. A method of drug distribution involving two or more separate pharmacies cannot, as a matter of law, be equivalent to a method of drug distribution involving a single, sole pharmacy.

Additionally, the patentees are estopped from asserting that distribution of AMNEAL's ANDA product infringes any claim of '730 patent under the doctrine of equivalents based on prosecution history estoppel. First, under the doctrine of argument-based estoppel, the patentees argued in response to a § 103 rejection that the cited prior art "advocates away from the use of a single pharmacy." Thus, the patentees made a clear and unmistakable surrender of drug distribution systems using two or more pharmacies and are therefore estopped from asserting equivalence between the method of distribution of AMNEAL's ANDA product and the distribution method claimed in the '730 patent.

Second, under the doctrine of amendment-based estoppel, the patentees amended the pending claims in response to a § 103 rejection and distinguished the prior art by stating that "the Applicant has amended the claims so that the prescriptions are received only at the central pharmacy and that all prescriptions are processed only by the exclusive pharmacy and using only the exclusive computer database."

This amendment constitutes a narrowing amendment made for a reason relating to patentability, thus creating a presumption that no range of equivalents is available for the amended element, *i.e.*, that all prescriptions are processed by the exclusive, *i.e.*, single, sole pharmacy. Based on controlling case law, the patentees would be unable to rebut the presumption of complete surrender of all methods of drug distribution involving more than one pharmacy, *i.e.*, where not all prescriptions are processed by an exclusive pharmacy. As such, there is no range of equivalents available for the claims of the '730 patent, and patentees are estopped from asserting equivalence between the method of distribution of AMNEAL's ANDA product and the distribution method claimed in the '730 patent.

Accordingly, for at least these reasons, the manufacture, use, importation, sale or offer for sale of AMNEAL's ANDA product will not infringe any claim of the '730 patent under the doctrine of equivalents.

E. U.S. Patent No. 7,765,107 ("the '107 patent")

Like the claims of the '730 patent, each of the claims of the '107 patent requires that the prescription drug be distributed under the control of an exclusive central pharmacy *i.e.*, a single, sole pharmacy. Accordingly, for at least the reasons given above for the '730 patent, the manufacture, use, importation, sale or offer for sale of AMNEAL's ANDA product will not infringe any claim of the '107 patent, either literally or under the doctrine of equivalents.

F. U.S. Patent No. 7,895,059 ("the '059 patent")

Like the claims of the '730 patent, each of the claims of the '059 patent requires that the prescription drug be distributed under the control of an exclusive central pharmacy *i.e.*, a single, sole pharmacy. Accordingly, for at least the reasons given above for the '730 patent, the manufacture, use, importation, sale or offer for sale of AMNEAL's ANDA product will not infringe any claim of the '059 patent, either literally or under the doctrine of equivalents.

G. U.S. Patent No. 7,765,106 ("the '106 patent")

Each of the claims of the '106 patent requires that the prescription drug be distributed by a method comprising "receiving, only into an exclusive central computer system, all prescriptions" or "receiving, only into an exclusive computer database in a computer system, . . . all prescriptions," *i.e.*, receiving all prescriptions into a single, sole computer system or database. In contrast to the claimed distribution method, not all prescriptions for AMNEAL's ANDA will be received into a single, sole computer system or database. Instead, at least some prescriptions for AMNEAL'S ANDA product will be received via facsimile or telephone by at least one pharmacy without the ability to connect to a central computer system or database, *i.e.*, not all prescriptions are received into a single, sole computer system or database.

Accordingly, for at least this reason, the manufacture, use, importation, sale or offer for sale of AMNEAL's ANDA product will not literally infringe any claim of the '106 patent.

Additionally, the manufacture, use, importation, sale or offer for sale of AMNEAL's ANDA product will not infringe any claim of the '106 patent under the doctrine of equivalents. Allowing the claims of the '106 patent to cover the method of distribution of AMNEAL's ANDA product by equivalence would vitiate an essential element of the claims, namely that the prescription drug be distributed by a method comprising "receiving, only into an exclusive central computer system, all prescriptions" or "receiving, only into an exclusive computer database in a computer system, . . . all prescriptions." A method of drug distribution involving receiving all prescriptions into a single, sole computer system or database cannot, as a matter of law, be equivalent to a method of drug distribution involving receiving via facsimile or telephone at least some prescriptions by at least one pharmacy without the ability to connect to a central computer system or database.

Accordingly, for at least this reason, the manufacture, use, importation, sale or offer for sale of AMNEAL's ANDA product will not infringe any claim of the '106 patent under the doctrine of equivalents.

H. U.S. Patent No. 7,851,506 ("the '506 patent")

Claim 1 of the '506 patent requires orally administering split liquid doses prior to and following initial sleep onset of about 4.5 to about 10 grams of sodium gamma-hydroxybutyrate having a concentration of greater than about 500 mg/ml to a patient suffering from a condition selected from apnea, sleep time disturbances, narcolepsy, cataplexy, sleep paralysis, hypnagogic

hallucination, sleep arousal, insomnia and nocturnal myoclonus. Claim 2 further requires that the condition is narcolepsy, and claim 3 further requires that the condition is cataplexy, which is a symptom of narcolepsy.

The term "about" is defined in the specification to generally mean "within about 10-20%," thus permitting variations of about 20%. Therefore, claim 1 of the '506 patent is properly construed to encompass a sodium gamma-hydroxybutyrate ("GHB") composition having a concentration greater than about 400 mg/ml (*i.e.*, the lower value of the range of 500 ± 20%). Furthermore, claim 1 is properly construed to encompass administering to a patient a dose of about 3.6 grams (*i.e.*, the lower value of the range of 4.5 ± 20%) to about 12 grams (*i.e.*, the upper value of the range of 10 ± 20%) of sodium GHB.

Scrima *et al.*, "The Effects of γ-Hydroxybutyrate on the Sleep of Narcolepsy Patients: a Double-Blind Study," *Sleep* 13(6):479-490 ("Scrima") was published in 1990 and is therefore available as § 102(b) prior art. Scrima discloses a double-blind study of the effects of GHB on patients with narcolepsy. Scrima administered GHB to patients immediately before going to bed, and three hours later (*i.e.*, split doses). The highest dose administered was about 5.65 grams. Scrima reported an improvement in sleep depth and continuity in patients treated with GHB.

In addition, U.S. Patent No. 4,983,632 ("the '632 patent") issued in 1991 and is therefore available as § 102(b) prior art. The '632 patent discloses that simple salts of GHB derivatives are used for their narcotic, or sleep-inducing, effect. The '632 patent further teaches sodium gamma-hydroxybutyrate as an example of a simple salt of GHB. Example 2 of the '632 patent discloses the preparation of an aqueous solution suitable for oral administration containing 302.5 mg/ml sodium GHB, but also teaches that the GHB salt content of the compositions can be up to 500 mg/ml.

Accordingly, claims 1-3 of the '506 patent would have been *prima facie* obvious over the combination of Scrima and the '632 patent.

The patentees cannot rebut the *prima facie* case of obviousness of claims 1-3 of the '506 patent established herein because (i) the patentees will be unable to meet its burden in establishing a nexus between the sales of Xyrem® and the scope of the claims; (ii) the patentees will be unable to demonstrate that the claimed invention exhibits the requisite unexpected results that may be utilized as evidence of secondary indicia of nonobviousness, particularly in view of the teachings in Scrima and the '632 patent as set forth above; (iii) the patentees have not provided any public information about any licensing agreements involving the '506 patent that may be utilized as evidence of secondary indicia of the claimed invention; (iv) evidence related to a generic drug manufacturer's allegedly "copying" of the claimed invention is insufficient to rebut the *prima facie* case of obviousness; and (v) there is no other publically available evidence that the patentees will be able to rely on to demonstrate that the claimed invention would not have been obvious.

Accordingly, claims 1-3 of the '506 patent are invalid under 35 U.S.C. § 103(a) for obviousness.

VI. Conclusion

For at least the reasons set forth above, the manufacture, use, sale or offer for sale within the United States, or importation into the United States, of AMNEAL's ANDA product will not directly or indirectly infringe any valid claim of U.S. Patent Nos. 6,780,889, 7,262,219, 7,668,730, 7,765,106, 7,765,107, 7,851,506, 7,895,059 and 8,263,650, either literally or under the doctrine of equivalents.

CONFIDENTIAL

NOT FOR PUBLIC DISTRIBUTION

AMNEAL PHARMACEUTICALS, LLC

DETAILED FACTUAL AND LEGAL BASIS OF

NON-INFRINGEMENT AND/OR INVALIDITY

I. Summary of the Detailed Factual and Legal Basis Memorandum

AMNEAL PHARMACEUTICALS, LLC ("AMNEAL") filed an Abbreviated New Drug Application ("ANDA") under 21 U.S.C. § 355(j) to obtain approval from the U.S. Food & Drug Administration ("FDA") to market Sodium Oxybate Oral Solution, 500 mg/mL ("AMNEAL's ANDA product"). As discussed in detail below, the manufacture, use, sale or offer for sale within the United States, or importation into the United States, of AMNEAL's ANDA product will not directly or indirectly infringe any valid claim of U.S. Patent No. 8,324,275, listed in the Orange Book for Xyrem®, either literally or under the doctrine of equivalents.

II. Drug Description

Sodium oxybate, sodium 4-hydroxybutyrate, is the active ingredient in Jazz's commercial product, Xyrem®. According to the package insert for Xyrem®, the product contains 500 mg of sodium oxybate per milliliter of USP Purified Water, neutralized to pH 7.5 with malic acid.

III. The Orange Book Listed Patents

As of December 12, 2012, the FDA's Orange Book lists nine patents for Xyrem® with expiration dates as follows: 6,780,889 (expiring July 4, 2020), 7,262,219 (expiring July 4, 2020), 7,668,730 (expiring June 16, 2024), 7,765,106 (expiring June 16, 2024), 7,765,107 (expiring June 16, 2024), 7,851,506 (expiring December 22, 2019), 7,895,059 (expiring December 17, 2022), 8,263,650 (expiring December 22, 2019) and 8,324,275 (expiring December 22, 2019). There is no unexpired exclusivity listed in the Orange Book for Xyrem®.

IV. AMNEAL's ANDA Product

AMNEAL's ANDA product contains sodium oxybate, 500 mg/mL. AMNEAL's ANDA product will be marketed for the currently approved indication for Xyrem®, *i.e.*, treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.

V. Detailed Factual & Legal Basis of Invalidity

U.S. Patent No. 8,324,275 ("the '275 patent") issued with four claims, of which claims 1 and 2 are independent. Taken together in their narrowest scope, the claims of the '275 patent require treating cataplexy or daytime sleepiness in a patient who has been diagnosed with narcolepsy, comprising: (i) diluting an aqueous solution comprising about 500 mg/mL of sodium gamma-hydroxybutyrate with an aqueous medium to provide a first dose of about 4.5 to about 9 grams sodium gamma-hydroxybutyrate; (ii) diluting an aqueous solution comprising about 500 mg/mL of sodium gamma-hydroxybutyrate with an aqueous medium to provide a second dose of

about 4.5 to about 9 grams of sodium gamma-hydroxybutyrate; (iii) orally administering to a patient having narcolepsy the first dose within an hour prior to initial sleep onset; (iv) orally administering to the patient having narcolepsy the second dose within 2.5 to 4 hours following initial sleep onset; and (v) wherein each of the doses administered to the patient having narcolepsy contains about 50-75 mg/ml of sodium gamma-hydroxybutyrate.

The term "about" is defined in the specification to generally mean "within about 10-20%," thus permitting variations of about 20%. Therefore, the claims of the '275 patent are properly construed to encompass diluting a sodium gamma-hydroxybutyrate ("GHB") composition having a concentration greater than about 400 mg/ml (*i.e.*, the lower value of the range of 500 ± 20%). Furthermore, the claims of the '275 patent are properly construed to encompass administering to a patient doses of about 3.6 grams (*i.e.*, the lower value of the range of 4.5 ± 20%) to about 10.8 grams (*i.e.*, the upper value of the range of 9 ± 20%) of sodium GHB, wherein each of the doses administered contains about 40 mg/ml sodium GHB (*i.e.*, the lower value of the range of 50 ± 20%) to about 90 mg/ml sodium GHB (*i.e.*, the upper value of the range of 75 ± 20%).

Scrima *et al.*, "The Effects of γ-Hydroxybutyrate on the Sleep of Narcolepsy Patients: A Double-Blind Study," *Sleep* 13(6):479-490 ("Scrima") was published in 1990 and is therefore available as § 102(b) prior art. Scrima discloses a double-blind study of the effects of GHB on patients with narcolepsy. Scrima administered GHB to patients immediately before going to bed, and three hours later. The GHB was diluted in water and orange syrup. The highest dose of GHB taught to induce sleep was about 5.65 grams (about 6.8 grams of sodium GHB). Scrima reported an improvement in sleep depth and continuity in patients treated with GHB.

In addition, Broughton and Mamelak, "The Treatment of Narcolepsy-Cataplexy with Nocturnal Gamma-Hydroxybutyrate," *Le Journal Canadien Des Sciences Neurologiques* 6(1):1-6 ("Broughton") was published in 1979 and is therefore available as § 102(b) prior art. Broughton teaches the nighttime treatment of patients with narcolepsy and cataplexy with sodium GHB. Broughton discloses that the total quantity of GHB given each night was 3.75 to 6.25 grams (about 4.5 to about 7.5 grams of sodium GHB)), with a usual initial dose given at bedtime of up to 2.25 grams (about 2.7 grams of sodium GHB) followed by further multiple 1.0-1.5 gram doses during the night with each major reawakening, if at least 2.5 hours had passed since the previous dose. The GHB doses were diluted in milk or juice to a concentration range of about 100-225 mg/ml (about 120-270 mg/ml of sodium GHB) to reduce GI upset and to retard the rate of GHB absorptions so that sleep induction was experienced as gradual and more normal.

Also, U.S. Patent No. 4,983,632 ("Gessa") issued in 1991 and is therefore available as § 102(b) prior art. Gessa discloses that simple salts of GHB derivatives are used for their narcotic, or sleep-inducing, effect. Gessa further teaches sodium gamma-hydroxybutyrate as an example of a simple salt of GHB. Example 2 of Gessa discloses the preparation of an aqueous solution suitable for oral administration containing 302.5 mg/ml sodium GHB, but also teaches that the GHB salt content of the compositions can be up to 500 mg/ml.

Based on the teachings of Scrima, Broughton and Gessa, one of ordinary skill in the art would have arrived at the subject matter claimed in the '275 patent with a reasonable expectation of success.

Accordingly, claims 1-4 of the '275 patent would have been *prima facie* obvious over the combination of Scrima, Broughton and Gessa.

The patentees cannot rebut the *prima facie* case of obviousness of claims 1-4 of the '275 patent established herein because (i) the patentees will be unable to meet its burden in establishing a nexus between the sales of Xyrem® and the scope of the claims; (ii) the patentees will be unable to demonstrate that the claimed invention exhibits the requisite unexpected results that may be utilized as evidence of secondary indicia of nonobviousness, particularly in view of the teachings in Scrima, Broughton and Gessa as set forth above; (iii) the patentees have not provided any public information about any licensing agreements involving the '275 patent that may be utilized as evidence of secondary indicia of the claimed invention; (iv) evidence related to a generic drug manufacturer's allegedly "copying" of the claimed invention is insufficient to rebut the *prima facie* case of obviousness; and (v) there is no other publically available evidence that the patentees will be able to rely on to demonstrate that the claimed invention would not have been obvious.

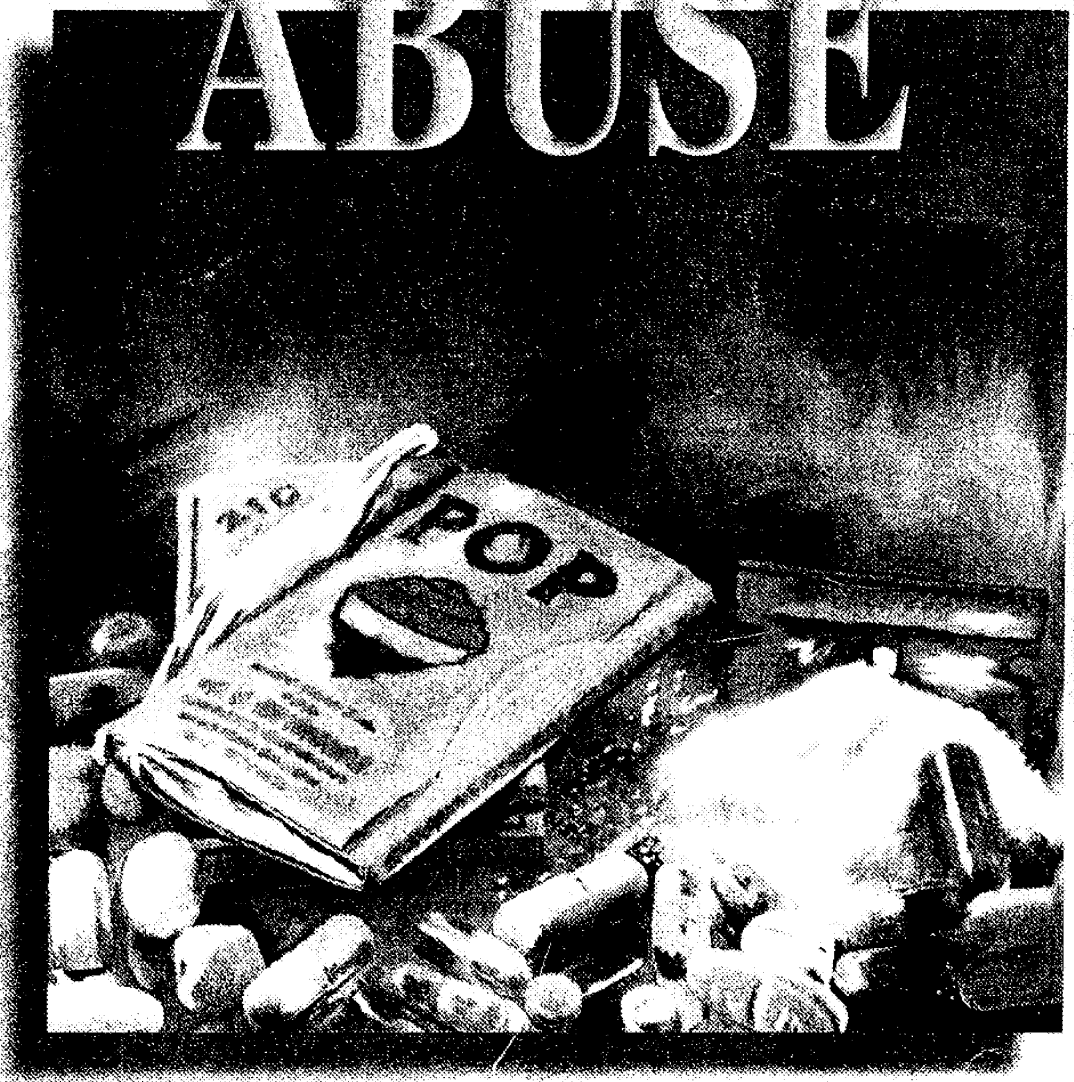
Accordingly, claims 1-4 of the '275 patent are invalid under 35 U.S.C. § 103(a) for obviousness.

VI. Conclusion

For at least the reasons set forth above, the manufacture, use, sale or offer for sale within the United States, or importation into the United States, of AMNEAL's ANDA product will not directly or indirectly infringe any valid claim of U.S. Patent No. 8,324,275, either literally or under the doctrine of equivalents.

U.S. Department of Justice
Drug Enforcement Administration

DRUGS of ABUSE



1997
Edition

Acknowledgments

Drugs of Abuse *has been well received both by members of law enforcement as a drug identification tool and by those involved in prevention of drug abuse interested in the physiological effects of drugs. This revision of* Drugs of Abuse *would not have been possible without the cooperation of many groups and individuals. Special thanks to:*

The National Guard, both for their support in making this publication possible, and for their support to DEA in reducing drug abuse;

DEA's Drug and Chemical Evaluation Section, especially to pharmacologists Judy Lawrence, Ph.D. and Gretchen Feussner, who provided the text dealing with all of the drugs and gave technical advice throughout every stage of production of this publication;

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and Charles Lyles of DEA's Graphics Department, who designed this issue of Drugs of Abuse.

Like the entire national effort to reduce the level of violence brought about by drug abuse, the publication of Drugs of Abuse *has been a cooperative effort. It is the wish of all those involved in this publication that those who read it will come to the realization that the physiological effects of drug abuse are destroying individual potential and subsequently the nation's well-being.*

The Editor

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CONTROLLED SUBSTANCES ACT

The Controlled Substances Act (CSA), Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, is the legal foundation of the government's fight against abuse of drugs and other substances. This law is a consolidation of numerous laws regulating the manufacture and distribution of narcotics, stimulants, depressants, hallucinogens, anabolic steroids and chemicals used in the illicit production of controlled substances.

I. CONTROLLING DRUGS OR OTHER SUBSTANCES

FORMAL SCHEDULING

The CSA places all substances which were in some manner regulated under existing Federal law into one of five schedules. This placement is based upon the substance's medical use, potential for abuse, and safety or dependence liability. The Act also provides a mechanism for substances to be controlled, or added to a schedule; decontrolled, or removed from control; and rescheduled or transferred from one schedule to another. The procedure for these actions is found in Section 201 of the Act (21 U.S.C. 811).

Proceedings to add, delete, or change the schedule of a drug or other substance may be initiated by the Drug Enforcement Administration (DEA), the Department of Health and Human Services (HHS), or by petition from any interested party: the manufacturer of a drug, a medical society or association, a pharmacy association, a public interest group concerned with drug abuse, a state or local government agency, or an individual citizen. When a petition is received by DEA, the agency begins its own investigation of the drug.

The agency also may begin an investigation of a drug at any time based upon information received from law enforcement laboratories, state and local law enforcement and regulatory agencies, or other sources of information.

Once DEA has collected the necessary data, the Administrator of DEA, by authority of the Attorney General, requests from HHS a scientific and medical evaluation and recommendation as to whether the drug or other substance should be controlled or removed from control. This request is sent to the Assistant Secretary of Health of HHS. HHS solicits information from the Commissioner of the Food and Drug Administration (FDA), evaluations and recommendations from the National Institute on Drug Abuse, and on occasion from the scientific and medical community at large. The Assistant Secretary, by authority of the Secretary, compiles the information and transmits back to DEA a medical and scientific evaluation regarding the drug or other substance, a recommendation as to whether the drug should be controlled, and in what schedule it should be placed.

The medical and scientific evaluations are binding on DEA with respect to scientific and medical matters. The recommendation on scheduling is binding only to the extent that if HHS recommends that the substance not be controlled, DEA may not control the substance.

Once DEA has received the scientific and medical evaluation from HHS, the Administrator will evaluate all available data and make a final decision whether to propose that a drug or other substance should be controlled and into which schedule it should be placed.

The threshold issue is whether the drug or other substance has potential for abuse. If a drug does not have a potential for abuse, it cannot be controlled. Although the term "potential for abuse" is not defined in the CSA, there is much discussion of the term in the legislative history of the Act. The following items are indicators that a drug or other substance has a potential for abuse:

Over 60 percent of the heroin that is sold in the United States originates in the poppy fields of Southeast Asia.

The milky fluid that oozes from the seedpod of the poppy is opium.

Heroin is manufactured in mobile "laboratories" (seen) rudimentary equipment

(1) There is evidence that individuals are taking the drug or other substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community; or

(2) There is significant diversion of the drug or other substance from legitimate drug channels; or

(3) Individuals are taking the drug or other substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs; or

(4) The drug is a new drug so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that the drug will have the same potential for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community. Of course, evidence of actual abuse of a substance is indicative that a drug has a potential for abuse.

In determining into which schedule a drug or other substance should be placed, or whether a substance should be decontrolled or rescheduled, certain factors are required to be considered. Specific findings are not required for each factor. These factors are listed in Section 201 (c), [21 U.S.C. 811 (c)], of the CSA and are as follows:

(1) *The drug's actual or relative potential for abuse.*

(2) *Scientific evidence of the drug's pharmacological effects.* The state of knowledge with respect to the effects of a specific drug is, of course, a major consideration. For example, it is vital to know whether or not a drug has a hallucinogenic effect if it is to be controlled because of that. The best available knowledge of the pharmacological properties of a drug should be considered.

(3) *The state of current scientific knowledge regarding the substance.* Criteria (2) and (3) are closely related. However, (2) is primarily concerned with pharmacological effects and (3) deals with all scientific knowledge with respect to the substance.

(4) *Its history and current pattern of abuse.* To determine whether or not a drug should be controlled, it is important to know the pattern of abuse of that substance, including the socio-economic characteristics of the segments of the population involved in such abuse.

(5) *The scope, duration, and significance of abuse.* In evaluating existing abuse, the Administrator must know not only the pattern of abuse but whether the abuse is widespread. In reaching his decision, the Administrator should consider the economics of regulation and enforcement attendant to such a decision. In addition, he should be aware of the social significance and impact of such a decision upon those people, especially the young, that would be affected by it.

(6) *What, if any, risk there is to the public health.* If a drug creates dangers to the public health, in addition to or because of its abuse potential, then these dangers must also be considered by the Administrator.

(7) *The drug's psychic or physiological dependence liability.* There must be an assessment of the extent to which a drug is physically addictive or psychologically habit-forming, if such information is known.

(8) *Whether the substance is an immediate precursor of a substance already controlled.* The CSA allows inclusion of immediate precursors on this basis alone into the appropriate schedule and thus safeguards against possibilities of clandestine manufacture.

After considering the above listed factors, the Administrator must make specific findings concerning the drug or other substance. This will determine into which schedule the drug or other substance will be placed. These schedules are established by the CSA. They are as follows:

Schedule I

- The drug or other substance has a high potential for abuse.
- The drug or other substance has no currently accepted medical use in treatment in the United States.
- There is a lack of accepted safety for use of the drug or other substance under medical supervision.

- Some Schedule I substances are heroin, LSD, marijuana, and methaqualone.

Schedule II

- The drug or other substance has a high potential for abuse.
- The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
- Abuse of the drug or other substance may lead to severe psychological or physical dependence.
- Schedule II substances include morphine, PCP, cocaine, methadone, and methamphetamine.

Schedule III

- The drug or other substance has a potential for abuse less than the drugs or other substances in Schedules I and II.
- The drug or other substance has a currently accepted medical use in treatment in the United States.
- Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.
- Anabolic steroids, codeine and hydrocodone with aspirin or Tylenol®, and some barbiturates are Schedule III substances.

Schedule IV

- The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III.
- The drug or other substance has a currently accepted medical use in treatment in the United States.
- Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.
- Included in Schedule IV are Darvon®, Talwin®, Equanil®, Valium® and Xanax®.

Schedule V

- The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule IV.
- The drug or other substance has a currently accepted medical use in treatment in the United States.
- Abuse of the drug or other substances may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.
- Over-the-counter cough medicines with codeine are classified in Schedule V.

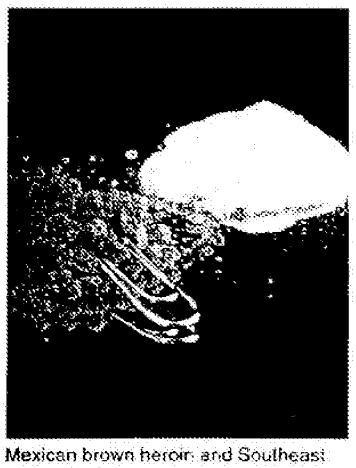
When the Administrator of DEA has determined that a drug or other substance should be controlled, decontrolled, or rescheduled, a proposal to take action is published in the *Federal Register.* The proposal invites all interested persons to file comments with DEA. Affected parties may also request a hearing with DEA. If no hearing is requested, DEA will evaluate all comments received and publish a final order in the *Federal Register*, controlling the drug as proposed or with modifications based upon the written comments filed. This order will set the effective dates for imposing the various requirements imposed under the CSA.

If a hearing is requested, DEA will enter into discussions with the party or parties requesting a hearing in an attempt to narrow the issue for litigation. If necessary, a hearing will then be held before an Administrative Law Judge. The judge will take evidence on factual issues and hear arguments on legal questions regarding the control of the drug. Depending on the scope and complexity of the issues, the hearing may be brief or quite extensive. The Administrative Law Judge, at the close of the hearing, prepares findings of fact and conclusions of law and a recommended decision which is submitted to the Administrator of DEA. The Administrator will review these documents, as well as the underlying material, and prepare his/her own findings of fact and conclusions of law (which may or may not be the same as those drafted by the Administrative Law Judge). The Administrator then publishes a final order in the *Federal Register* either scheduling the drug or other substance or declining to do so.

Once the final order is published in the *Federal Register*, interested parties have 30 days to appeal to a U.S. Court of Appeals to challenge the order. Findings of fact by the Administrator are deemed conclusive if supported by "substantial evidence." The order imposing controls is not stayed during the

Heroin can then be pressed into bricks for bulk shipment to destination countries.

In another method of smuggling heroin, couriers swallow heroin-filled latex balloons before boarding commercial airlines.



Mexican brown heroin and Southeast Asian heroin.

The Upper Huallaga Valley of Peru is the primary source of the coca leaf.

After they are picked, coca leaves are dried in the open air.

Coca leaves are "cheapened" in crude pits called pozos or pozas by the persons to extract cocaine.

appeal, however, unless so ordered by the Court.

Emergency or Temporary Scheduling

The CSA was amended by the Comprehensive Crime Control Act of 1984. This Act included a provision which allows the Administrator of DEA to place a substance, on a temporary basis, into Schedule I when necessary to avoid an imminent hazard to the public safety.

This emergency scheduling authority permits the scheduling of a substance which is not currently controlled, is being abused, and is a risk to the public health while the formal rule making procedures described in the CSA are being conducted. This emergency scheduling applies only to substances with no accepted medical use. A temporary scheduling order may be issued for one year with a possible extension of up to six months if formal scheduling procedures have been initiated. The proposal and order are published in the *Federal Register* as are the proposals and orders for formal scheduling. [21 U.S.C. 811 (h)]

Controlled Substance Analogues

A new class of substances was created by the Anti-Drug Abuse Act of 1986. Controlled substance analogues are substances which are not controlled substances, but may be found in the illicit traffic. They are structurally or pharmacologically similar to Schedule I or II controlled substances and have no legitimate medical use. A substance which meets the definition of a controlled substance analogue and is intended for human consumption is treated under the CSA as if it were a controlled substance in Schedule I.

International Treaty Obligations

U. S. treaty obligations may require that a drug or other substance be controlled under the CSA, or rescheduled if existing controls are less stringent than those required by a treaty. The procedures for these scheduling actions are found in Section 201 (d) of the Act. [21 U.S.C. 811 (d)]

The United States is a party to the Single Convention on Narcotic Drugs of 1961, designed to establish effective control over international and domestic traffic in narcotics, coca leaf, cocaine, and cannabis. A second treaty, the Convention on Psychotropic Substances of 1971, which entered into force in 1976, is designed to establish comparable control over stimulants, depressants, and hallucinogens. Congress ratified this treaty in 1980.

II. REGULATION

The CSA creates a closed system of distribution for those authorized to handle controlled substances. The cornerstone of this system is the registration of all those authorized by DEA to handle controlled substances. All individuals and firms that are registered are required to maintain complete and accurate inventories and records of all transactions involving controlled substances, as well as security for the storage of controlled substances.

Registration

Any person who handles or intends to handle controlled substances must obtain a registration issued by DEA. A unique number is assigned to each legitimate handler of controlled drugs: importer, exporter, manufacturer, distributor, hospital, pharmacy, practitioner, and researcher. This number must be made available to the supplier by the customer prior to the purchase of a controlled substance. Thus, the opportunity for unauthorized transactions is greatly diminished.

Recordkeeping

The CSA requires that complete and accurate records be kept of all quantities of controlled substances manufactured, purchased, and sold. Each substance must be inventoried every two years. Some limited exceptions to the recordkeeping requirements may apply to certain categories of registrants.

From these records it is possible to trace the flow of any drug from the time it is first imported or manufactured through the distribution level, to the pharmacy or hospital that dispensed it, and then to the actual patient who received the drug. The mere existence of this requirement is sufficient to discourage many forms of diversion. It actually serves large drug corporations as an internal check to uncover diversion, such as pilferage by employees.

There is one distinction between scheduled items for recordkeeping requirements. Records for Schedule I and II drugs must be

kept separate from all other records of the handler; records for Schedule III, IV, and V substances must be kept in a "readily retrievable" form. The former method allows for more expeditious investigations involving the highly abusable substances in Schedules I and II.

Distribution

The keeping of records is required for distribution of a controlled substance from one manufacturer to another, from manufacturer to distributor, and from distributor to dispenser. In the case of Schedule I and II drugs, the supplier must have a special order form from the customer. This order form (DEA Form 222) is issued by DEA only to persons who are properly registered to handle Schedules I and II. The form is preprinted with the name and address of the customer. The drugs must be shipped to this name and address. The use of this device is a special reinforcement of the registration requirement; it makes doubly certain that only authorized individuals may obtain Schedule I and II drugs. Another benefit of the form is the special monitoring it permits. The form is issued in triplicate: the customer keeps one copy; two copies go to the supplier who, after filling the order, keeps a copy and forwards the third copy to the nearest DEA office.

For drugs in Schedules III, IV, and V, no order form is necessary. The supplier in each case, however, is under an obligation to verify the authenticity of the customer. The supplier is held fully accountable for any drugs which are shipped to a purchaser who does not have a valid registration.

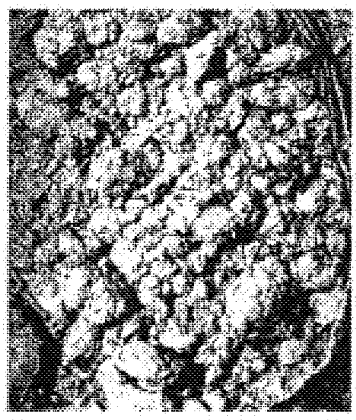
Manufacturers must submit periodic reports of the Schedule I and II controlled substances they produce in bulk and dosage forms. They also report the manufactured quantity and form of each narcotic substance listed in Schedules III, IV, and V, as well as the quantity of synthesized psychotropic substances listed in Schedules I, II, III, and IV. Distributors of controlled substances must report the quantity and form of all their transactions of controlled drugs listed in Schedules I and II and narcotics listed in Schedule III. Both manufacturers and distributors are required to provide reports of their annual inventories of these controlled substances. This data is entered into a system called the Automated Reports and Consolidated Orders System (ARCOS). It enables DEA to monitor the distribution of controlled substances throughout the country, and to identify retail level registrants that receive unusual quantities of controlled substances.

Dispensing to Patients

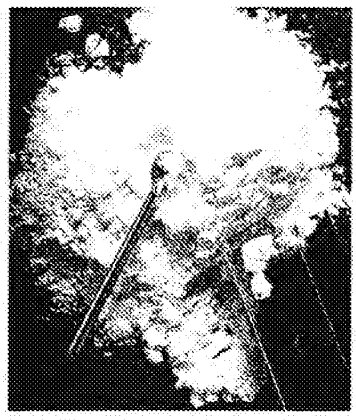
The dispensing of a controlled substance is the delivery of the controlled substance to the ultimate user, who may be a patient or research subject. Special control mechanisms operate here as well. Schedule I drugs are those which have no currently accepted medical use in the United States; they may, therefore, be used in the United States only in research situations. They generally are supplied by only a limited number of firms to properly registered and qualified researchers. Controlled substances may be dispensed by a practitioner by direct administration, by prescription, or by dispensing from office supplies. Records must be maintained by the practitioner of all dispensing of controlled substances from office supplies and of certain administrations. The CSA does not require the practitioner to maintain copies of prescriptions, but certain states require the use of multiple copy prescriptions for Schedule II and other specified controlled substances.

The determination to place drugs on prescription is within the jurisdiction of the FDA. Unlike other prescription drugs, however, controlled substances are subject to additional restrictions. Schedule II prescription orders must be written and signed by the practitioner; they may not be telephoned into the pharmacy except in an emergency. In addition, a prescription for a Schedule II drug may not be refilled; the patient must see the practitioner again in order to obtain more drugs. For Schedule III and IV drugs, the prescription order may be either written or oral (that is, by telephone to the pharmacy). In addition, the patient may (if authorized by the practitioner) have the prescription refilled up to five times and at anytime within six months from the date of the initial dispensing.

Schedule V includes some prescription drugs and many over-the-counter narcotic preparations, including antitussives and antidiarrheals. Even here, however, the law imposes restrictions beyond those normally required for the over-the-counter sales; for example, the patient must be at least 18 years of age, must offer some form of identification, and have his or her name entered into a



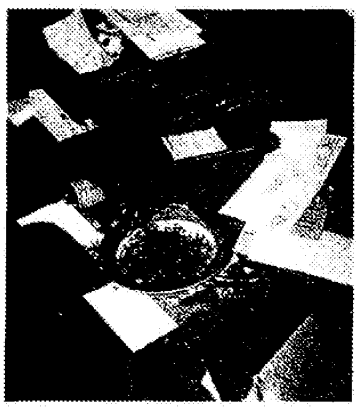
The process results in coca paste.



Powdered cocaine.

The bright green plants in the center of the photo are cannabis, hidden among other foliage to avoid detection.

Because of successful marijuana eradication efforts by law enforcement, many illicit growers cultivate the plant indoors.



In the past, it was the marijuana leaves that were dried, crushed and smoked.

Today, marijuana abusers prefer the *cola*, or buds of the plant, because of its higher THC content. Leaves are now discarded or used as filler.

special log maintained by the pharmacist as part of a special record.

Quotas

DEA limits the quantity of Schedule I and II controlled substances which may be produced in the United States in any given calendar year. By utilizing available data on sales and inventories of these controlled substances, and taking into account estimates of drug usage provided by the FDA, DEA establishes annual aggregate production quotas for Schedule I and II controlled substances. The aggregate production quota is allocated among the various manufacturers who are registered to manufacture the specific drug. DEA also allocates the amount of bulk drug which may be procured by those companies which prepare the drug into dosage units.

Security

DEA registrants are required by regulation to maintain certain security for the storage and distribution of controlled substances. Manufacturers and distributors of Schedule I and II substances must store controlled substances in specially constructed vaults or highly rated safes, and maintain electronic security for all storage areas. Lesser physical security requirements apply to retail level registrants such as hospitals and pharmacies.

All registrants are required to make every effort to ensure that controlled substances in their possession are not diverted into the illicit market. This requires operational as well as physical security. For example, registrants are responsible for ensuring that controlled substances are distributed only to other registrants that are authorized to receive them, or to legitimate patients and consumers.

III. PENALTIES

The CSA provides penalties for unlawful manufacturing, distribution, and dispensing of controlled substances. The penalties are basically determined by the schedule of the drug or other substance, and sometimes are specified by drug name, as in the case of marijuana. As the statute has been amended since its initial passage in 1970, the penalties have been altered by Congress. The charts on pages 8 and 9 are an overview of the penalties for trafficking or unlawful distribution of controlled substances. This is not inclusive of the penalties provided under the CSA.

User Accountability/Personal Use Penalties

On November 19, 1988, Congress passed the Anti-Drug Abuse Act of 1988, P. L. 100-690. Two sections of this Act represent the Federal Government's attempt to reduce drug abuse by dealing not just with the person who sells the illegal drug, but also with the person who buys it. The first new section is titled "User Accountability" and is codified at 21 U.S.C. § 862 and various sections of Title 42, U.S.C. The second involves "personal use amounts" of illegal drugs, and is codified at 21 U.S.C. § 844a.

User Accountability

The purpose of User Accountability is to not only make the public aware of the Federal Government's position on drug abuse, but to describe new programs intended to decrease drug abuse by holding drug abusers personally responsible for their illegal activities, and imposing civil penalties on those who violate drug laws.

It is important to remember that these penalties are in addition to the criminal penalties drug abusers are already given, and do not replace those criminal penalties.

The new User Accountability programs call for more instruction in schools, kindergarten through senior high, to educate children on the dangers of drug abuse. These programs will include participation by students, parents, teachers, local businesses and the local, state and Federal Government.

User Accountability also targets businesses interested in doing business with the Federal Government. This program requires those businesses to maintain a drug-free workplace, principally through educating employees on the dangers of drug abuse, and by informing employees of the penalties they face if they engage in illegal drug activity on company property.

There is also a provision in the law that makes public housing projects drug-free by evicting those residents who allow their units to be used for illegal drug activity, and denies Federal benefits, such as housing assistance and student loans, to individuals convicted of illegal drug activity. Depending on the of-

fense, an individual may be prohibited from ever receiving any benefit provided by the Federal Government.

Personal Use Amounts

This section of the 1988 Act allows the government to punish minor drug offenders without giving the offender a criminal record if the offender is in possession of only a small amount of drugs. This law is designed to impact the "user" of illicit drugs, while simultaneously saving the government the costs of a full-blown criminal investigation.

Under this section, the government has the option of imposing only a civil fine on individuals possessing only a small quantity of an illegal drug. Possession of this small quantity, identified as a "personal use amount" carries a civil fine of up to $10,000.

In determining the amount of the fine in a particular case, the drug offender's income and assets will be considered. This is accomplished through an administrative proceeding rather than a criminal trial, thus reducing the exposure of the offender to the entire criminal justice system, and reducing the costs to the offender and the government.

The value of this section is that it allows the government to punish a minor drug offender without saddling the offender with a criminal record. This section also gives the drug offender the opportunity to fully redeem himself or herself, and have all public record of the proceeding destroyed. If this was the drug offender's first offense, and the offender has paid all fines, can pass a drug test, and has not been convicted of a crime after three years, the offender can request that all proceedings be dismissed.

If the proceeding is dismissed, the drug offender can lawfully say he or she had never been prosecuted, either criminally or civilly, for a drug offense.

Congress has imposed two limitations on this section's use. It may not be used if (1) the drug offender has been previously convicted of a Federal or state drug offense; or (2) the offender has already been fined twice under this section.

Marijuana buds are hung out to dry.

Marijuana is still rolled into cigarettes and smoked

Hollowed out cigars packed with marijuana are called blunts, and are gaining in popularity.

✎JS 44 (Rev. 11/04)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS

Jazz Pharmaceuticals, Inc.

(b) County of Residence of First Listed Plaintiff Santa Clara, CA
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorney's (Firm Name, Address, and Telephone Number)

Charles M. Lizza, Esq., Saul Ewing LLP, One Riverfront Plaza, Newark, New Jersey 07102-5426, (973) 286-6700, clizza@saul.com

DEFENDANTS

Amneal Pharmaceuticals, LLC

County of Residence of First Listed Defendant Somerset, NJ
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ❒ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ❒ 2 U.S. Government Defendant
- ❒ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	❒ 1	❒ 1	Incorporated *or* Principal Place of Business In This State	❒ 4	❒ 4
Citizen of Another State	❒ 2	❒ 2	Incorporated *and* Principal Place of Business In Another State	❒ 5	❒ 5
Citizen or Subject of a Foreign Country	❒ 3	❒ 3	Foreign Nation	❒ 6	❒ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ❒ 110 Insurance
- ❒ 120 Marine
- ❒ 130 Miller Act
- ❒ 140 Negotiable Instrument
- ❒ 150 Recovery of Overpayment & Enforcement of Judgment
- ❒ 151 Medicare Act
- ❒ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ❒ 153 Recovery of Overpayment of Veteran's Benefits
- ❒ 160 Stockholders' Suits
- ❒ 190 Other Contract
- ❒ 195 Contract Product Liability
- ❒ 196 Franchise

REAL PROPERTY
- ❒ 210 Land Condemnation
- ❒ 220 Foreclosure
- ❒ 230 Rent Lease & Ejectment
- ❒ 240 Torts to Land
- ❒ 245 Tort Product Liability
- ❒ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ❒ 310 Airplane
- ❒ 315 Airplane Product Liability
- ❒ 320 Assault, Libel & Slander
- ❒ 330 Federal Employers' Liability
- ❒ 340 Marine
- ❒ 345 Marine Product Liability
- ❒ 350 Motor Vehicle
- ❒ 355 Motor Vehicle Product Liability
- ❒ 360 Other Personal Injury

PERSONAL INJURY
- ❒ 362 Personal Injury - Med. Malpractice
- ❒ 365 Personal Injury - Product Liability
- ❒ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ❒ 370 Other Fraud
- ❒ 371 Truth in Lending
- ❒ 380 Other Personal Property Damage
- ❒ 385 Property Damage Product Liability

CIVIL RIGHTS
- ❒ 441 Voting
- ❒ 442 Employment
- ❒ 443 Housing/ Accommodations
- ❒ 444 Welfare
- ❒ 445 Amer. w/Disabilities - Employment
- ❒ 446 Amer. w/Disabilities - Other
- ❒ 440 Other Civil Rights

PRISONER PETITIONS
- ❒ 510 Motions to Vacate Sentence

Habeas Corpus:
- ❒ 530 General
- ❒ 535 Death Penalty
- ❒ 540 Mandamus & Other
- ❒ 550 Civil Rights
- ❒ 555 Prison Condition

FORFEITURE/PENALTY
- ❒ 610 Agriculture
- ❒ 620 Other Food & Drug
- ❒ 625 Drug Related Seizure of Property 21 USC 881
- ❒ 630 Liquor Laws
- ❒ 640 R.R. & Truck
- ❒ 650 Airline Regs.
- ❒ 660 Occupational Safety/Health
- ❒ 690 Other

LABOR
- ❒ 710 Fair Labor Standards Act
- ❒ 720 Labor/Mgmt. Relations
- ❒ 730 Labor/Mgmt.Reporting & Disclosure Act
- ❒ 740 Railway Labor Act
- ❒ 790 Other Labor Litigation
- ❒ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ❒ 422 Appeal 28 USC 158
- ❒ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ❒ 820 Copyrights
- ☒ 830 Patent
- ❒ 840 Trademark

SOCIAL SECURITY
- ❒ 861 HIA (1395ff)
- ❒ 862 Black Lung (923)
- ❒ 863 DIWC/DIWW (405(g))
- ❒ 864 SSID Title XVI
- ❒ 865 RSI (405(g))

FEDERAL TAX SUITS
- ❒ 870 Taxes (U.S. Plaintiff or Defendant)
- ❒ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ❒ 400 State Reapportionment
- ❒ 410 Antitrust
- ❒ 430 Banks and Banking
- ❒ 450 Commerce
- ❒ 460 Deportation
- ❒ 470 Racketeer Influenced and Corrupt Organizations
- ❒ 480 Consumer Credit
- ❒ 490 Cable/Sat TV
- ❒ 810 Selective Service
- ❒ 850 Securities/Commodities/ Exchange
- ❒ 875 Customer Challenge 12 USC 3410
- ❒ 890 Other Statutory Actions
- ❒ 891 Agricultural Acts
- ❒ 892 Economic Stabilization Act
- ❒ 893 Environmental Matters
- ❒ 894 Energy Allocation Act
- ❒ 895 Freedom of Information Act
- ❒ 900Appeal of Fee Determination Under Equal Access to Justice
- ❒ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

☒ 1 Original Proceeding ❒ 2 Removed from State Court ❒ 3 Remanded from Appellate Court ❒ 4 Reinstated or Reopened ❒ 5 Transferred from another district (specify) ❒ 6 Multidistrict Litigation ❒ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity)**:
35 United States Code

Brief description of cause:
This is an action for patent infringement arising out of the patent laws of the United States of America.

VII. REQUESTED IN COMPLAINT:

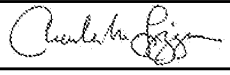
❒ CHECK IF THIS IS A **CLASS ACTION** UNDER F.R.C.P. 23

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ❒ Yes ☒ No

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE Hon. Esther Salas, U.S.D.J. DOCKET NUMBER See Attachment "A"

DATE 01/18/2013

SIGNATURE OF ATTORNEY OF RECORD 

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

ATTACHMENT "A"

RELATED CASES:

I. The Honorable Esther Salas, U.S.D.J.
Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.
Civil Action No. 10-6108 (ES)(CLW)

II. The Honorable Esther Salas, U.S.D.J.
Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.
Civil Action No. 11-660 (ES)(CLW)

IIII. The Honorable Esther Salas, U.S.D.J.
Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.
Civil Action No. 11-2523 (ES)(CLW)

IV. The Honorable Esther Salas, U.S.D.J.
Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.
Civil Action No. 12-6761 (ES)(CLW)

V. The Honorable Esther Salas, U.S.D.J.
Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.
Civil Action No. 12-7495 (ES)(CLW)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Dayton T. Reardan Ph.D et al.	Examiner:	Lena Najarian
Serial No.:	13/592,202	Group Art Unit:	3686
Filed:	August 22, 2012	Docket:	101.031US9
Customer No.:	21186	Confirmation No.:	5805
Title:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD		

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In compliance with the duty imposed by 37 C.F.R. § 1.56, and in accordance with 37 C.F.R. §§ 1.97 *et. seq*., the enclosed materials are brought to the attention of the Examiner for consideration in connection with the above-identified patent application. Applicants respectfully request that this Information Disclosure Statement be entered and the documents listed on the attached PTO 1449 Form be considered by the Examiner and made of record. Pursuant to the provisions of MPEP 609, Applicant requests that a copy of the PTO 1449 Form, initialed as being considered by the Examiner, be returned to the Applicant with the next official communication.

Pursuant to 37 C.F.R. § 1.97(b), it is believed that no fee or statement is required with the Information Disclosure Statement. However, if an Office Action on the merits has been mailed after filing of the application or after the filing of the most recent RCE, the Commissioner is hereby authorized to charge the required fees to Deposit Account No. 19-0743 in order to have this Information Disclosure Statement considered.

Pursuant to 37 C.F.R. § 1.98(a)(2), copies of cited U.S. Patents and Published Applications, and Non-Published Applications identifiable by USPTO Serial Number, are no longer required to be provided to the Office. Applicants acknowledge the requirement to submit copies of foreign patent documents and non-patent literature in accordance with 37 C.F.R § 1.98(a)(2).

The Examiner is invited to contact the undersigned at the telephone number indicated if there are any questions regarding this communication.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 371-2140

Date March 4, 2013 By /David D'Zurilla/

David D'Zurilla
Reg. No. 36,776

DDZ:vam

Modified form PTO/SB/08A(04-07) OMB 651-0031
US Patent & Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)	*Complete if Known*	
	Application Number	13/592,202
	Filing Date	August 22, 2012
	First Named Inventor	Dayton T. Reardan Ph.D
	Group Art Unit	3686
	Examiner Name	Lena Najarian
Sheet 1 of 1	Attorney Docket No: 101.031US9	

US PATENT DOCUMENTS			
Examiner Initial *	**USP Document Number**	**Publication Date**	**Name of Patentee or Applicant of cited Document**
	US-20030074225	4/17/2003	Borsand, Gerlad, et al.

OTHER DOCUMENTS – NON PATENT LITERATURE DOCUMENTS		
Examiner Initial *	**Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.**	**T 1**
	"Briefing Booklet for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting", Orphan Medical, Inc., (6/6/01), 353 pgs	
	"Civil Cover Sheet", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey, (1/18/13), 2 pgs	
	"Complaint for Patent Infringement", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey, (1/18/13), 17 pgs	
	"Controlled Substances Act", Drugs of Abuse, U.S. Department of Justice, Drug Enforcement Administration, (1997), 9 pgs	
	"Detailed Factual and Legal Basis of Non-Infringement and/or Invalidity", Amneal Pharmaceuticals, LLC, (12/12/12), 3 pgs	
	"Detailed Factual and Legal Basis of Non-Infringement and/or Invalidity", Amneal Pharmaceuticals, LLC, (12/7/12), 6 pgs	
	"Exhibits A-D", Jazz Pharmaceuticals v Amneal Pharmaceuticals, LLC, (1/18/2013), 151 pgs	
	"Exhibits D-G", Jazz Pharmaceuticals v Amneal Pharmaceuticals, LLC, (1/18/13), 123 pgs	
	"Fed. R. Civ. P. Rule 7.1 Disclosure Statement", (1/18/13), 2 pgs	
	"Making Good in Your Own Mail-Order Business", Changing Times - The Kiplinger Magazine, (October 1980), 66-68	
	"Notice of Electronic Filing: Civil Inital Pleadings (Attorney/Credit Card) USE CASE 33-1", US District Court, District of new Jersey [LIVE], (1/18/13), 2 pgs	
	"Notice of Paragraph IV Certification Concerning ANDA 203631 for Sodiium Oxybate Oral Solution, 500 mg/mL", Amneal Pharmaceuticals, LLC, (12/7/12), 4 pgs	
	"Notice of Paragraph IV Certification Concerning ANDA 203631 for Sodiium Oxybate Oral Solution. 500 mg/mL", Amneal Pharmaceuticals, LLC, (12/12/12), 4 pgs	
	"Peripheral and Central Nervous System Drugs Advisory Committee - Transcript", Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, Holiday Inn, Bethesda, Maryland, (6/6/01), 381 pgs	
	"Xyrem Prescription and Distribution Process-Video Script", (2/2/01), 10 pgs	
	DEUTSCH, SHERYL, "The Verification and Information-Gathering Process", The Credentialing Handbook, Aspen Publishers, Inc., (1999), 231-275	
	MANI, RANJIT, "Preliminary Clinical Safety Review of NDA No. 21196", Orphan Medical, Inc., (05/03/01), 122 pgs	

EXAMINER **DATE CONSIDERED**

* EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant is to place a check mark here if English language Translation is attached

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William C. Baton
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Newark, New Jersey 07102-5426
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiff
Jazz Pharmaceuticals, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **v.** **AMNEAL PHARMACEUTICALS, LLC,** **Defendant.**	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiff Jazz Pharmaceuticals, Inc. ("Jazz Pharmaceuticals"), by its undersigned attorneys, for its Complaint against defendant Amneal Pharmaceuticals, LLC ("Amneal"), alleges as follows:

Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. §100, *et seq.*, arising from Amneal's filing of an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market a generic version of Jazz Pharmaceuticals' XYREM® drug product prior to the expiration of United States Patent Nos. 6,472,431 (the "'431 patent"), 6,780,889 (the "'889 patent"), 7,262,219 (the "'219 patent"), 7,851,506 (the "'506 patent"), 7,895,059 (the "'059 patent"), 8,263,650 (the "'650 patent"), and 8,324,275 (the "'275 patent")

owned by Jazz Pharmaceuticals (collectively, "the patents-in-suit") owned by Jazz Pharmaceuticals.

The Parties

2. Plaintiff Jazz Pharmaceuticals is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304.

3. On information and belief, defendant Amneal is a corporation organized under the laws of the State of Delaware, having a principal place of business 440 U.S. Highway 22 East, Suite 104, Bridgewater, New Jersey 08807.

Jurisdiction and Venue

4. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

5. This Court has personal jurisdiction over Amneal by virtue of, *inter alia,* its systematic and continuous contacts with the State of New Jersey. On information and belief, Amneal has purposefully availed itself of this forum by, among other things, operating its headquarters in the State of New Jersey, making, shipping, using, offering to sell or selling, or causing others to use, offer to sell, or sell, pharmaceutical products in the State of New Jersey and deriving revenue from such activities. Further, on information and belief, Amneal has customers in the State of New Jersey.

6. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

The Patent-In-Suit

7. On October 29, 2002, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '431 patent, entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy" to inventors Harry Cook,

Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan. The '431 patent was later assigned to Jazz Pharmaceuticals. A copy of the '431 patent is attached hereto as Exhibit A.

8. On August 24, 2004, the USPTO duly and lawfully issued the '889 patent, entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy" to inventors Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan. The '889 patent was later assigned to Jazz Pharmaceuticals. A copy of the '889 patent is attached hereto as Exhibit B.

9. On August 28, 2007, the USPTO duly and lawfully issued the '219 patent, entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy" to inventors Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan. The '219 patent was later assigned to Jazz Pharmaceuticals. A copy of the '219 patent is attached hereto as Exhibit C.

10. On December 14, 2010, the USPTO duly and lawfully issued the '506 patent, entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy" to Jazz Pharmaceuticals as assignee of the inventors Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan. A copy of the '506 patent is attached hereto as Exhibit D.

11. On February 22, 2011, the USPTO duly and lawfully issued the '059 patent, entitled "Sensitive Drug Distribution System and Method" to Jazz Pharmaceuticals as assignee of the inventors Dayton Reardan, Patti Engle and Bob Gagne. A copy of the '059 patent is attached hereto as Exhibit E.

12. On September 11, 2012, the USPTO duly and lawfully issued the '650 patent, entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy" to Jazz Pharmaceuticals as assignee of the inventors Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan. A copy of the '650 patent is attached hereto as Exhibit F.

13. On December 4, 2012, the USPTO duly and lawfully issued the '275 patent, entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy" to Jazz Pharmaceuticals as assignee of the inventors Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan. A copy of the '275 patent is attached hereto as Exhibit G.

The XYREM® Drug Product

14. Jazz Pharmaceuticals holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for sodium oxybate oral solution (NDA No. 21-196), which it sells under the trade name XYREM®. The claims of the patents-in-suit cover, *inter alia*, pharmaceutical compositions containing sodium oxybate, and methods of use and administration of sodium oxybate or pharmaceutical compositions containing sodium oxybate. Jazz Pharmaceuticals owns the patents-in-suit.

15. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the '889, '219, '506, '059, '650, and '275 patents are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to XYREM®.

Acts Giving Rise to This Suit

16. Pursuant to Section 505 of the FFDCA, Amneal filed ANDA No. 203631 ("Amneal's ANDA") seeking approval to engage in the commercial use, manufacture, sale, offer

for sale or importation of 500 mg/mL sodium oxybate oral solution ("Amneal's Proposed Product"), before the patents-in-suit expire.

17. In connection with the filing of its ANDA as described in the preceding paragraph, Amneal has provided a written certification to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Amneal's Paragraph IV Certification"), alleging that the claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Amneal's ANDA.

18. No earlier than December 10, 2012, Jazz Pharmaceuticals received written notice of Amneal's Paragraph IV Certification ("Amneal's Notice Letter") pursuant to 21 U.S.C. § 355(j)(2)(B). Amneal's Notice Letter alleged that the claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Amneal's ANDA. Amneal's Notice Letter also informed Jazz Pharmaceuticals that Amneal seeks approval to market Amneal's Proposed Product before the patents-in-suit expire.

Count I: Infringement of the '431 Patent

19. Plaintiff repeats and realleges the allegations of paragraphs 1-18 as though fully set forth herein.

20. Amneal, through its submission of its Paragraph IV Certification as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '431 patent. Amneal's actions with respect to its ANDA show that there is a substantial controversy, between the parties, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment.

21. Amneal's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution,

prior to the expiration of the '431 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

22. There is a justiciable controversy between the parties hereto as to the infringement of the '431 patent.

23. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe the '431 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States.

24. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of the '431 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '431 patent and knowledge that its acts are encouraging infringement.

25. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe the '431 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes the '431 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

26. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Amneal's infringement of the '431 patent is not enjoined.

27. Jazz Pharmaceuticals does not have an adequate remedy at law.

28. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count II: Infringement of the '889 Patent

29. Plaintiff repeats and realleges the allegations of paragraphs 1-28 as though fully set forth herein.

30. Amneal's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '889 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

31. There is a justiciable controversy between the parties hereto as to the infringement of the '889 patent.

32. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe the '889 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States.

33. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of the '889 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '889 patent and knowledge that its acts are encouraging infringement.

34. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe the '889 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's

Proposed Product is especially adapted for a use that infringes the '889 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

35. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Amneal's infringement of the '889 patent is not enjoined.

36. Jazz Pharmaceuticals does not have an adequate remedy at law.

37. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count III: Infringement of the '219 Patent

38. Plaintiff repeats and realleges the allegations of paragraphs 1-37 as though fully set forth herein.

39. Amneal's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '219 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

40. There is a justiciable controversy between the parties hereto as to the infringement of the '219 patent.

41. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe the '219 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States.

42. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of the '219 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally

encourage acts of direct infringement with knowledge of the '219 patent and knowledge that its acts are encouraging infringement.

43. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe the '219 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes the '219 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

44. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Amneal's infringement of the '219 patent is not enjoined.

45. Jazz Pharmaceuticals does not have an adequate remedy at law.

46. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IV: Infringement of the '506 Patent

47. Plaintiff repeats and realleges the allegations of paragraphs 1-46 as though fully set forth herein.

48. Amneal's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '506 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

49. There is a justiciable controversy between the parties hereto as to the infringement of the '506 patent.

50. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe the '506 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States.

51. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of the '506 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '506 patent and knowledge that its acts are encouraging infringement.

52. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe the '506 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes the '506 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

53. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Amneal's infringement of the '506 patent is not enjoined.

54. Jazz Pharmaceuticals does not have an adequate remedy at law.

55. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count V: Infringement of the '059 Patent

56. Plaintiff repeats and realleges the allegations of paragraphs 1-55 as though fully set forth herein.

57. Amneal's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '059 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

58. There is a justiciable controversy between the parties hereto as to the infringement of the '059 patent.

59. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe the '059 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States.

60. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of the '059 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '059 patent and knowledge that its acts are encouraging infringement.

61. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe the '059 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes the '059 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

62. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Amneal's infringement of the '059 patent is not enjoined.

63. Jazz Pharmaceuticals does not have an adequate remedy at law.

64. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VI: Infringement of the '650 Patent

65. Plaintiff repeats and realleges the allegations of paragraphs 1-64 as though fully set forth herein.

66. Amneal's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '650 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

67. There is a justiciable controversy between the parties hereto as to the infringement of the '650 patent.

68. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe the '650 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States.

69. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of the '650 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '650 patent and knowledge that its acts are encouraging infringement.

70. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe the '650 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On

information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes the '650 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

71. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Amneal's infringement of the '650 patent is not enjoined.

72. Jazz Pharmaceuticals does not have an adequate remedy at law.

73. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VII: Infringement of the '275 Patent

74. Plaintiff repeats and realleges the allegations of paragraphs 1-73 as though fully set forth herein.

75. Amneal's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '275 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

76. There is a justiciable controversy between the parties hereto as to the infringement of the '275 patent.

77. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe the '275 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States.

78. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of the '275 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally

encourage acts of direct infringement with knowledge of the '275 patent and knowledge that its acts are encouraging infringement.

79. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe the '275 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes the '275 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

80. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Amneal's infringement of the '275 patent is not enjoined.

81. Jazz Pharmaceuticals does not have an adequate remedy at law.

82. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff Jazz Pharmaceuticals respectfully requests the following relief:

(A) A Judgment be entered that Amneal has infringed the patents-in-suit by submitting ANDA No. 203631;

(B) A Judgment be entered that Amneal has infringed, and that Amneal's making, using, selling, offering to sell, or importing Amneal's Proposed Product will infringe one or more claims of the patents-in-suit;

(C) An Order that the effective date of FDA approval of ANDA No. 203631 be a date which is not earlier than the later of the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Amneal and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, selling, offering to sell, or importing Amneal's Proposed Product until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(E) A permanent injunction be issued, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Amneal, its officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any methods as claimed in the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit, until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(F) A Declaration that the commercial manufacture, use, importation into the United States, sale, or offer for sale of Amneal's Proposed Product will directly infringe, induce and/or contribute to infringement of the patents-in-suit;

(G) To the extent that Amneal has committed any acts with respect to the compositions and methods claimed in the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), that Plaintiff Jazz Pharmaceuticals be awarded damages for such acts;

(H) If Amneal engages in the commercial manufacture, use, importation into the United States, sale, or offer for sale of Amneal's Proposed Product prior to the expiration of the patents-in-suit, a Judgment awarding damages to Plaintiff Jazz Pharmaceuticals resulting from such infringement, together with interest;

(I) Attorneys' fees in this action as an exceptional case pursuant to 35 U.S.C. § 285;

(J) Costs and expenses in this action; and

(K) Such further and other relief as this Court may deem just and proper.

Dated: January 18, 2012

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CERTIFICATION PURSUANT TO L. CIV. R. 11.2

I hereby certify that the matters captioned, *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, Civil Action No. 10-6108 (ES)(SCM), *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, Civil Action No. 11-660 (ES)(SCM), *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, Civil Action No. 11-2523 (ES)(SCM), *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, Civil Action No. 12-6761 (ES)(SCM), and *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, Civil Action No. 12-7459 (ES)(SCM) are related to the matter in controversy because the matter in controversy involves the same plaintiff and the same patents.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: January 18, 2013

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ORPHAN MEDICAL

May 3, 2001

Advisors and Consultants Staff
Center for Drug Evaluation and Research, ORM
Food and Drug Administration
HFD-21, Room 1093
5630 Fishers Lane
Rockville, MD 20852
Peripheral and Central Nervous System Drugs Advisory Committee,
c/o Dr. Sandra Titus; 301-827-7001

Subject: **Xyrem® (sodium oxybate) oral solution, NDA #21-196**
USER FEE NUMBER 3,814, ORPHAN DESIGNATION NUMBER 94-858

Peripheral and Central Nervous System Drugs Advisory Committee
Briefing Booklet for June 6, 2001 Presentation

Dear Advisory Committee Member:

This briefing booklet presents data for the use of Xyrem for treatment in narcolepsy, a seriously debilitating disease. The disease is lifelong after onset, which usually occurs in the second and third decade of life. Historically, diagnosis takes an average of ten years due to low physician awareness. These factors and disease symptomatology negatively affect patients' education, employment potential and interpersonal relationships for the rest of their lives. Current treatments are unsatisfactory, and although approved therapies for daytime sleepiness exist, no therapies are approved for the auxiliary REM-related symptoms of cataplexy, hypnagogic hallucinations, and sleep paralysis. For these reasons Xyrem represents an important new therapeutic advance to meet an unmet medical need.

Narcolepsy affects an estimated 125,000 individuals in the United States, an incidence that qualifies for orphan drug designation. Excessive daytime sleepiness is diagnostic of this disease, while the REM-related symptoms affect 60-90% of patients. About 25,000 individuals have cataplexy of severity requiring pharmacologic intervention.

Limited patient availability has influenced the size of the database. Xyrem safety, efficacy, pharmacokinetics, abuse pharmacology, scheduling and risk management are summarized in this booklet from over 250 volumes of electronic and paper information which has been submitted to FDA for review.

This NDA was designated a priority by the FDA shortly after submission in recognition of the fact that narcolepsy is serious and debilitating with inadequate therapeutic options, particularly for cataplexy. The compelling medical need of narcoleptic patients for additional therapeutic options is summarized in section 2.

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952-513-6900 • Fax: 952-541-9209 • www.orphan.com

The premise for approval for efficacy is based upon four double-blind controlled clinical trials, two of which were sponsored by the company and two of which were conducted by academics, one in the US and one in the Netherlands. Efficacy is summarized in section 3 of this booklet.

The company has collected data from over 400 patients during the course of its two INDs, including a treatment IND approved by FDA in 1998 (section 4). In addition, an investigator in this country has been treating a small group of patients (N=143) for up to 18 years under his IND. The company has collected information from his database that reflects over 900 patient years of clinical safety data. Information from such a database is not usually available for a new chemical entity. Questions related to this database led to the cancellation of the initial advisory committee review scheduled for March 15th. The company has now addressed these questions and our response is under review by FDA. Overall the safety data set, while not large (604 patients and subjects), supports the safe use of Xyrem for the proposed indication.

The pharmacokinetics and abuse pharmacology are included for completeness in sections 5 and 6 respectively. Also included are sections dealing with scheduling and risk management.

Public health issues related to GHB have been well recognized for over 10 years. FDA took action to remove GHB from the market in 1990 due to public health risks of abuse and its illegal promotion as a 'dietary supplement'. FDA subsequently approached Orphan Medical to develop this compound in narcolepsy in 1994. FDA again took additional action when analogues began to surface over the last 5 years. The scheduling of Xyrem was completed in 2000 following extensive public debate in Congress with advice from FDA, DEA and other stakeholders. A federal law was enacted in 2000 to create a bifurcated schedule for GHB with all illicit use falling under schedule 1 and medical use placed into schedule 3. This law, along with the 2000 World Health Organization expert working committee recommendation for schedule 4, and the HHS recommendation to Congress is included in section 7. Regrettably, these laws do not adequately address promotion of precursor chemicals as abuse alternatives to GHB.

The advisory committee has also been asked to review and discuss the risk management of Xyrem. Risk management refers to minimization of public health issues associated with a pharmaceutical product. There is no evidence that Xyrem has been diverted or used for any purpose but to evaluate its safety and efficacy in treating narcolepsy. We believe that the precautions included in the Company's post-marketing program will constrain in every way possible the risks associated with this medicine while allowing its use by patients to meet their medical needs. These precautions include mechanisms to educate physicians and patients about the proper use of Xyrem, the unique implications of the bifurcated schedule, as well as closed-loop prescription and distribution systems to restrict the opportunity for diversion or misuse. Included with this package of information from Orphan Medical is a short 8-minute video on the prescription process, along with patient and physician education materials (the two binders). The risk of diversion and abuse of Xyrem is further reduced when these post-

marketing processes to which the Company has committed are combined with the scheduling restrictions recommended by FDA and imposed by Public Law 106-172. It should be noted that narcolepsy patients and their physicians are already very familiar with the responsible use of controlled substances since they typically manage symptoms with schedule 2 amphetamine related medications and other medications in schedule 4.

It is an unfortunate fact that illicit GHB substances, not Xyrem, represent a risk to the public health. This risk will neither be increased by approval of Xyrem, nor decreased by denial of approval due to the easy availability of analogues of GHB. While Orphan Medical has no legal responsibility for the illicit use of GHB or its precursor chemicals, we have made a moral and practical commitment to assist the FDA, DEA and other law enforcement and abuse specialists in their efforts to minimize the public health risk of illicit GHB substances.

Sodium oxybate, or gamma hydroxybutyrate, is defined as a new chemical entity since it has never been approved for human use in the United States. Products containing oxybate have been approved in Europe, as an anesthetic since the 1960s, and in Italy for use in treatment of alcoholism since 1994. We believe the data presented herein establish the medical need, efficacy and safety of Xyrem, and provide the basis for our request for approval of the following proposed indication:

> *Xyrem® (sodium oxybate) oral solution is indicated to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy.*

Should you have any questions not addressed in this briefing booklet, please let us know through Dr. Sandra Titus, the Committee's Executive Secretary.

Sincerely yours,

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cc: Russell Katz MD for NDA #21-196

Xyrem® (sodium oxybate) oral solution

NDA #21-196

Briefing Booklet for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting

June 6, 2001

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

SECTION 1
TABLE OF CONTENTS, LIST OF ABBREVIATIONS, AND DEFINITION OF TERMS

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LIST OF ABBREVIATIONS

λ_z	elimination rate constant
5-HT	serotonin
5HIAA	5-hydoxyindolacetic acid
6-OHDA	6-hydroxydopamine
^{14}C	carbon-14
ACh	acetylcholine
NDA	New Drug Application
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AHI	Apnea Hypopnea Index
Alk phos	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ASDA	American Sleep Disorders Association
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{ext}	area under the curve from the time of the last quantified concentration to time infinity
AUC_{inf}	area under the curve from time zero to time infinity
AUC_{last}	area under the curve from time zero to the time of the last quantified concentration
AUC_{SS}	area under the curve at steady-state
A-V	atrioventricular
BDS	bulk drug substance
bpm	beats per minute
BUN	blood urea nitrogen
C	Centigrade/Celsius
C of A	Certificate of Analysis
CAS	Chemical Abstract Services
CBF	cerebral blood flow
CCA	complete cataplexy attacks
CFR	Code of Federal Regulations
CGI-c	Clinical Global Impressions of Change
CGI-s	Clinical Global Impressions of Severity
CHA	cyclohexyladenosine
CL/F	oral plasma clearance divided by absolute bioavailability
Cm	centimeter
C_{max}	observed maximum plasma concentration
CMR_{O2}	cerebral metabolic rate for oxygen
CMR_{glc}	cerebral metabolic rate for glucose
CNS	central nervous system
COSTART	coding symbols for a thesaurus of adverse reactions terms
CRA	Clinical Research Associate
CRF	case report form

CRO	contract research organization
CSF	cerebrospinal fluid
CV	coefficient of variation
CYP2C	cytochrome P450 2C
CYP2C9	cytochrome P450 2C9
CYP2D6	cytochrome P450 2D6
CYP3A	cytochrome P450 3A
CYP3A4	cytochrome P450 3A4
DAGO	(D-Ala^2, *N*-Me-Phe^4, glycinol^5)-enkephalin
DAWN	Drug Abuse Warning Network
DDMAC	division of drug marketing, advertising and communications
DHA	dihydroalprenalol
DOPAC	dihydroxyphenylacetic acid
DP	drug product
DS	drug substance
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	electrocardiogram
ECoG	electrocorticogram
EDS	excessive daytime sleepiness
EEG	electroencephalogram
EMG	electromyogram
ESS	Epworth Sleepiness Scale
ºF	degrees Fahrenheit
F	absolute bioavailability
FDA	Food and Drug Administration
FDP	fructose 1,6 diphosphate
FFTs	first fourier transforms
g, G	gram
G6P	glucose-6-phosphate
g/d	grams per day
GABA	gamma aminobutyric acid
GABA-T	gamma aminobutyric acid transaminase
GBL	gamma butyrolactone
GCP	Good Clinical Practice
GLM	general linear model
GHB	gamma hydroxybutyrate
GMP	Good Manufacturing Practice
GTI	Global Therapeutic Impression of Change
HCT	hematocrit
HGB	hemoglobin
HH	hypnagogic hallucinations
HPLC	high pressure liquid chromatography
hr	hour
HVA	homovanillic acid
HZ	Hertz
ICH	International Conference on Harmonization
ICV	intracerebraventricular

ID	identification
IG	intragastric
IND	investigation new drug
IP	intraperitoneal
IR	infrared
IV, iv	intravenous
IRB	Institutional Review Board
k_a	apparent first-order absorption rate constant
kg	kilogram
KF	Karl Fisher
L	liter
LD50	median lethal dose
LDH	lactate dehydrogenase
ln	natural logarithm
LOQ	limit of quantification
MAO	monoamine oxidase
MABP	mean arterial blood pressure
MAX	maximum
MES	maximal electroshock
mg	milligram
MIN	minimum
MK-801	(+)-5-methyl-10,11-dihydro-5H-dibenzo [a,d] cyclohepten-5,10-imine maleate; dizocilpine
mL, ml	milliliter
mm	millimeter
mm Hg	millimeter of mercury
MSE	mean square error
MSLT	Multiple Sleep Latency Test
MWT	maintenance of wakefulness test
n	number
NA	not available
NADDI	national association of drug diversion investigators
NaGHB	sodium gamma–hydroxybutyric acid (sodium oxybate)
NASOA	National Association of State Controlled Substance Authorities
NCS	not clinically significant
NCS-356	γ-*p*-chlorophenyl-*trans*-4-hydroxycrotonate
NCS-382	6,7,8,9-tetrahydro-5-[*H*]benzocycloheptene-5-ol-4-ylidene acetic acid
ND	not determined
NDTI	national disease and therapeutic index
NIDA	National Institute on Drug Abuse
NMDA	N-methyl-D-aspartate
NOAEL	no adverse-effect level
NREM	nonrapid eye movement
NTP	National Toxicology Program
OMI	Orphan Medical, Inc
PBO	placebo
PL	public law

PO	*per os*, oral
PCA	partial cataplexy attacks
PCP	phencyclidine
PSG	polysomnography
PTH	parathyroid hormone
QA	quality assurance
QC	quality control
QNB	quinuclinidinyl benzylate
RBC	red blood cell
REM	rapid eye movement
SAS	Statistical Analysis System
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SEM	standard error of the mean
SGOT	serum glutamic-oxalacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOREMP	sleep onset REM peroids
SqRt	square root
SSA	succinic semialdehyde
SSR	succinic semialdehyde reductase
SSRI	selective serotonin re-uptake inhibitor
SWS	slow wave sleep
SXB	sodium oxybate
$T_{1/2}$	half-life of terminal phase
TBPS	*t*-butylbicyclophosphorothionate
TCA	tricyclic antidepressant
TST	total sleep time
T_{max}	time to observed maximum plasma concentration from dosing
TNCA	total number of cataplexy attacks
V_Z/F	apparent volume of distribution divided by oral bioavailability
WBC	white blood cell

DEFINITION OF TERMS

Safety for the clinical trials represented in the original NDA, and all subsequent submissions to date, is based on the following criteria set down during the first of the clinical trials represented:

Adverse Experience:
An adverse experience is any pathologic, noxious, or unintended change in anatomical, metabolic or physiologic function as dictated by physical signs, symptoms, and/or laboratory changes occurring in any phase of a clinical trial, whether or not considered related to study medication and whether associated with study medication or placebo. This includes exacerbation of a pre-existing condition or the significant failure of pharmacologic action.

Adverse experience shall be considered synonymous with the term adverse event.

Severity:
The severity of adverse experiences should be rated as mild, moderate, or severe in accordance with the following guidelines:

1. Mild:
   The adverse experience does not interfere with the patient's normal functioning, although it may be an annoyance.

2. Moderate:
   The adverse experience interferes to some extent with normal functions, but it is not hazardous to health; the event may be uncomfortable or cause embarrassment; the event may require discontinuation of drug as well as other counteractive measures.

3. Severe:
   The adverse experience interferes substantially with normal functions and presents a definite hazard to the patient's health. These experiences virtually always require discontinuation of drug and may require counteractive measures.

Causality:
The relationship between the administration of trial medication and an adverse experience is a judgment based the medical information available at the time of the assessment. The information that is usually considered in making this judgment includes but is not limited to the following.

a) The temporal sequence of the adverse experience with the administration of test medication.
b) The known characteristics of the patient/subjects' clinical state, environment, or toxic factors, or other therapy administered to the patient.

c) The disappearance of the adverse experience on cessation of test medication or reduction in dose (dechallenge).
d) The reappearance of the adverse experience on resuming treatment with test medication (rechallenge).
e) The known response pattern of the test medication.

The relationship between trial medication and adverse experiences will be rated using the following guidelines:

1. Definitely Related:
   This category is usually chosen when the connection between administration of test medication and the adverse experience is certain, based on dechallenge and rechallenge or obviousness (e.g., pain at the site of injection).

2. Probably Related:
   This category applies when the connection between administration of test medication and the adverse experience is considered to be over 50% likely.

3. Possibly Related:
   This category applies when the connection between administration of test medication and the adverse experience is considered to be less than 50% likely.

4. Not Related:
   This category applies to those adverse experiences which are clearly due to non-trial medication causes (e.g., disease, environment).

5. Unknown:
   This category applies to those adverse experiences which after careful consideration of all other categories can not be considered definitely related, probably related, possibly related, or not related usually because of inadequate information.

Frequency:
The frequency of an event was initially rated as either
continuous or intermittent. This criteria was later broadened to include the term isolated for events which resolved immediately.

Serious:
A serious adverse experience is defined as an adverse experience wherein the outcome is death, life-threatening, temporarily or permanently disabling, or which results in or prolongs inpatient hospitalization. In addition, an overdose, congenital anomaly, or the occurrence of cancer are considered to be serious adverse experiences.

SECTION 2
MEDICAL NEED

2.0 MEDICAL NEED

2.1 Disease and Pathogenesis

Narcolepsy is among the leading causes of excessive daytime sleepiness (EDS) and is the most common neurological cause (Bassetti 1996). Narcolepsy is now recognized as a prevalent but underdiagnosed neurological disorder (Hubin 1994) that has a socio-economic impact that may be as high as that of epilepsy. The first consensus definition of narcolepsy was produced by the First International Symposium on Narcolepsy, July 1975, in France:

> "A syndrome of unknown origin that is characterized by abnormal sleep tendencies, including excessive daytime sleepiness and often disturbed nocturnal sleep, and pathological manifestations of REM sleep. The REM sleep abnormalities include sleep-onset REM periods and the disassociated REM sleep inhibitory processes, cataplexy and sleep paralysis. EDS and cataplexy and, less often, sleep paralysis and hypnagogic hallucinations are the major symptoms of the disease." (Gulleminault 1976).

Characterized by this descriptive definition, narcolepsy is not just excessive sleep, but rather an inability to maintain either wakefulness or consolidated sleep. Patients are typically excessively sleepy during daytime and insomniacs at night. In addition, narcoleptic patients experience abnormal episodes of REM sleep, such as cataplexy and sleep paralysis representing dissociated manifestations of REM sleep atonia or dream-like hallucinations occurring either in active wake, at sleep onset, or while waking from sleep (Nishino 1997).

Its classic form - narcolepsy with cataplexy - is a distinct neurologic disease with characteristic clinical and paraclinical findings. The definition of the variants of narcolepsy, however, remain a matter of controversy. The International Classification Of Sleep Disorders has defined narcolepsy as:

> "A disorder of unknown etiology, which is characterized by excessive sleepiness that typically is associated with cataplexy and other REM sleep phenomena such as sleep paralysis and hypnagogic hallucinations."

This is the definition adopted by the American Sleep Disorders Association, International Classification of Sleep Disorders, Diagnostic and Coding Manual, Diagnostic Classification Steering Committee, Thorpy MJ (Chairman) 1990.

Thus it remains a purely descriptive disease state in the absence of a defining diagnostic test or investigative measurement and can be a diagnostic challenge in the absence of cataplexy as both EDS and REM phenomena can occur in diseases other than narcolepsy. New information is now emerging as to cause, with the relationship of animal data implicating the hypocretin II receptors to the narcolepsy/cataplexy syndrome in dogs (Lin 1999) and the deficiency of the hypocretin peptide transmitters in a knockout mouse model lacking the hypocretin gene producing abnormalities of sleep control

resembling aspects of narcolepsy (Chemelli 1999). Together these two studies implicate dysfunction of the hypocretin system, or closely related systems, to the pathophysiology of narcolepsy.

Anatomical studies determined that the sources of the hypocretin producing cells were restricted to the hypothalamus and concentrated in the perifornical nucleus and in the dorsal, lateral and posterior hypothalamus. This hypothalamic restriction applies only to the cell bodies and they have widespread neuronal projections to sites centrally related to sleep and arousal. In addition to dense hypothalamic projections, the limbic system, thalamus, subthalamic nucleus, substantia nigra, raphe, locus coeruleus, ventral tegmental area, medullary reticular formation, nucleus of the solitary tract, and other brainstem regions are innervated by these cells (Peyron 1998).

Further pathogenic support for the relationship of the hypocretins and narcolepsy has come from recent discovery of low levels of hypocretin II in the CSF of human narcoleptics (Mignot 2000) and the even more recent discovery of the significant reduction in the number of hypocretin neurons in the brains of narcoleptics (Siegel 2000, Mignot 2000).

Mutations of the hypocretic system may be responsible for some proportion of human narcolepsy cases. However, it is unlikely that most human narcoleptics have a mutation as in the canine model. Most narcoleptics have no narcoleptic relatives, ruling out the autosomal recessive mode of inheritance seen in the dogs. The typical onset of symptoms in the second decade of life or later suggests that damage has occurred to a normally functioning sleep and motor control system. Approximately 75% of the pairs of identical twins examined are discordant for the disease (Partinen 1994) suggesting that environmental factors are critical in the triggering of the disease.

More than 85% of all narcoleptic patients with cataplexy share a specific HLA allele, HLADQB1, 0602, compared with 12% to 38% of the general population (Mignot 1998). Because of the role of HLA gene products in immune regulation, in that most HLA-linked diseases are autoimmune in nature, and because of the possibility of the involvement of environmental triggers, it is speculated that narcolepsy might be an autoimmune disorder. Immune-mediated reduction in the numbers of hypocretin neurons is an exciting new hypothesis requiring research. It is certainly an attractive hypothesis implicating irreversible damage to the hypocretin neurones or to axon terminals as a plausible cause for the disorder. However, there may well be other factors "downstream" of the hypocretin system.

Even though these exciting new discoveries shed some light on the pathogenesis of the disease, treatments remain symptomatic and sodium oxybate provides new potential to favorably modify the debilitating symptom profile that defines narcolepsy.

2.2 History

Although the clinical condition was described as early as 1672 by Willis, by Schindler in 1829, Gélineau gave the first precise description of the disease and coined the term

"narcolepsy" from the Greek meaning "seized by somnolence" in 1880. The term "cataplexy" was proposed in 1902 by Löwenfeld, and confirmed as the clinical term for the loss of muscle tone by Henneberg in 1916.

Hypnagogic hallucinations and sleep paralysis were first linked to narcolepsy in the 1920's (Bassetti 1996).

After World War II, Yoss and Daly (1957) introduced the notion of the narcolepsy "tetrad" – excessive daytime sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis. In its typical form, narcolepsy patients also experience disturbed nocturnal sleep (narcolepsy "pentad") (Nishino 1997).

Shortly after the discovery of REM sleep (Aserinsky and Kleitman 1953) the discovery that narcoleptic patients often begin their night sleep with a period of REM sleep (Vogel 1960) suggested that narcolepsy might involve abnormal REM sleep. In the same year, Rectschaffen (1963) and Takahashi (1963) independently confirmed that narcoleptic patients often have sleep onset REM periods (SOREMP's), and suggested that cataplexy, sleep paralysis and hypnagogic hallucinations were abnormal manifestations of dissociated REM sleep. This led to the generally accepted model that sleep disturbances seen in narcolepsy are divided into the two distinct categories of disturbance in the sleep/wake distribution (EDS/sleep attacks and fragmented nighttime sleep) and abnormal REM sleep related symptoms (cataplexy, hypnagogic hallucinations and sleep paralysis) (Roth 1969, Takahashi 1971). The fact that EDS and abnormal REM sleep are most often treated to date with distinct medications (stimulants for EDS and antidepressants for REM-related phenomena) also adds credence to this concept of a duality in the symptoms of narcolepsy).

2.3 Epidemiology

Narcolepsy is now recognized as a relatively prevalent but underdiagnosed neurological disorder (Hublin 1994). Following Daniel's classic review in 1934 of 147 patients with narcolepsy seen at the Mayo Clinic in Minnesota, the disease was no longer considered rare. In the same clinic, 241 cases were observed over a five year period of 1950-1954 (Yoss and Daly 1957). The exact prevalence remains unknown, with a reported variation from 0.0002% to 0.50% in different populations (Hublin 1994). The estimated prevalence for narcolepsy with cataplexy is 0.03% to 0.07% of the general adult population in whites (Dement 1973, Hublin 1994, Ohayon 1996).

Narcolepsy often remains undiagnosed or misdiagnosed for several years. In part this may occur because physicians may not include narcolepsy in the differential diagnosis of other diseases with complaints or fatigue, tiredness, problems with concentration, attention, memory and performance, and other illnesses (e.g., seizures, hallucinatory states).

Narcolepsy occurs in both sexes equally, and in all races with a lower prevalence suggested in Israeli-Jews (Wilner 1988). Rigorous clinical and paraclinical testing shows that the percentage of "true" familial narcolepsy does not exceed 4% to 7% (Goode

1962, Billiard 1994, Parkes 1985). The risk of children of narcoleptics developing the disease is about 1% (Bassetti 1996).

2.4 Clinical Picture

2.4.1 EXCESSIVE DAYTIME SLEEPINESS (EDS)

By definition, narcolepsy can be diagnosed only in the presence of EDS, although this symptom rarely appears after the onset of other elements of the tetrad. Sleepiness is usually the most disabling symptom. It most typically mimics the feeling of sleep deprivation, but may also manifest itself as chronic tiredness or fatigue (Nishino 1997). Clinically, narcoleptic and physiologic sleepiness (i.e. after sleep deprivation) are similar in character but differ in temporal pattern and severity. In both, transition from wake to sleep is usually gradual, with increased sleep propensity in the afternoons, in situations of boredom or limited physical activity, post-prandial, and in a warm environment. Narcoleptic sleepiness, however, is usually constant, severe and only transiently and partially improved with sleep.

This continuous sleepiness fluctuates in severity and episodically becomes irresistible, with involuntary brief naps, or "sleep attacks" occurring during such unusual circumstances as talking, eating, standing, walking, driving in traffic, or even during intercourse. Honda and colleagues (1988) reported two or more sleep attacks per day in 68% of 170 patients studied. Naps are usually brief, refreshing, easily terminated by external stimuli and, in one third of cases, are associated with dream experiences (Roth 1980). The duration of the naps may be affected by situational rather than pathophysiologic differences.

Variations in the intensity of sleep attacks, the ability to resist sleep, and in the subjective awareness of sleepiness explain the differences in the phenotypical presentation of EDS. Up to 80% of patients experience fluctuations in vigilance lasting from seconds to hours, during which they can perform semipurposeful, complex acts with no recollection. The perception of the transition from wakefulness to sleep may be altered, and short, involuntary episodes of sleep or decreased vigilance (sometimes referred to as blackouts) may be experienced as paroxysmal loss of consciousness (Bassetti 1996).

2.4.2 CATAPLEXY

Cataplexy is defined as a sudden episode of muscle weakness triggered by emotions, most typically laughter, elation and joy but also anger, annoyance, embarrassment, grief, surprise, and even sexual intercourse. It is normally associated with normal consciousness, is bilateral, and lasts less than a few minutes.

Cataplexy is clinically an extremely variable symptom (Gelb 1994), and only certain muscle groups may be involved. Most often it is mild and occurs as a simple buckling of the knees, head dropping, sagging of the jaw or weakness of the arms. Slurred speech or mutism is also frequently associated. In other cases, it escalates to episodes of muscle paralysis and collapse that may last up to a few minutes. Most often the patient

will have time to seek support or sit down. Long episodes of cataplexy occasionally blend into sleep and may be associated with hypnagogic hallucinations. Its duration exceeded twenty minutes in 2% of a series of 130 patients (Honda 1988). Rare episodes lasting longer than thirty minutes, termed status cataplecticus, can be precipitated by the abrupt discontinuation of antidepressant drugs (Hishikawa 1976) and can render the patient virtually helpless.

2.4.3 SLEEP PARALYSIS

Whereas EDS and cataplexy are cardinal symptoms of narcolepsy, sleep paralysis occurs frequently as an isolated phenomenon affecting 5% to 40% of the narcoleptic population (Dahlitz 1993). Sleep paralysis is best described as a brief inability to perform voluntary movements at the onset of sleep, or upon awakening during the night or in the morning. The patient is unable to perform even a small movement, and the episode may last a few minutes. Sleep paralysis is easily interrupted by noise or other external stimuli. It is present in 20% to 50% of narcoleptic subjects. Episodes are more common with stress, with irregular sleep or sleep deprivation, and frequency varies widely from a few life events to almost daily episodes.

2.4.4 HYPNAGOGIC HALLUCINATIONS

Abnormal visual (most often) or auditory perceptions that occur while falling asleep (hypnagogic) or upon waking up (hypnopompic) are observed frequently in narcoleptic subjects (15% to 66%), and in up to 50% of cases, they occur at least once weekly (Honda 1988). Hypnagogic hallucinations are the expression of a changing state of consciousness in which, as opposed to dreaming, elements of the normal awake mentation are still present, and they may involve one or more senses. Unlike psychotic hallucinations, subjects usually are aware of the unreal nature of the hallucination. The intensity and the accompanying fear and anxiety are sometimes the most distressing symptoms of narcolepsy.

2.4.5 OTHER SYMPTOMS

Disrupted nighttime sleep with frequent awakenings is reported by 60% to 80% of patients with narcolepsy (Billard 1985, Montplaisir 1978). Patients often complain of difficulties with concentration, visual disturbances, problems with memory and perceptual disturbances. Frequently associated problems are periodic leg movements, REM behavior disorder, and other parasomnias.

2.5 Evolution of Narcolepsy

Narcolepsy usually starts around adolescence, occasionally very abruptly, but most often insidiously. Its peak onset is in the second decade of life, with a smaller peak in the third decade. A few cases are recognized in a pediatric context, manifesting as early as five to six years of age (Challamel 1994). In most cases, however, the diagnosis of narcolepsy is made several years after the onset of the clinical condition.

Sleepiness is usually the first symptom to appear, followed by cataplexy, hypnagogic hallucinations, and sleep paralysis. In approximately one-half of the cases, the onset of cataplexy is simultaneous with the appearance of daytime somnolence and within five years in approximately two-thirds of the cases (Honda 1988, Roth 1962). The mean time of the onset of sleep paralysis and hypnagogic hallucinations is also two to seven years later than that of sleepiness.

Sleepiness almost invariable persists over time, although a late decline in severity is not rare, and even short remissions are possible. Conversely, cataplexy, sleep paralysis and hypnagogic hallucinations may disappear spontaneously in 16% to 37% of patients (Billiard 1993).

2.6 Psychosocial Impact of Narcolepsy

Despite dynamic progress in the understanding of narcolepsy, the disease continues to cause the sufferer severe negative life effects. Before and after diagnosis, narcoleptics often experience unrelenting severe psychosocial stress, with differing stresses in each decade of life. Child and adolescent narcoleptics report embarrassment, academic decline and feelings of loss of self-worth related to the symptoms of their disease. Personality characteristics may be adopted that seek to avoid social situations that would precipitate cataplexy or draw attention to the patient's degree of somnolence. More than one-half of narcoleptics believed their symptoms caused poor performances at school (Broughton 1981). Teachers often misinterpret early symptoms and the accompanying irritability, frustration and mood swings as laziness, indifference, or even malingering. Hypnagogic hallucinations may lead individuals to question their own sanity and, at times, these occurrences are mistakenly diagnosed as psychotic episodes (Douglass 1991). Although no inherent memory disturbance has been associated with the disease, somnolence and lapses of concentration (possibly micro-sleeps) may explain the commonly reported problems with memory. Misdiagnosis may result in inappropriate treatment and underestimation of an individual's potential. Denial of the condition may further delay their seeking treatment.

Adult narcoleptics face major concerns, particularly in the workplace, and with secure interpersonal relationships. The effects of sleepiness and cataplexy have major effects on personal and public safety. Broughton (1981) examined the effects on driving. Narcoleptics reported marked increases in the following (percent narcoleptics compared to percent of controls):

	Narcoleptics	Controls
Falling asleep while driving	66%	6.2%
Cataplexy while driving	29%	0%
Sleep paralysis while driving	11.5%	0%
Frequent near accidents	67%	0%
Motor vehicle accidents	37%	5.3%
Increased insurance rates	16%	1%
Suspended drivers' licenses	6.l%	3.9%

In the workplace, narcoleptics face not only danger of accidental injury but the reality of poor performance and job loss. In the 1981 Broughton survey narcoleptics reported the following occupational effects attributed to their symptoms.

	Narcoleptics	Controls
Reduced job performance	78%	9%
Fear of losing job	49%	0%
Decreased earnings	47%	1.2%
Actual job loss	21%	0%
Loss of promotion	3.8%	0%
Disability insurance	11%	0%

Accidental injury in narcoleptics also occurs in the home. Smoking accidents due to narcoleptic symptoms were found in 49% of patients, falls 37%, burns from hot objects 15%, cuts from sharp objects 13%, and "breaking things" 10% were reported by Cohen in 1992.

Interpersonal relations also suffer. Poor self-image and social withdrawal have been mentioned. Narcoleptics frequently feel that others view them as lazy or bored. Sleep attacks during conversations can alienate others.

Marital stress is a major problem and has been reported as high as 72% (Kales 1982). Besides interpersonal problems, financial problems resulting from job loss or accidents add external pressure on the marriage. Sexual dysfunction and loss of libido are commonly reported complaints.

A body of data supports the idea that a large number of narcoleptics also carry diagnosable psychiatric disorders, in most cases thought to result from the symptomatology of the disease and its life effects. In a study by Kales et al in 1982, more than 50% of narcoleptics had a diagnosable psychiatric disorder, all assigned as variants of depression and/or personality disorders.

The psychosocial impacts of narcolepsy disease have been thoroughly detailed in a special journal issue edited by Goswani, Polack, Cohen, Thorpy, Kovey: Psychosocial Aspects of Narcolepsy, Loss Grief Care 1992; 5,1-203.

The culmination of the deleterious effects of narcolepsy upon work, education, occupational and household safety, recreation, personality and interpersonal relations were compared with those of epilepsy and the psychosocial impact of narcolepsy was found to be higher in all categories except driving (Broughton 1984). These data support the medical need for effective treatment.

SECTION 3
EFFICACY

3.0 EFFICACY

Overview of efficacy clinical trials: Four controlled and 3 uncontrolled clinical trials have been performed to evaluate the efficacy of Xyrem for the treatment of narcolepsy. These trials are summarized below:

Controlled Trials: 201 patients

- *OMC-GHB-2* – 136 patients
  Placebo, 3.0, 6.0, 9.0 g/d sodium oxybate
- *Scrima Trial* – 20 patients
  Placebo, 50 mg/kg (4.2 g/d) sodium oxybate
- *Lammers Trial* – 25 patients
  Placebo, 60 mg/kg (4.7 g/d) sodium oxybate
- *OMC-SXB-21* – 55 patients
  Placebo, 3.0, 4.5, 6.0, 7.5, and 9.0 g/d sodium oxybate

Uncontrolled Trials: 323 patients

- *OMC-GHB-3* – 117 patients
  3.0, 4.5, 6.0, 7.5, and 9.0 g/d sodium oxybate
- *OMC-SXB-6* – 185 patients
  3.0, 4.5, 6.0, 7.5, and 9.0 g/d sodium oxybate
- *OMC-SXB-20* – 21 patients
  4.5, 6.0, 7.5, and 9.0 g/d sodium oxybate

3.1 Controlled Studies

3.1.1 OMC-GHB-2

In initial discussions with the FDA in 1995, the Agency indicated that adequate prospective studies to ascertain the appropriate therapeutic dose range of sodium oxybate had not been conducted. This trial was designed to provide that information. The study was designed as a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial with three doses of sodium oxybate and placebo in narcoleptic patients meeting specific American Sleep Disorders Association (ASDA) criteria for narcolepsy. The objectives of the trial were to evaluate and compare the efficacy and safety of three doses (3g, 6g and 9g) of sodium oxybate and placebo in the treatment of the symptoms of narcolepsy. A rating of the change in the severity of the patient's narcolepsy symptoms as measured by the Clinical Global Impression of Change was provided by the investigator at the end of the four-week treatment period, compared to the rating of Clinical Global Impression of Severity of Disease at the end of the baseline period.

Patients who completed this study and continued to meet all other entry criteria except for the minimum number of cataplexy attacks, were eligible to enter a long-term, open label study (OMC-GHB-3) if they desired and if the physician responsible for their care concurred.

3.1.1.1 Study Objectives

Primary Objective: To evaluate and compare the efficacy of three doses (3g, 6g, and 9g) of sodium oxybate and placebo in the treatment of the symptoms of narcolepsy.

Secondary Objective: To evaluate and compare the safety of sodium oxybate and placebo when used in a narcoleptic patient population.

3.1.1.2 Investigational Plan

The study was conducted at sixteen centers, and a total of 136 patients were enrolled. The study was divided into five periods as follows:

Table 3.1 Time Periods of OMC-GHB-2 Trial

Screening	Washout	Baseline	Double-blind Treatment			Follow-up
one day to 4 weeks	5-28 days	2 to 3 weeks	4 weeks			3-5 days
Visit 1	Visit 2	Visit 3	Visits			Visit 7
			4	5	6	
Withdrawal of treatment for cataplexy	No treatment for cataplexy		Placebo or GHB 3g, 6g, or 9g			No treatment for cataplexy

Screening Period: Lasted one day to four weeks. For patients taking tricyclic antidepressants (TCAs) or other drugs used to treat cataplexy, these were gradually withdrawn. Patients not on TCAs proceeded directly to the next study period if they met entry criteria. Patients were permitted to continue taking stable doses of stimulant medication throughout the study.

Washout Period: Lasted five to twenty-eight days. This period allowed time to eliminate any clinical effects of TCAs, for rebound cataplexy (cataplexy that with greater frequency and severity than usual) to abate, and to train patients on the use of the diary. The duration of this period was determined by considering the prior anticataplectic medication, and was five times the half-life of that medication, with a minimum of five days for diary training and a maximum of twenty-eight days.

Baseline Period: Lasted two to three weeks. This period was an opportunity to assess the patients' attacks of cataplexy and to establish a stable number of attacks. Eligibility for admission into the double-blind treatment period required patients to report an average of three or more complete and/or partial cataplexy attacks per week, during the last two weeks of the baseline period.

Double-Blind Treatment Period: Lasted four weeks. Eligible patients were randomly assigned to receive each night 3g, 6g, or 9g GHB or placebo in two divided doses. Patients returned approximately every two weeks during this period for assessment of safety and efficacy.

Follow-up Period: A visit for final assessment three to five days after study medication was discontinued.

Entry criteria included adult patients with a diagnosis of narcolepsy, a history of excessive daytime sleepiness and an average of three or more cataplexy attacks per week during the baseline period. Patients with a diagnosis of sleep apnea, women of child bearing potential (unless using an accepted form of birth control), patients taking hypnotics, tranquilizers, or sedating antihistamines, and patients with a history of seizures or head trauma were excluded from the study.

Approximately 104 patients (26 in each of the four treatment groups) were planned to be enrolled in this study. One hundred and thirty-six patients were actually enrolled and randomly assigned to receive four weeks of treatment with study medication. Additional patients were enrolled to ensure that a sufficient number of evaluable patients completed the study. Medication was packaged in foil pouches and mixed with water. One dose was taken at bedtime, and the second dose was taken 2.5 to 4 hours later. A third party dispenser was employed at each site so that the investigator and the study coordinator did not handle the medication and the integrity of the blind was maintained.

The primary efficacy variable was the change from baseline in the total number of cataplexy attacks (complete + partial) recorded by patients on their diary (the change was calculated from baseline): last two weeks before study medication was started in a patient; to endpoint (the last two weeks a patient was on study medication). Other efficacy variables included the number of complete cataplexy attacks, the number of partial cataplexy attacks, changes in daytime sleepiness, changes in the number and duration of inadvertent naps/sleep attacks, changes in the number of awakenings during the night, change in the total amount of sleep, changes in the incidence of hypnagogic hallucinations, changes in the incidence of sleep paralysis, and the clinical global impressions of change.

3.1.1.3 Discussion of Study Design

Patients naïve to GHB were selected. Patients with a history of excessive daytime sleepiness, cataplexy, a current diagnosis of narcolepsy for at least six months according to Criteria A of the American Sleep Disorders Association were included. Patients were excluded if they had a diagnosis of sleep apnea syndrome or any other cause of daytime sleepiness. Patients were excluded if they were taking hypnotics, tranquilizers, antihistamines (except for non-sedating antihistamines), or clonidine at the start of the baseline period. Patients taking tricyclic antidepressants or other medication to treat cataplexy were withdrawn from those treatments gradually. The list of tricyclic antidepressants and other anticataplexy medication included: protriptyline, imipramine, clomipramine, desipramine, viloxazine, fluoxetine, paroxetine, sertraline or other serotonin reuptake inhibitors or other tricyclic or heterocyclic antidepressants. Patients taking anticonvulsants were not eligible to participate in the study. Patients were allowed to continue taking stimulant medication to include amphetamine, methamphetamine, methylphenidate, or pemoline for the treatment of daytime

sleepiness. Patients were advised not to consume alcoholic beverages during the entire course of the trial and also to use caution in the use of any opioid analgesics or skeletal muscle relaxants. Patients were otherwise free of medication for narcolepsy during the trial. The screening, washout, and baseline periods were variable lengths of time, determined by the investigator within defined limits.

A screening period of one day to four weeks was added to the design for safety purposes. The screening period enabled investigators to gradually withdraw patients from tricyclic antidepressants or other anticataplexy medication. These medications are commonly associated with rebound cataplexy on withdrawal. The rebound cataplexy was perceived to be of sufficient magnitude to constitute a safety concern. The importance of having a companion or other support system available during the screening, washout and baseline periods was stressed to each patient. Patients were instructed to begin keeping daily diaries at the screening period in order to train them on its use prior to the baseline period.

A washout period of five to twenty-eight days was added to the design to eliminate any clinical effects of tricyclic antidepressant or other anticataplexy medication prior to baseline. The washout period started when the last dose of a tricyclic antidepressant or other anticataplexy medication was taken by the patient. The length of the washout period was determined by the investigator by considering the pharmacokinetic and pharmacodynamic profile of the tricyclic antidepressant or other anticataplexy medication being used by the patient during the screening. A minimum of five days of washout was required for patients not taking anticataplexy mediation for the purpose of insuring adequate training on the patient diary. The investigators were required to employ a washout period equivalent to a minimum of five times the half-life of the anticataplexy medication in use (for a maximum of twenty days). The investigators were provided with a list of the drugs typically used to treat cataplexy along with their half-lives and a suggested time for washout for each.

A baseline period of two to three weeks enabled the investigator to assess the patient's cataplexy incidence in the absence of anticataplectic medications, and daily dairy recording habits. The patients qualified for admission to the treatment phase by reporting an average $\geq$ three cataplexy attacks per week during the last two weeks of the baseline period.

The treatment period was four weeks in length with a clinic visit at two weeks. The treatment period was confined to four weeks because it was not ethically sound to continue a symptomatic patient randomized to placebo for a longer period. The investigators contacted each patient on the morning following the first dose of test medication to assess the patient's tolerance of the test medicine. Thereafter patients were contacted at least three times weekly for assessments of compliance, diary completion, and adverse events.

After four weeks of treatment the patients were withdrawn from test medication. The appearance of any rebound cataplexy and other adverse events were noted at a follow-up visit scheduled three to five days following the end of treatment visit.

3.1.1.4 Assignment of Patients to Treatment Groups

At Visit 1, all patients were assigned a unique, four-digit, patient identification number in the order they were seen at the clinic. The first two digits identified the site number and the last two digits identified the patient number assigned sequentially starting with 01. At Visit 4, patients who met the entry criteria were sequentially assigned a unique three-digit randomization number in the order they entered treatment. The patients were dispensed medication labeled with the correct assigned randomization.

3.1.1.5 Selection and Timing of Dose

Individual patient treatment, including the dose of sodium oxybate, was determined by random allocation. No provisions were made in the protocol to permit modification of the dosage regimen. Each patient self-administered two doses of their assigned study medication each day. The first dose was taken at bedtime, and the second 2.5 to four hours later. Patients were instructed to use an alarm to insure that they awakened to take the second dose no more than four hours after the first.

3.1.1.6 Concomitant Medications

Patients were not permitted to take any of the following medications at any time during the study: hypnotics, tranquilizers, antihistamines (except nonsedating antihistamines), clonidine, tricyclic antidepressants, serotonin reuptake inhibitors, monoamine oxidase (MAO) inhibitors, tetracyclic antidepressants, or anticonvulsants. Patients were also not permitted to use alcohol during the study and were cautioned on the use of opioid analgesics and skeletal-muscle relaxants. Women of childbearing potential were permitted to use oral contraceptives. Periodic use of over-the-counter and prescription medicines for treatment of colds, flu, allergies, headaches, etc. required careful review by the investigator prior to use.

3.1.1.7 Primary Efficacy Variable

The primary efficacy variable for this study as defined in the protocol was the total number of cataplexy attacks which is the sum of complete and partial cataplexy attacks that occurred. The median of the total number of cataplexy attacks that occurred in each treatment group during the last two weeks of the baseline period was compared with the median number of events that occurred during the last two weeks of the treatment period (endpoint). Other efficacy measures such as daytime sleepiness and improvement in inadvertent naps were measured along with reduction in the number of episodes of cataplexy.

3.1.1.8 Statistical and Analytical Plans

As described in the protocol, the efficacy analyses were done on the intent-to-treat population. The planned analyses called for an analysis of variance on the change from baseline to endpoint including in the model the factors of treatment, site, and their

interaction. The interaction term was then to be removed if found to be not statistically significant. In addition, an analysis of covariance (ANCOVA) was planned for the primary efficacy variable (change in total number of cataplexy attacks) using the baseline value as covariate.

Prior to the completion of the study and database lock, an analysis plan was written and approved that detailed performing a log transformation, if the assumptions for ANCOVA were not satisfied. It was anticipated that for many, if not all, of the efficacy variables, the log transformation would result in a more normal distribution conforming to the requirements of the ANCOVA.

At the time of analysis, each of the primary and secondary efficacy variables was assessed for normality and whether a log transformation would improve the distribution. The reassessment was based on using the Wilk-Shapiro test for normality on the residuals from the fitted model and a plot of the residuals against the predicted response, also from the fitted model. If the untransformed data indicated a non-normal distribution, based on the Wilk-Shapiro test, and if the transformed data demonstrated improvement (tending toward a more normal distribution) through both the Wilk-Shapiro test and the plot of the residuals against the predicted, the log transformation was used. Those measures that were analyzed using the log transformation included the following:

- Total number of cataplexy attacks
- Partial cataplexy attacks
- Complete cataplexy attacks
- Duration of inadvertent naps/sleep attacks/day
- Sleep paralysis (episodes/day)
- Hypnagogic hallucinations
- Number of awakenings

For each of these measures, because a 0 was possible, the value 1 was added prior to the log transformation. As a result, the variable analyzed was log (endpoint + 1) – log (baseline + 1). The ANCOVA model used to assess overall treatment group comparisons included treatment, site, and log (baseline + 1). The interaction of treatment and site and treatment with log (baseline + 1) were included in the model and then removed when found to be not statistically significant. Comparisons of GHB dose to placebo were performed using least-squares means with Dunnett's adjustment. The significance of the median change from baseline for each treatment group was assessed using a paired t-test.

Several measures did show a normal distribution without a log transformation. They included:

- Epworth Sleepiness Scale
- Total amount of sleep/night
- Number of inadvertent naps/day

For these variables, the analysis procedures were consistent with those previously described, but were based on the untransformed values.

The Clinical Global Impressions of Change (CGI-c) was assessed by correlation analysis using Cochran-Mantel-Haenszel Test for Nonzero Correlation between the CGI-c score and treatment.

3.1.1.9 Determination of Sample Size

The required sample size for this study was calculated using the change from baseline in the total number of cataplexy attacks (primary efficacy variable) occurring in one week. Previous studies suggested than can effective dose of sodium oxybate would produce a mean reduction of at least 2 cataplexy attacks, based upon the number per week at baseline, in the number of weekly attacks with a standard deviation of 2.5. Using a power of 80% and a two-sided significance level of 0.05, 100 patients were needed, 25 per treatment group, to detect a treatment group difference of 2 with respect to change in cataplexy attacks.

3.1.1.10 Disposition of Patients

One hundred and thirty-six patients were enrolled in the study from sixteen centers, and sixteen patients withdrew from the study before completion, for the reasons shown in Table 3.2.

Table 3.2 Disposition of Patients

			Xyrem dose (g)		
Disposition	**All patients**	**Placebo**	**3**	**6**	**9**
Received study medication	136	34	34	33	35
Withdrew from study					
Adverse event	10	1	1	2	6
Protocol deviation	1		1		
Patient request	2		1		1
Lost to follow-up	1			1	
Lack of efficacy	2		1	1	
Total withdrawals	16	1	4	4	7
Completed the study	120	33	30	29	28

The primary reason for withdrawal from the study was the development of adverse events (10 patients). Patient withdrawals for adverse events were more frequent in the 9g GHB dose group than in the other three treatment groups. Patients who withdrew

from the study were followed until adverse events or laboratory abnormalities resolved or were fully characterized.

3.1.1.11 Data Sets Analyzed

Since the analysis performed in this study was an intent-to-treat analysis, no patients were excluded from the analysis.

3.1.1.12 Demographic and Other Baseline Characteristics

The demographic characteristics of the 136 patients who received study medication are summarized in Table 3.3.

Table 3.3 Demographic Characteristics of Study Population

			Xyrem dose (g)			
Characteristic	**All Patients**	**Placebo**	**3**	**6**	**9**	**p-value***
Age						0.2737
n	136	34	34	33	35	
mean (years)	43.06	40.82	47.06	43.52	43.91	
SD	15.03	14.33	16.89	14.98	13.53	
Gender						0.0027
Male	57	12	7	21	17	
Female	79	22	27	12	18	
Race						0.1379
Caucasian	124	29	33	31	31	
African American	9	4	0	1	4	
Asian	1	0	0	1	0	
Other	2	1	1	0	0	
Height						0.0283
N	131	31	33	33	34	
mean (cm)	170.91	171.97	166.7	173.1	171.9	
SD	9.53	8.18	8.78	10.39	9.64	
Weight						0.4847
N	134	34	33	33	34	
mean (kg)	82.87	83.98	78.86	85.04	83.56	
SD	17.36	18.89	15.65	15.54	19.08	

*p-value based on ANOVA (GLM)

Significant between group differences in gender and height were noted. The 6g GHB group was predominantly male, while the placebo and 3g GHB groups were predominantly female. Consistent with the large difference in distribution of males and females in the 3g GHB group, the height of this group was less than the other treatment groups.

The severity of narcolepsy in the patient population was assessed by documenting the historical frequency of symptoms that were reported in the three months prior to screening.

Table 3.4 summarizes the narcolepsy symptom profile recorded in the patient diaries during the last two weeks of baseline, representing narcolepsy symptoms in the absence of anticataplectic or sedative/hypnotic medications, but with continued stable stimulant medication.

Table 3.4 Summary of Baseline (Visit 4) Narcolepsy Symptoms by Treatment Group

		Xyrem Dose (g)			
Type of event	**Placebo**	**3**	**6**	**9**	**p-value Kruskal-Wallis**
Total cataplexy attacks/week					0.7749
N	34	33	33	35	
Mean	34.27	28.57	38.85	34.60	
Median	20.21	20.00	23.00	23.50	
SD	46.63	30.53	55.04	33.92	
Complete cataplexy attacks/week					0.5151
N	34	33	33	35	
Mean	6.86	7.08	15.26	8.61	
Median	1.12	4.50	4.85	2.00	
SD	12.37	8.50	27.53	14.01	
Partial cataplexy attacks/week					0.7289
N	34	33	33	35	
Mean	27.44	21.49	23.59	26.12	
Median	15.03	15.00	16.15	18.79	
SD	42.08	28.30	29.01	26.14	
Hypnagogic hallucinations/day					0.9766
N	34	33	33	34	
Mean	0.57	0.58	1.14	0.53	
Median	0.23	0.43	0.33	0.29	
SD	0.74	0.68	3.72	0.70	
Sleep paralysis episodes/day					0.9597
N	34	33	33	35	
Mean	0.51	0.42	0.73	0.41	
Median	0.26	0.14	0.08	0.10	
SD	0.74	0.55	1.84	0.60	
Inadvertent naps/day					0.7008
N	34	33	33	35	
Mean	1.71	1.91	1.70	1.72	
Median	1.57	1.93	1.45	1.27	
SD	0.96	1.43	1.12	1.56	

3.1.1.13 Excessive Daytime Sleepiness

Daytime sleepiness was the subjective assessment of a patient's ability to remain alert and awake. Excessive daytime sleepiness was defined as difficulty remaining awake and was usually accompanied by rapid entrance into sleep when the patient was sedentary. This variable was assessed through the use of the Epworth Sleepiness Scale (ESS). The ESS is a subjective report of propensity to sleep, difficulty in maintaining an alert awake state, usually accompanied by a rapid entrance into sleep when the person is sedentary. The ESS was used at the end of baseline (Visit 4), at the end-of-treatment (Visit 6), and again at the last follow-up visit (Visit 7). Patients were to rate their "chance of dozing" on a scale of 0-3 (never, slight, moderate, and high chance of dozing) in each of eight possible situations:

- Sitting and reading
- Watching TV
- Sitting, inactive in a public place (i.e. a theater or a meeting)
- As a passenger in a car for an hour without a break
- Lying down to rest in the afternoon when circumstances permit
- Sitting talking to someone
- Sitting quietly after lunch without alcohol
- In a car, while stopped for a few minutes in traffic

The ESS measures sleep propensity based on the retrospective report of the subject's dozing behavior in eight everyday situations. This brief, self-administered questionnaire asks that the subject rate the chances that over the recent past (i.e. since the last prior rating) whether he or she would have dozed in each of the eight situations. The relative soporific nature of these situations has been described both for "sleepy patients" and a normal population of medical studies and are known to remain stable within individuals over a period of months (Johns 1991). The ESS score is the sum of eight individual item scores and ranges from 0 to 24. In one study ESS scores for narcoleptics averaged 16.8, general sleep disorder patients averaged 10.2, and healthy medical studies averaged 7.4 to 7.6 (Johns 1991).

Excessive daytime sleepiness at baseline as assessed by the Epworth Sleepiness Scale is presented in Table 3.5. This mean Epworth score can be considered in the moderately severe to markedly severe range, in spite of maintained stable stimulant medication.

Table 3.5 Summary of Excessive Daytime Sleepiness at Baseline as Assessed by the Epworth Sleepiness Scale

		Xyrem Dose (g)		
Statistic	**Placebo**	**3**	**6**	**9**
N	34	34	32	35
Mean	18.47	17.06	17.28	16.66
SD	3.13	3.71	3.49	4.07

3.1.1.14 Clinical Global Impression of Severity (CGI-S)

This parameter was the investigator's assessment of the severity of a patient's narcolepsy and was recorded at Visit 4. It was made in relation to the investigator's total experience with the narcoleptic population using the following assessments:

- Not assessed
- Normal – no signs of illness
- Borderline ill
- Slightly ill
- Moderately ill
- Markedly ill
- Among the most extremely ill

The CGI-severity score is an expert clinical measure of the patient's general condition at baseline. The majority of patients were judged to be markedly or extremely ill, followed by those who were judged moderately ill and with much fewer patients in the borderline, slightly, or normal categories as seen in Table 3.6 below. There were no significant differences in the percentage of patients enrolled in any severity response category. Subsequent changes from the baseline CGIs score are captured in the Clinical Global Impression of change (CGI-c) score.

Table 3.6 Baseline Clinical Global Impression of Severity (CGI-S)

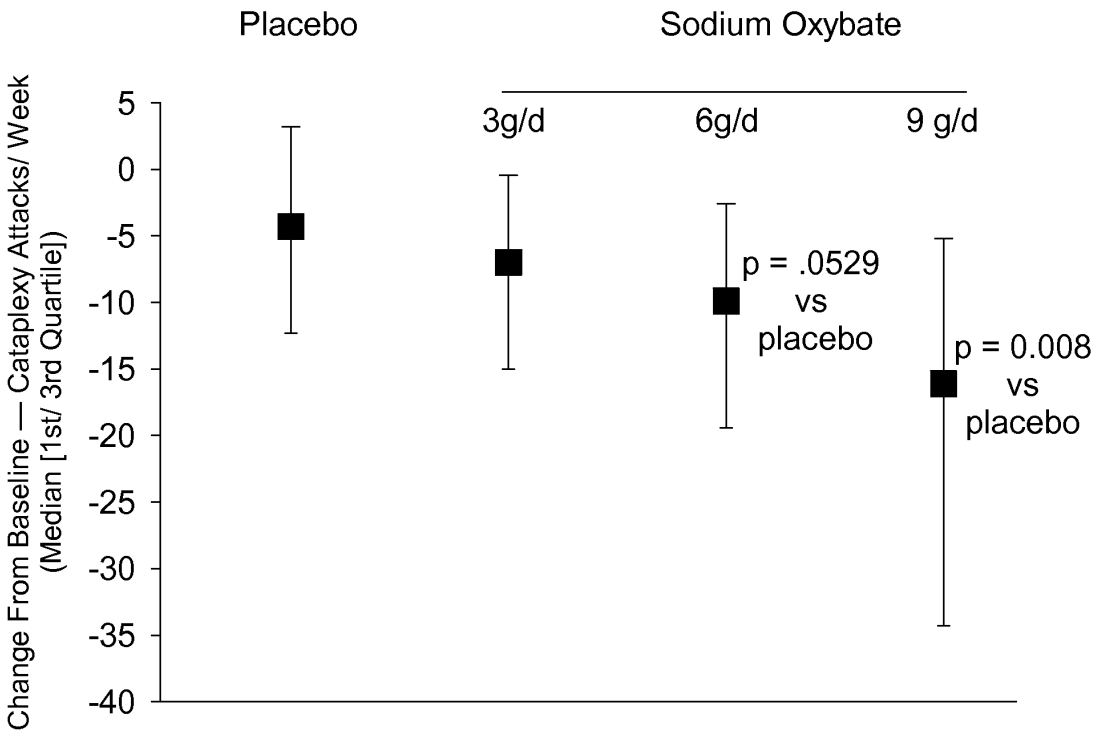
Treatment	Normal	Borderline	Slightly ill	Moderately ill	Markedly ill	Extremely ill
Placebo	0	2	2	8	12	10
3g Xyrem	0	1	1	11	17	4
6g Xyrem	1	1	0	14	11	6
9g Xyrem	0	1	2	13	15	4
Total	1	5	5	46	55	24

3.1.1.15 Analysis of Efficacy

3.1.1.15.1 Primary Efficacy Variable

The primary efficacy variable was the change from baseline in the total number of cataplexy attacks. As shown in Table 3.7, the median and mean values for total cataplexy attacks/week were noted to be similar across dose groups. As noted in Table 3.7, there was a significant (p=0.0021) difference among treatment groups in change from baseline to endpoint in total number of cataplexy attacks/week with treatment. The change in total number of cataplexy attacks exceeded placebo, and was in the clinically meaningful range in all Xyrem treatment groups (Table 3.7 and Figure 3.1). Like most neuropharmacology studies, there was also considerable placebo response, potentially in part the consequence of the disciplined sleep hygiene imposed by the protocol and diary recording of sleep habits during the treatment period. As a result, the difference between Xyrem treatment groups compared to placebo response showed marginal significance in the 6g Xyrem group (p=0.0529), and unambiguous statistical significance in the 9g Xyrem group (p=0.0008).

Figure 3.1 Changes in Total Number of Cataplexy Attacks (Baseline to Endpoint) — OMC-GHB-2



However, these results still indicate an important clinical response to the three dosages of sodium oxybate. The median frequency of cataplectic events at the end of four weeks of treatment shows similarity in the three dosage groups (3 g/day = 9.5, 6 g/day = 8, 9 g/day 8.7), all of which differ markedly from the median placebo response of 16.3 (see Table 3.7).

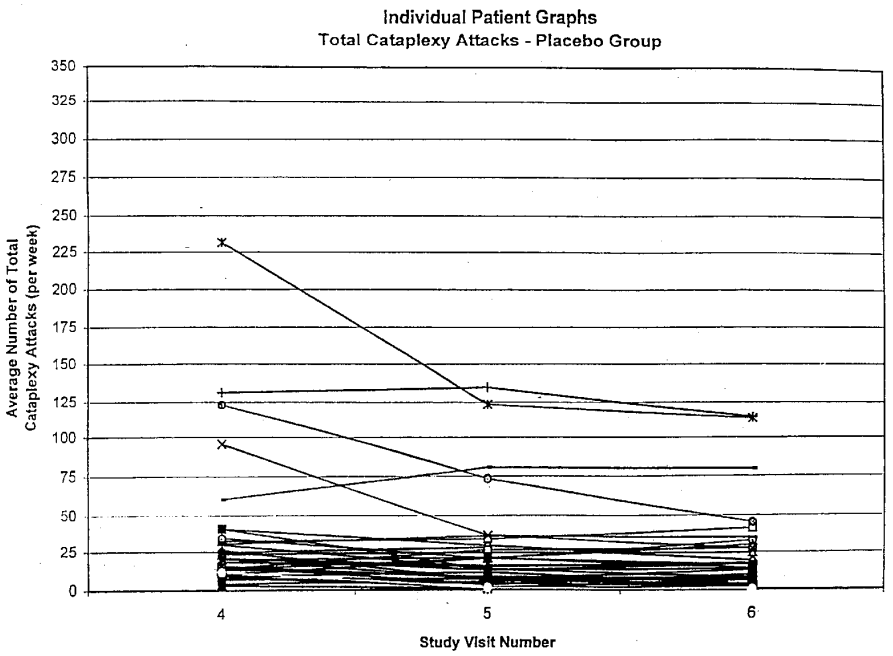
Table 3.7 Total Number of Cataplexy Attacks

Dose group	Statistic	Observed		Change from baseline to endpoint	Comparison with placebo (p-value)
		Baseline	Endpoint		
Placebo	N	33	33	33	
	Mean	35.1	24.0	-11.1	
	Median	20.5	16.3	-4.3	
	SD	47.1	28.4	27.7	
	p-value			0.028	
3g	N	33	33	33	
	Mean	28.6	19.5	-9.1	
	Median	20.0	9.5	-7.0	0.5235
	SD	30.5	27.5	22.4	
	p-value			0.026	
6g	N	31	31	31	
	Mean	33.8	24.6	-9.2	
	Median	23.0	8.0	-9.9	0.0529
	SD	45.6	62.9	27.3	
	p-value			0.070	
9g	N	33	33	33	
	Mean	35.7	14.4	-21.3	
	Median	23.5	8.7	-16.1	0.0008
	SD	34.5	19.3	29.8	
	p-value			<0.001	

P=0.0021 for overall treatment group comparison

Interpretation of this data clinically is complicated by the fact that frequency of cataplexy attacks in this trial is not normally distributed data (incidence ranging from 2.8 cataplexy attacks/week to 249/week at baseline, with a median frequency of 21.0/week). When plots of individual patient data are considered it is possible that outlier data such as one patient in the 6 g dosage group may have represented ongoing REM rebound phenomena, directly affecting statistical interpretations. The consideration of these individual patient responses in the spaghetti plots (Figures 3.2, 3.3, 3.4, and 3.5) indicated the dose response in all dosage groups.

Figure 3.2



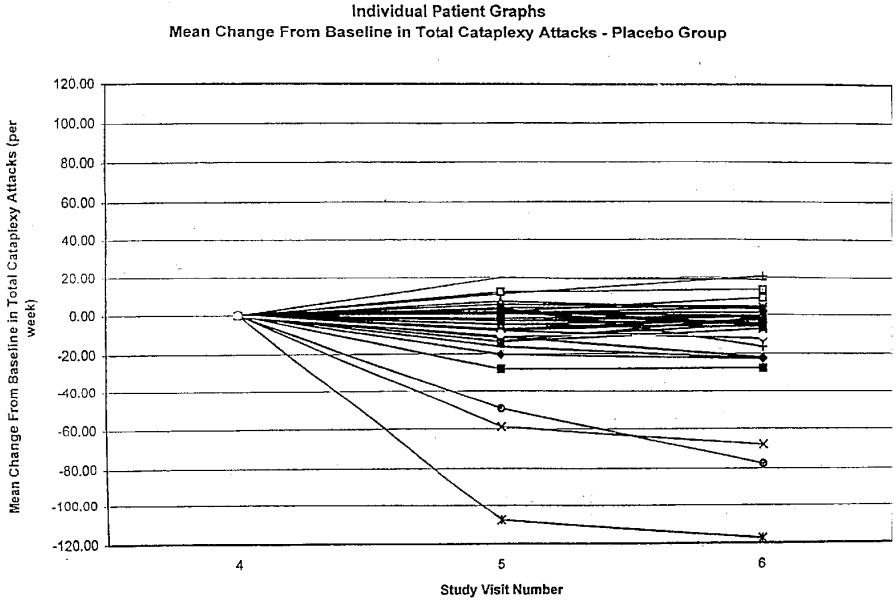
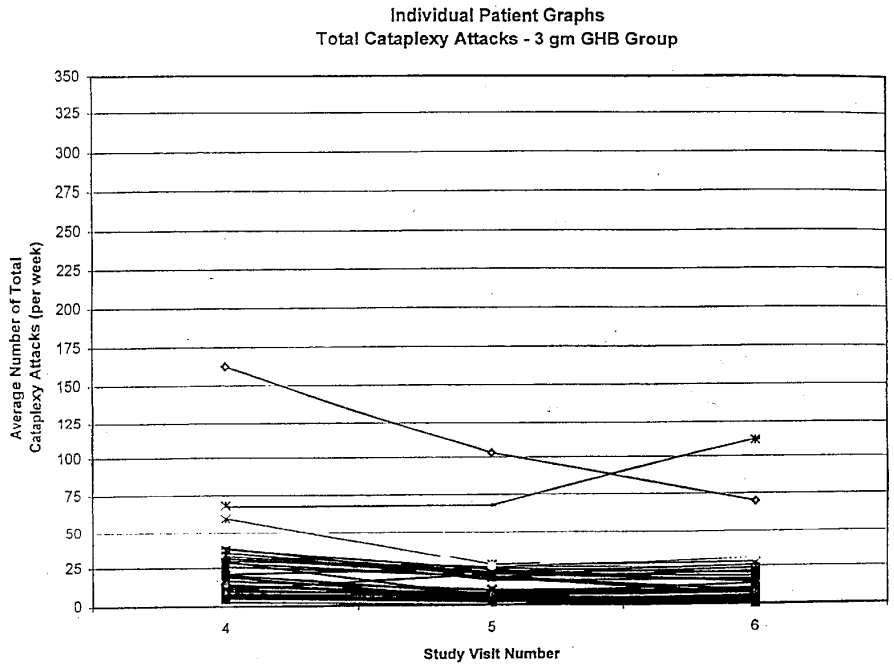


Figure 3.3



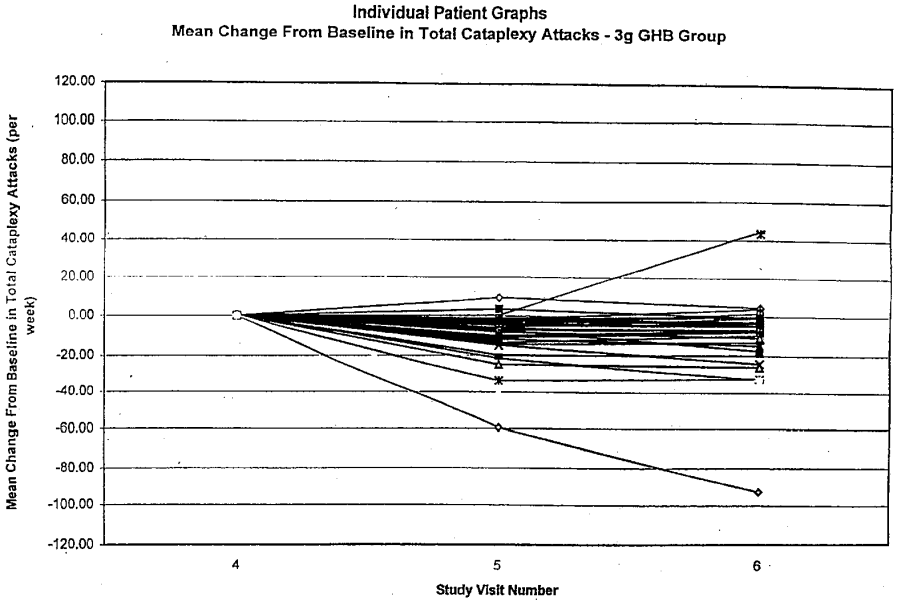
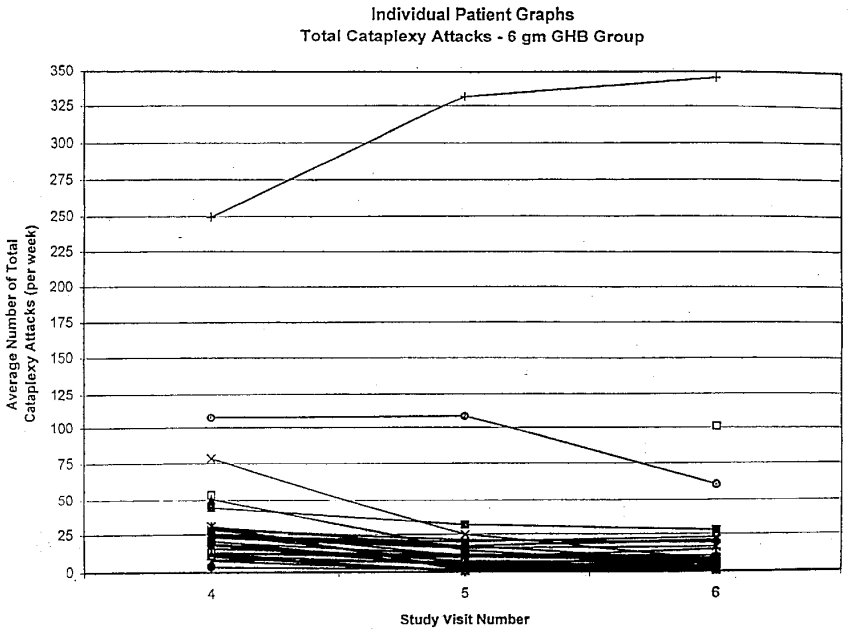


Figure 3.4



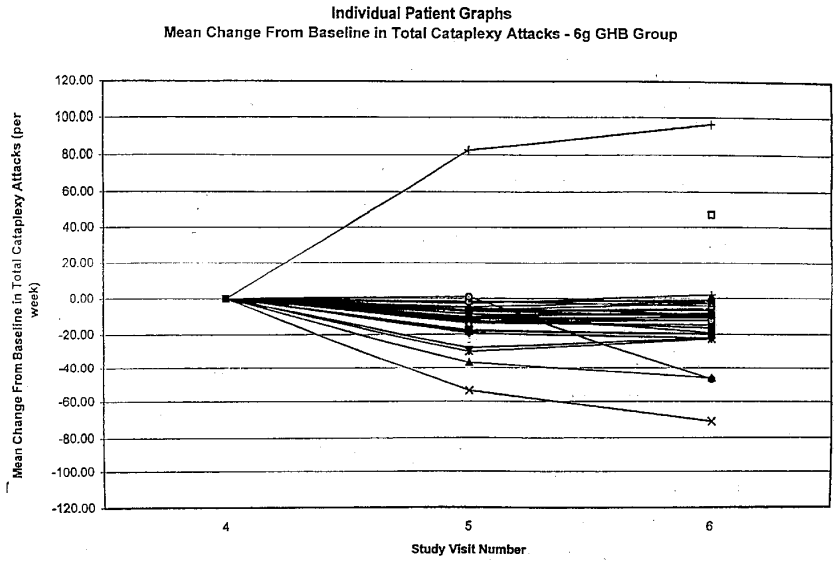
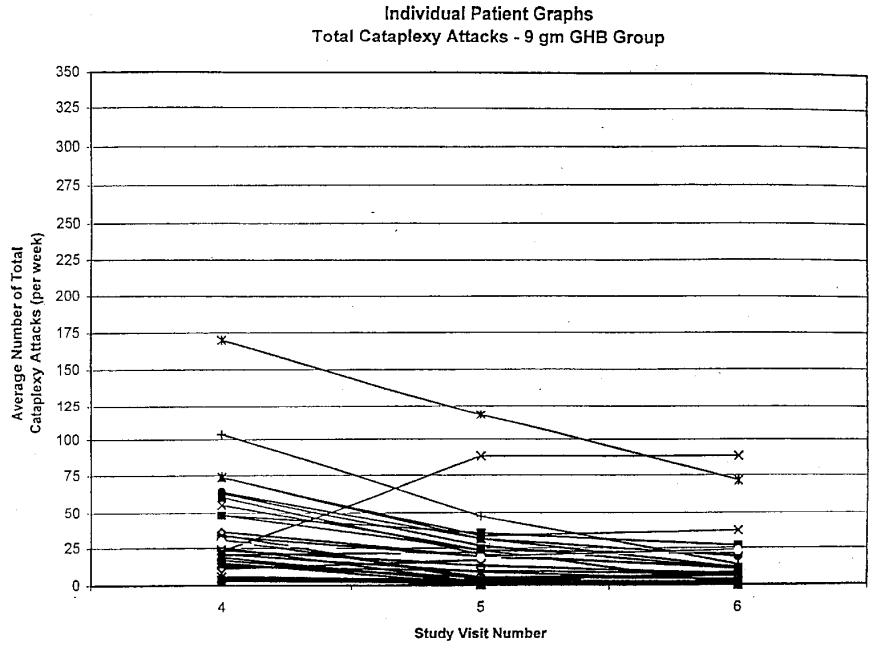
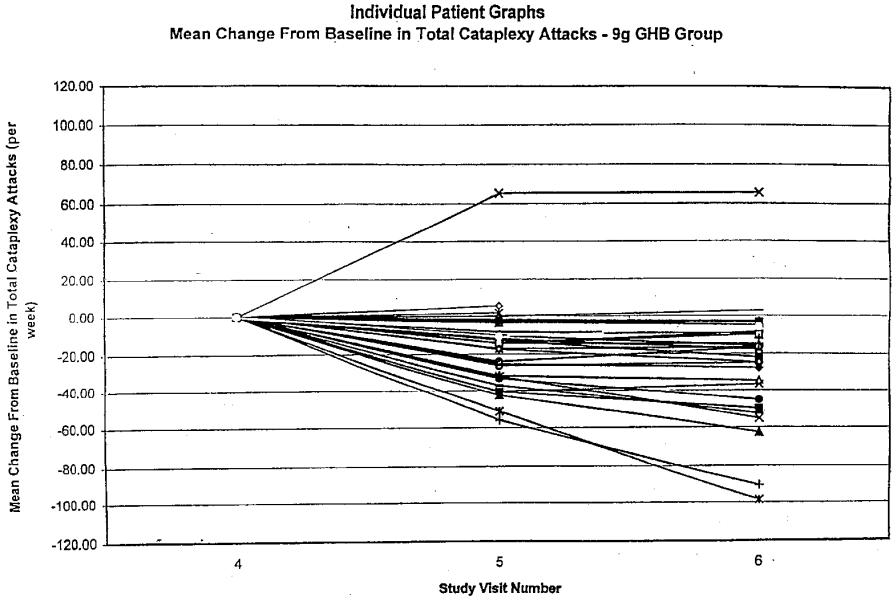


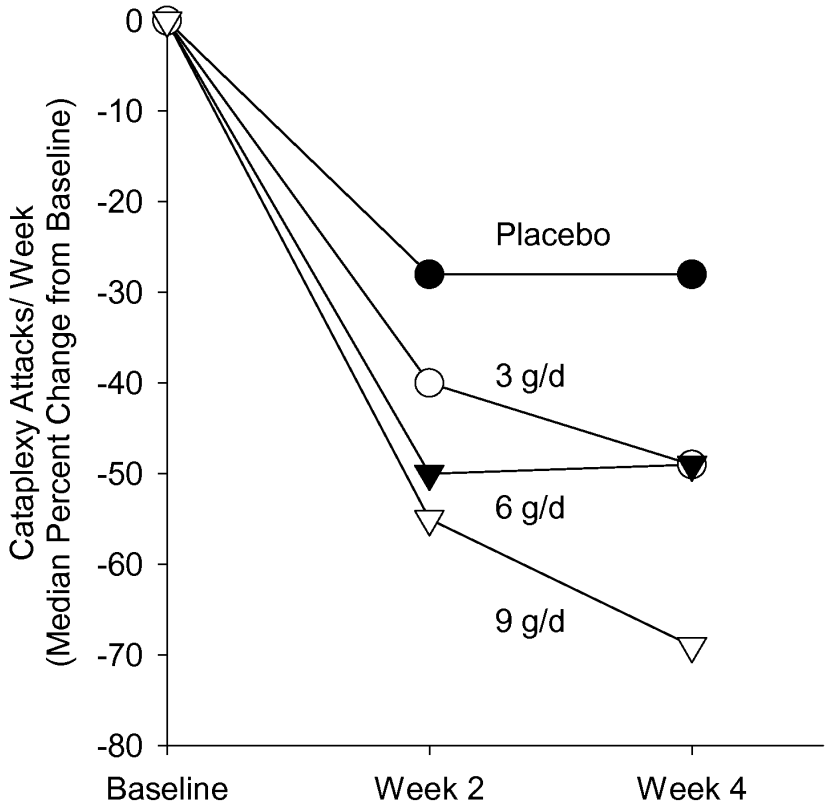
Figure 3.5





In Figure 3.6, the percentage change in the total number of cataplexy attacks from baseline (median) was calculated on the distribution of change values for each individual patient at baseline, two weeks, and four weeks of treatment. This indicates that with the exception of the 9g treatment group, the majority of the reduction in cataplexy attacks occurred during the first two weeks of treatment, as is also represented by the previous graphs of individual patients.

Figure 3.6 Changes in Number of Cataplexy Attacks by Dosage Group Over Time — OMC-GHB-2



3.1.1.15.2 Secondary Efficacy Variables

3.1.1.15.2.1 Complete Cataplexy Attacks

As shown in Table 3.7, at baseline the median number of complete cataplexy attacks was 1.2, 4.5, 4.7, and 2.0 in the placebo, 3g, 6g and 9g treatment groups respectively. Complete cataplexy attacks were much less frequent than partial cataplexy attacks although clinically they are particularly dangerous. At endpoint the median number of complete cataplexy attacks changed by 0, -1.00, -1.62, and –1.62 in the placebo, 3g, 6g and 9g treatment groups respectively. While there appears to be a dose response, none of the decreases reached statistical significance when compared to placebo, although the pattern of changes were in a dose response manner.

3.1.1.15.2.2 Partial Cataplexy Attacks

Also shown in Table 3.7, at baseline the median number of partial cataplexy attacks was 15.05, 15.00, 15.15, and 18.79 in the place, 3g, 6g and 9g treatment groups respectively. From baseline to endpoint the median number of partial cataplexy attacks changed by –2.72, -3.69, -6.35, and –10.00 in the placebo, 3g, 6g, and 9g treatment groups respectively exhibiting a dose response relationship that was statistically significant from placebo at 9g (p=0.0009). Hence the patterns of change were similar in complete and partial cataplexy attacks although the much more frequent partial cataplexy attacks were statistically more powerful in showing the dose response.

3.1.1.15.2.3 Clinical Global Impression of Change (CGI-c)

The Clinical Global Impression of Change was an integrated clinical measure based on the investigator's overall impression of the change in the patient's condition. This measure was based on comparison of the patient's condition at the time of a comprehensive baseline interview defining the severity of patient illness at the time of entry into the study captured in the Clinical Global Impression of Severity (CGI-s). The CGI-c focused on overall clinical change in severity including all narcolepsy symptoms and effectiveness in activities of daily living and incorporating any problems in overall functioning deriving from adverse experiences.

During Visit 6 (the last treatment visit) and Visit 7, investigators rated their impressions of any change in the severity of the patient's overall condition of narcolepsy using the CGI-c rating scale as follows:

- Very much improved
- Much improved
- Minimally improved
- No change
- Minimally worse
- Much worse
- Very much worse

As shown in Table 3.8 and Figure 3.7 below, a highly significant treatment effect was noted on the CGI-c scale. The majority of placebo patients were observed to have a modal value of *no change*, with 35% *no change*. The placebo population distributed mainly into the *no change*, *minimally improved* and *much improved* brackets with the population distribution weighted to the *no change/minimally improved* group. The majority of placebo patients fell in the combined *no change/minimally improved* brackets. A similar distribution was noted in the 3g group although with higher proportions in the *minimally improved* and *much improved* groups and a model value at the *much improved* group and half the patients in the *no change/minimally improved* brackets. In the 6g dose group, the distribution is seen to have shifted upwards with fewer *no change* and more *very much improved* patients and a majority of patients in the *minimally improved/much improved* brackets. In the 9g dose group a marked shift of distribution is seen with a large majority of patients in the *much improved* (43%) and *very much improved* (37%) brackets. Hence a global clinical assessment measure incorporating all aspects of the patient's disease strongly demonstrates the dose response trend to Xyrem.

Table 3.8 Summary of Clinical Global Impression of Change at Endpoint by Treatment Group

		Xyrem Dose (g)		
Impression	**Placebo**	**3**	**6**	**9**
Very much improved	3 (9%)	3 (10%)	5 (16%)	11 (37%)
Much improved	8 (24%)	11 (37%)	11 (35%)	13 (43%)
Minimally improved	8 (24%)	9 (30%)	9 (29%)	3 (10%)
No change	12 (35%)	6 (20%)	5 (16%)	1 (3%)
Minimally worse	0	0	0	0
Very much worse	1 (3%)	0	1 (3%)	0

P=0.0010 for overall treatment group comparison based on Cochran-Mantel-Haenzel Test for Nonzero Correlation

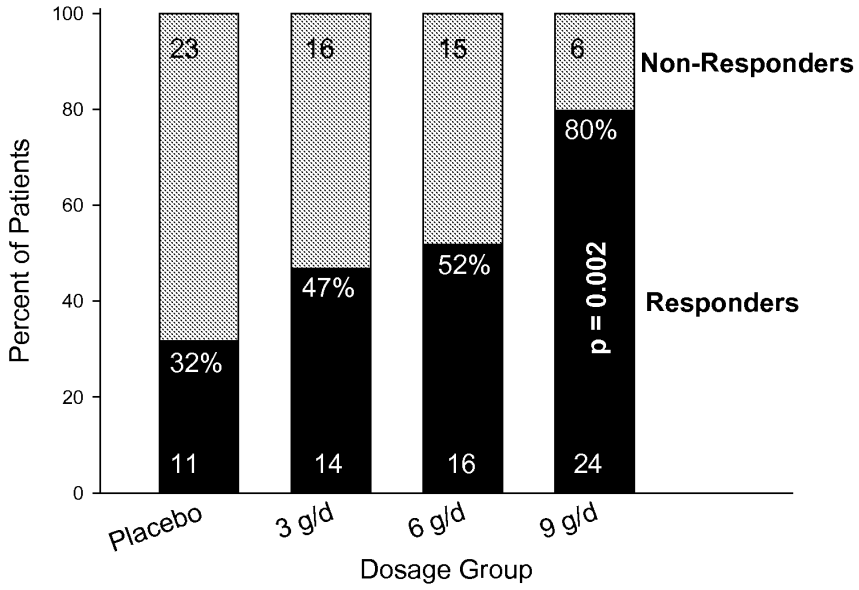
The CGI-c data can also be viewed in another manner as defining a responder analysis (see Table 3.9 and Figure 3.7). Given that the majority of placebo patients fall into the *no change/minimally improved* brackets, a responder was defined as a patient falling into the *much improved* or *very much improved* category. This responder definition also has the virtue of defining patients who, on face value, showed a clear clinical benefit since an experienced clinician rated them as *much improved* or *very much improved*. For this post hoc analysis, responders included the *very much improved* or *much improved* categories; and nonresponder included all other categories of CGI-c except not assessed. Patients not assessed or with missing CGI-c scores were not included in Table 3.9.

Table 3.9 Summary of Clinical Global Impression of Change to Endpoint by Treatment Group for Responders and Nonresponders

		Xyrem Dose (g)			
Category	**Placebo**	**3**	**6**	**9**	**p-value* (overall comparison)**
Responders	11 (32%)	14 (47%)	16 (52%)	24 (80%)	0.0014
Nonresponders	23 (68%)	16 (53%)	15 (48%)	6 (20%)	
p-value (group vs placebo)		0.3075	0.1368	0.0002	

*Based on Fisher's Exact Test

Figure 3.7 Summary of CGIc at Endpoint by Treatment Group — OMC-GHB-2



In Figure 3.7 the percentage of responders improved across the treatment groups in a dose response manner with a particularly sharp improvement to 80% in the 9g group (p=0.0002) as compared to 32% in the placebo group.

This post hoc responder analysis detects the same dose response trend evident in the inspection of the categorical analysis of the patients seen in Table 3.9.

3.1.1.15.2.4 Excessive Daytime Sleepiness

The Epworth data provide another independent confirmation of the dose response of narcoleptic symptoms to Xyrem. The Epworth Sleepiness Scale draws on the patient's subjective assessment of their propensity to fall asleep in different circumstances. As presented in Table 3.10, Figure 3.8 below, excessive daytime sleepiness as assessed by the Epworth Sleepiness Scale improved in all Xyrem treated groups and the improvement compared with placebo was highly significant in the 9g group (p=0.0001) where the change from baseline was nearly twice that seen in the 3g and 6g groups.

Figure 3.8 Daytime Sleepiness (Baseline to Endpoint)

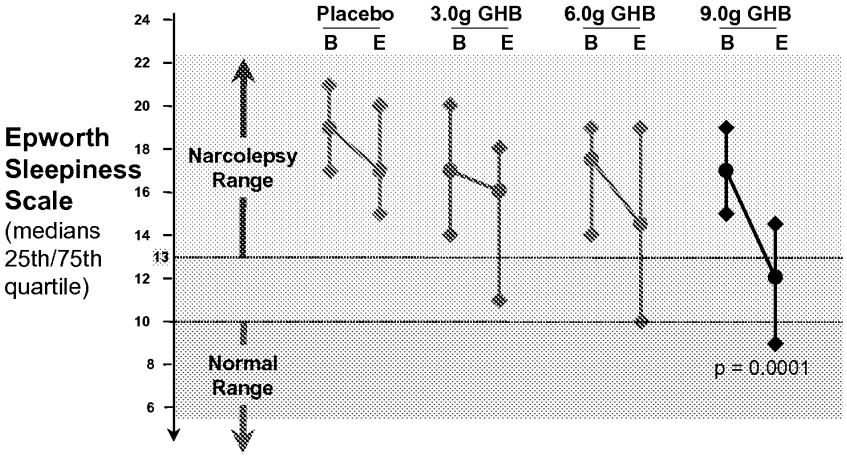


Table 3.10 Summary of Changes from Baseline to Endpoint in Excessive Daytime Sleepiness as Assessed by Epworth Sleepiness Scale

Dose group	Statistic	Observed		Change from baseline to endpoint	Comparison with placebo (p-value)
		Baseline	Endpoint		
Placebo	N	33	31	33	
	Mean	18.4	17.3	-1.1	
	Median	19.0	17.0	-1.0	
	SD	3.2	3.6	3.1	
	p-value			0.043	
3g	N	31	31	31	
	Mean	17.1	14.6	-2.5	
	Median	17.0	16	-1.0	0.1137
	SD	3.7	5.2	3.8	
	p-value			0.001	
6g	N	30	30	30	
	Mean	16.9	14.6	-2.4	
	Median	17.0	13.5	-2.0	0.1860
	SD	3.3	4.6	3.5	
	p-value			0.001	
9g	N	28	28	28	
	Mean	16.4	11.8	-4.7	
	Median	17.0	12.0	-3.5	0.0001
	SD	3.9	4.2	4.3	
	p-value			<0.001	

P= 0.006 for overall treatment group comparison

The reduction in ESS from baseline to endpoint was observed in all treatment groups, with again a dose-response trend as with cataplexy response. This change reached statistical significance (p=0.0001) in patients in the 9g/day dosage group compared to placebo. The first and second quartile lines represent that some patients in all three treatment groups have reduced ESS scores to the extent that they no longer reach the level considered characteristic of narcolepsy (13 to 24; Johns 1991). The median score in the 9g/day dosage group was outside the narcoleptic range, and over 25% of these patients had scores that were within the "normal" range (≤ 10), indicating a highly clinically significant reduction in patients' subjective rating of somnolence, and this change was incremental beyond the status achieved with stable dosages of stimulant medications continued during the trial.

3.1.1.15.3 Other Secondary Efficacy Measures

As presented in Figure 3.9 and Figure 3.10, compared with placebo a significant decrease in the number of inadvertent naps/sleep attacks was seen in both the 6g and 9g Xyrem groups (p=0.0497 and p=0.0122, respectively), and a significant decrease in the number of awakenings was seen in the 9g Xyrem group (p=0.0035). These data are consistent with the dose response pattern of reduced excessive daytime sleepiness reflected in the Clinical Global Impression of change and the Epworth Sleepiness Scale. No significant differences between treatments were seen in the change from baseline in the median number of hypnagogic hallucinations, sleep paralysis episodes, total amount of sleep, and duration of inadvertent naps/sleep attacks.

Figure 3.9 Median Changes for Number of Inadvertent Naps/Sleep Attacks From Baseline to Endpoint

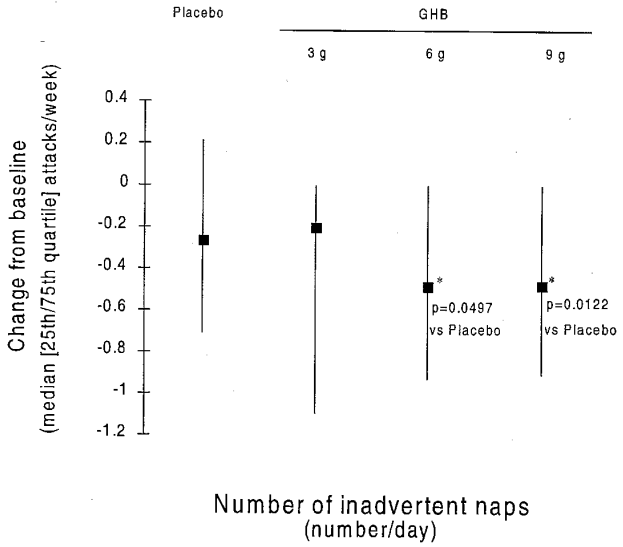
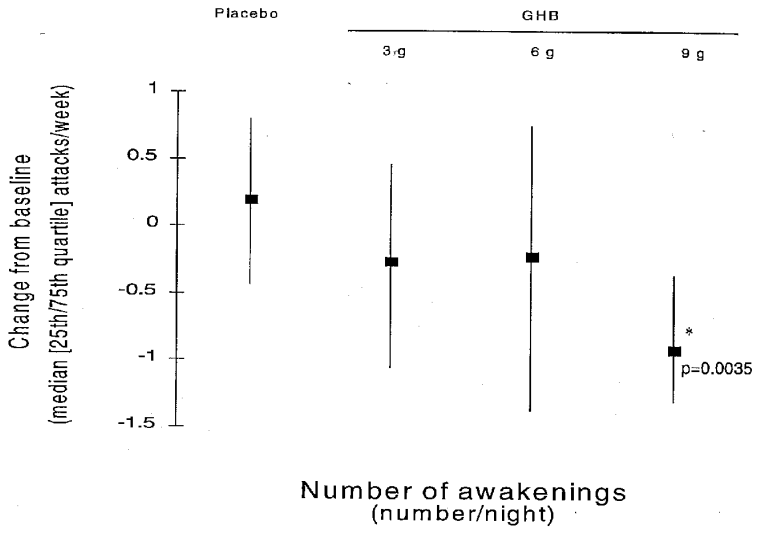


Figure 3.10 Median Changes for Number of Awakenings From Baseline to Endpoint



An exploratory analysis was conducted of the changes from baseline to endpoint in the parameters of subjective rating of quality of sleep, level of alertness, and ability to concentrate as rated by the patients. These parameters were measured on a four-point scale: 1-excellent, 2-good, 3-fair, 4-poor. For the 6g and 9g dose groups, there was a statistically significant increase in the subjective quality of sleep (p=0.0028 and p=0.0010), level of alertness (p=0.0006 and p=0.0004), and overall reported ability to concentrate (p=0.0229 and p=0.0007).

3.1.1.15.4 Abrupt Cessation of Double-Blind Medication

The change in incidence of cataplexy attacks that occurred following discontinuation of double-blind treatment (Visit 6) through the end of the trial three to five days later (Visit 7), and from baseline to Visit 7 was calculated. Only patients for which there were data at baseline (Visit 4), Visit 6 and Visit 7 were included in this analysis.

Table 3.11 Total Cataplexy Attacks per Week by Treatment Group – Medians Change from Visit 6 to Visit 7 and from Baseline to Visit 7

					V6-V7		Baseline to V7	
Treatment Group	**N**	**Baseline**	**V6**	**V7**	**Change**	**P-Value**	**Change**	**P-Value**
Placebo	30	20.6	16.5	17.5	1.9	0.06	-3.8	0.10
3g	29	18.7	9.5	13.0	2.3	0.09	-5.4	0.07
6g	29	23.0	8.0	16.3	6.1	0.0001	-3.3	0.13
9g	27	29.2	8.0	14.0	4.7	0.0017	-11.6	0.0001

Total cataplexy attacks per week were determined by first calculating the average daily number of cataplexy attacks based on the numbers recorded in the patient diaries, then multiplying this number by seven to get Total Cataplexy Attacks per Week.

Patients discontinued sodium oxybate treatment at Visit 6 (Week 4) and were to return to the clinic for assessment of cataplexy at Visit 7, three to five days later. According to their daily diary recordings, the median number of total cataplexy attacks per week for all patients in all treatment groups trended toward their higher baseline values. A significant change from Visit 6 to Visit 7 in the median number of cataplexy attacks per week occurred in the 6g group (p=0.0001) and 9g group (p=0.0017). The 9g dose group exhibited a significantly lower median number of weekly cataplexy attacks at Visit 7 than at baseline (p=0.0001).

In all treatment groups, acute rebound cataplexy was not in evidence as the median number of attacks at Visit 7 was lower than their baseline values.

Adverse events, for the time period of up to five days prior to Visit 6 and up to five days prior to Visit 7, were compared to determine if REM rebound effects (i.e. rebound cataplexy) occur on withdrawal of Xyrem. Adverse events suggestive of REM rebound

(sleep disturbance, hallucinations, and dream abnormal) which were present at up to five days before Visit 6 were compared with those adverse events that occurred up to five days before Visit 7. There was not an exacerbation of adverse events suggestive of REM rebound effects corresponding with the cessation of treatment with Xyrem at Visit 6. The difference in the number of events between these two periods is not statistically significant. REM rebound effects did not appear when stopping Xyrem for three to five days

3.1.1.16 Efficacy Conclusions

Table 3.12 OMC-GHB-2 Efficacy Conclusions

Parameters	Treatment	Baseline (median)	Endpoint (median)	P-value (vs. Placebo)
Total Number of Cataplexy Attacks Per Week	Placebo 3g 6g 9g	20.5 20.0 23.0 23.5	16.5 9.5 8.0 8.7	-- n.s. 0.0529 0.0008
Excessive Daytime Sleepiness (Epworth Sleepiness Scale)	Placebo 3g 6g 9g	19.0 17.0 17.5 17.0	17.0 16.0 14.5 12.0	-- n.s. n.s. 0.0001
		Change in Medians		
Frequency of Inadvertent Naps/Sleep Attacks/Day	Placebo 3g 6g 9g	-0.26 -0.20 -0.48 -0.48		-- n.s. 0.0497 0.0122
Number of Awakenings at Night	Placebo 3g 6g 9g	+0.20 -0.25 -0.21 -0.91		-- n.s. n.s. 0.0002
Clinical Global Impressions of Change	Placebo 3g 6g 9g	32% 47% 52% 80%		-- 0.3075 0.1368 0.0002

- In study OMC-GHB-2, a statistically significant greater (compared to placebo) reduction from baseline to endpoint in the total number of cataplexy attacks ($p = 0.0008$) was seen among patients in the 9.0 g/d dosage group compared to placebo-treated group, and a reduction in the number of cataplexy attacks ($p = 0.0529$) also was seen among patients in the 6.0 g/d dosage group.

- A reduction in Epworth Sleepiness Scale from baseline to endpoint was observed in all treatment groups (including placebo) with a dose-response trend similar to that seen for cataplexy; this change reached statistical significance ($p = 0.0001$) in patients in the 9 g/d dosage group compared to placebo.

- The number of inadvertent naps or sleep attacks occurring during a day, an index of excessive daytime sleepiness, was reduced by a statistically significant amount from baseline to endpoint (compared to placebo) in the 6 g/d (p = 0.0497) and 9 g/d (p = 0.0122) dosage groups.

- The clinical investigator's assessment of change in overall disease severity, the (Clinical Global Impression of change [CGI-c]) shows a clear improvement, with the 80% responder rate in the 9.0 g/d group being significantly different from the 32% responder rate in the placebo group (p = 0.0002). Patients in the 3.0 g/d and 6.0 g/d dosage groups showed a dose-response trend in level of improvement.

- No significant differences between treatments were seen in the change from baseline in the median number of hypnagogic hallucinations, sleep paralysis episodes, total amount of sleep, and duration of inadvertent naps/sleep attacks.

- Following cessation of treatment at Visit 6, there was no exacerbation of cataplexy or other adverse events above baseline, suggesting that REM rebound does not occur.

3.1.2 SCRIMA TRIAL

3.1.2.1 Design

The Scrima trial (US) was a Phase II, randomized, double-blind, placebo-controlled, 2-way crossover (balanced for sequence group and gender), single-center trial comparing the efficacy of 50 mg/kg (mean 4.2 g) of sodium oxybate with placebo for the treatment of narcolepsy. The total nightly dose of trial medication was taken in 2 equal doses: at bedtime, and again approximately 3-4 hours later. Each dose was administered orally in Syrup of Orange (25 mL) and distilled water (to 100 mL). The trial design is summarized in Table 3.13.

Table 3.13 Scrima Trial Design

Baseline	Treatment 1	Washout	Treatment 2	Washout
14 Days	29 Days	6 Days	29 Days	6 Days
X	Sodium Oxybate (50 mg/kg)	X	Placebo	X
	Placebo	X	Sodium Oxybate (50 mg/kg)	X

The trial consisted of a screening period during which anticataleptic medications were withdrawn, a 14-day baseline period, two 29-day treatment periods separated by a 6-day washout period, and a washout/follow-up period of at least 5 days. In each of the treatment periods, patients took randomly assigned trial medication (50 mg/kg [mean 4.2 g] sodium oxybate) or a similar volume of diluted Syrup of Orange as placebo. A total of 10 men and 10 women were treated and all completed the trial.

To enter the trial, patients were required to have a history of narcolepsy and cataplexy diagnosed by an accredited clinical polysomnographer, sleep onset REM periods ≥ 2 on the diagnostic Multiple Sleep Latency Test (MSLT), and a sleepiness index* ≥ 75 on the diagnostic MSLT. In addition, to continue into the randomized portion of the trial, following the withdrawal of other anticataplectic medications a patient was required to have a minimum of 10 cataplexy attacks subjectively reported during a 14-day baseline period.

Patients with moderate to severe cataplexy (averaging 20 attacks per week) were enrolled into the trial, and other anti-cataplectic treatment was withdrawn prior to baseline.

3.1.2.2 Objectives

The objectives of the trial were:

- To evaluate as primary variables the average daily number of cataplexy attacks and objective daytime sleepiness (using the sleepiness index determined by the MSLT) in narcolepsy patients during treatment with sodium oxybate as compared to placebo and baseline
- To evaluate as secondary variables the average number of sleep attacks per day, average number of awakenings per night, dosing requirements of methylphenidate, feelings on awakening, mood in the morning and evening, sleep patterns identified on the PSG, and average number of REM onsets determined by the MSLT during treatment with sodium oxybate as compared to placebo and baseline

Safety variables included the incidence of adverse events and changes in laboratory values.

3.1.2.3 Statistical Analysis

Age, weight, age at diagnosis, and the number of sleep and cataplexy attacks were analyzed using a 2-factor ANOVA (analysis of variance). The effects in the model were sequence group, gender, and the interaction of gender and sequence group. The distribution of patients with/without histories of hypnagogic hallucinations or sleep paralysis was tested for independence from gender and sequence group using contingency table methods. All patients enrolled in the study were included. (n = 20). Only patients with baseline data who were included in the post-treatment analysis were analyzed for baseline comparability. A 2-factor ANOVA was performed. The effects in the model were sequence group, gender, and the interaction of gender and sequence group.

Repeated measures ANOVA was performed on the observed data. There were 2 between-patient factors, sequence group and gender, and the 2 within-patient factors,

* Sleepiness Index = 100-(5X total sleep latency minutes/number of naps); abnormal >75, borderline 50-75, normal <50

treatment and week. Since week was frequently significant, either as a main effect or as part of an interaction, further repeated measures analysis for the individual weeks were performed to support the overall analysis. If indicated, supportive analyses on ranks were to be performed.

Only the diary data documented the patient's status prior to treatment in Treatment Period 2. Thus, comparison to the patient's status prior to treatment in Treatment Period 1 and the return to this level was restricted to diary data. A repeated measures ANOVA was performed on the change from baseline data. This analysis was a single within-patient factor, days, and 2 between-patient factors, sequence group and gender. Separate univariate supportive analyses for washout days 1 to 5 were performed, with sequence group, gender, and their interaction as factors. The intercept was tested in each model to identify departure from baseline.

Washout from treatment in Period 1 and 2 (follow-up) was compared for the variables in the diary. A repeated measures ANOVA was performed on the change from baseline data. There were 2 between-patient factors, sequence group and gender, and the 2 within-patient factors, Day 1 to 5 of washout and follow-up.

3.1.2.4 Efficacy Results

Table 3.13a summarized the mean number of cataplexy attacks per day by treatment.

Table 3.13a Mean Number of Cataplexy Attacks Per Day

Treatment Group	Pre-Treatment	Treatment Phase				Overall (SE)	Baseline to Endpoint
	Baseline (SE)	Week 1 (SE)	Week 2 (SE)	Week 3 (SE)	Week 4 (SE)		
GHB	2.9 (0.5)	1.4 (0.2)	1.4 (0.2)	0.9 (0.2)	0.9 (0.2)	1.2 (0.2)	2.9 to 1.2 (p=0.007)
Placebo		1.5 (0.2)	2.0 (0.3)	2.1 (0.4)	1.9 (0.3)	1.9 (0.3)	2.9 to 1.9 (p=0.117)
p-value between treatments	---	n.s.	n.s.	0.005	0.004	0.013	---

n.s. - not significant

During active treatment periods over 4 weeks, a mean of 1.2 cataplexy attacks per day was reported by patients receiving sodium oxybate treatment compared to 1.9 cataplexy attacks per day by patients receiving placebo treatment, representing a mean decrease from baseline of 1.6 for sodium oxybate treatment (p = 0.007) and of 1.0 for placebo treatment (p = 0.117).

By Week 4, treatment with sodium oxybate was superior to placebo for 84% (16/19) of patients, with a mean of 0.9 cataplexy events per day after treatment with sodium oxybate compared to 1.9 per day after treatment with placebo. No cataplexy events

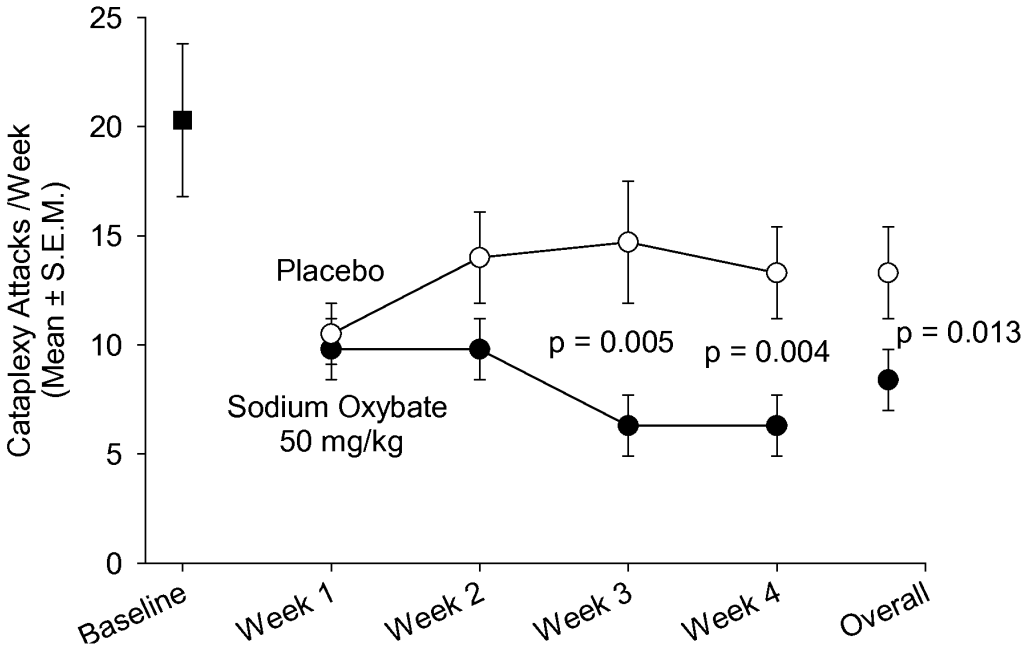
were reported for 21% (4/19) of patients during Week 4 of sodium oxybate treatment compared to 5% (1/19) of patients on placebo. Nine patients (47%) reported an average of at least one fewer cataplexy attacks per day while taking sodium oxybate than while taking placebo (1/19 patients taking placebo averaged at least one less attack than while taking sodium oxybate).

There were also significantly fewer ($p = 0.013$) cataplexy attacks per day during sodium oxybate treatment overall compared to placebo. However, the data suggest an interaction, ie, there was very little difference between treatments at Week 1 ($p = 0.735$, sodium oxybate = 1.4, placebo = 1.5) and a greater difference at Week 2 ($p = 0.073$, sodium oxybate = 1.4, placebo = 2.0). At Weeks 3 and 4, significant differences were detected ($p = 0.005$, sodium oxybate = 0.9, placebo = 2.1; and $p = 0.004$, sodium oxybate = 0.9, placebo = 1.9, respectively). No other significant main effects or interactions were identified, in particular sequence group ($p=0.775$), or treatment x sequence group interaction ($p=0.713$). Thus, no evidence of carryover effect was detected (PLC:GHB-GHB:PLC for PLC-GHB=0.2 with 95% interval-0.9 to 1.3).

The mean number of cataplexy attacks decreased from Week 2 to Week 3 or Week 4 during sodium oxybate treatment and remained lower at Week 4 than Week 1. In contrast, the mean number of a cataplexy attacks increased from Week 1 to Week 2 during placebo treatment and remained higher than Week 1 at Week 4. The crossover design shows no carry-over effect of any variable, indicating that a 5-day washout was sufficient.

The number of cataplexy attacks per week by treatment group for the Scrima trial are presented in Figure 3.11 as mean cataplexy attacks/week ± SEM.

Figure 3.11 Number of Cataplexy Attacks by Treatment Group — Scrima Trial



Data Source: Scrima Trial Report

No significant treatment effects were detected overall for the MSLT sleepiness index [sleepiness index = 100-(5X total sleep latency in minutes/number of naps); abnormal >75, borderline 50-75, normal <50)], although the mean sleepiness index was less during sodium oxybate treatment (87.2) than placebo (90.3).

The mean number of sleep attacks per day during the 4 weeks of treatment decreased significantly from baseline for both sodium oxybate ($p = 0.002$) and placebo ($p = 0.007$), but differences between treatments were not significant. There was no significant difference compared to baseline in the mean number of subjective awakenings at night for either sodium oxybate or placebo, but significantly ($p = 0.042$) fewer awakenings occurred during sodium oxybate treatment versus placebo. There were no significant differences between sodium oxybate or placebo treatments versus baseline or between sodium oxybate and placebo in amount of methylphenidate taken, how patients felt upon awakening, or average morning mood.

For objective PSG studies (Table 3.14), there were statistically significant overall between treatment differences in sleep efficiency ($p = 0.023$), sleep latency ($p = 0.028$),

percentages of Stage 1 and 3 sleep (p = 0.042 and 0.003, respectively), stage shifts (p = 0.006), and number of objective awakenings (p = 0.012), following 50 mg/kg sodium oxybate in the Scrima trial. Hence, the polysomnography data demonstrated that the continuity (increased sleep efficiency and reduced number of awakenings) and depth of sleep (decrease in Stage 1 light sleep and increase in Stage 3 deep sleep) were improved.

Table 3.14 Overnight Sleep in Narcolepsy Patients During GHB vs. Placebo Treatment: Means ± SD for 10 Males and 10 Females

		Placebo		GHB	
	Baseline	Day 1	Day 29	Day 1	Day 29
Sleep measures					
PSG time (min)	475.9 ± 13.5	472.6 ± 29.4	473.9 ± 26.2	474.7 ± 19.3	480.8 ± 3.5
Total sleep (min)	397.4 ± 46.7	413.6 ± 46.5	416.5 ± 41.3	397.2 ± 59.1	409.1 ± 41.7
Stage 0 (min)[a]	78.5 ± 45.5*	58.9 ± 39.2*	57.4 ± 38.6	77.5 ± 50.5	71.6 ± 40.7
No. of wakes[b]	27.2 ± 9.6	25.4 ± 10.2	29.4 ± 11.7	20.6 ± 6.4	23.0 ± 6.2
Sleep efficiency	83.5 ± 9.5*	87.5 ± 8.1*	88.0 ± 7.9	83.5 ± 11.1	85.1 ± 8.5
Sleep stages (%)					
Stage 1[a]	28.8 ± 11.0	26.8 ± 8.7	29.3 ± 10.8	22.4 ± 11.6	24.1 ± 8.4
Stage 2	40.6 ± 8.5*	44.6 ± 8.8*	44.0 ± 10.8	46.4 ± 10.7	44.6 ± 6.3
Stage 3[b]	3.4 ± 3.4	3.1 ± 3.6	2.3 ± 2.6	4.0 ± 4.2	5.8 ± 5.3
Stage 4	4.2 ± 6.6	3.5 ± 6.2	4.4 ± 5.8	5.3 ± 6.7	4.6 ± 4.8
Non-REM	77.0 ± 4.6	77.9 ± 5.1	80.1 ± 5.5	78.1 ± 5.7	79.1 ± 5.3
Delta[a]	7.6 ± 9.5	6.6 ± 9.4	6.8 ± 7.2	9.3 ± 9.3	10.4 ± 9.1
REM sleep	23.0 ± 4.6	22.1 ± 5.1	19.9 ± 5.5	21.9 ± 5.7	20.9 ± 5.3
No. of REM epochs	14.2 ± 6.4	13.6 ± 4.6	12.0 ± 4.7	12.1 ± 5.4	10.8 ± 4.5
Stage shifts[b]	123.4 ± 23.8	127.0 ± 25.6	132.2 ± 32.2	101.9 ± 24.8	114.8 ± 29.2
Latency to					
Sleep[a]	4.2 ± 4.6†	2.4 ± 1.6†	2.4 ± 2.1	3.5 ± 2.9	3.2 ± 2.5
Stage 2	11.0 ± 12.2	10.8 ± 12.4	8.1 ± 12.5	18.0 ± 21.3	11.4 ± 14.1
Delta sleep	39.0 ± 22.3	36.6 ± 17.2	37.7 ± 18.0	67.8 ± 67.4	47.4 ± 52.2
REM sleep	48.5 ± 78.2	31.6 ± 31.1	46.1 ± 47.4	29.8 ± 49.1	23.7 ± 27.5
First 6 h					
Stage 0 (min)	60.0 ± 41.8	44.5 ± 30.9	37.6 ± 25.2	48.0 ± 40.2	42.3 ± 23.5
Sleep efficiency	83.3 ± 11.6	87.6 ± 8.6	89.6 ± 7.0	86.7 ± 11.2	88.3 ± 6.5
Last 2 h					
Stage 0 (min)[a]	18.5 ± 12.7	15.2 ± 12.4	19.9 ± 18.2	29.4 ± 22.0	29.3 ± 23.7
Sleep efficiency	84.1 ± 10.3	87.3 ± 10.2	81.5 ± 15.5	71.7 ± 24.4	75.4 ± 20.4

Repeated-measures ANOVA of treatment differences from baseline: GHB (day 1 and 29) vs. placebo (day 1 and 29): $^{a}p < 0.05$, $^{b}p < 0.01$.
Baseline vs. placebo day 1: *paired-*t*: $p < 0.05$, †paired-*t*: $p < 0.10$.

Source: Scrima L, Hartman PG, Johnson FH, Thomas EE, Hiller FC. The effects of γ-hydroxybutyrate on sleep of narcolepsy patients: a double-blind study. Sleep 1990; 13(6):479-490.

3.1.2.5 Conclusions

Compared to placebo, sodium oxybate, given as a nightly divided dose of 50mg/kg (mean 4.2 g) for 4 weeks, significantly reduced the frequency of cataplexy attacks in a population of chronic narcolepsy patients. The reduction in cataplexy was greater during the last 2 weeks of sodium oxybate treatment than during the first 2 weeks. As assessed by the MLST sleep index, daytime sleepiness was not significantly reduced by this dosage or duration of sodium oxybate treatment. Polysomnography data demonstrated that sodium oxybate significantly enhanced both the continuity and the depth of nocturnal sleep as shown by a reduction in the number of awakenings, a

decrease in the percentage of Stage 1 (light) sleep, and an increase in the percentage of Stage 3 (deep) sleep. Sodium oxybate was generally well-tolerated.

3.1.3 OMC-SXB-21

3.1.3.1 Rationale for OMC-SXB-21

In January 2000, the FDA indicated a requirement for a trial to assess the long-term efficacy of Xyrem in narcoleptic patients. Conventional controlled clinical trial designs to assess long-term efficacy require patients to be randomized into prolonged placebo and active treatment groups. In narcolepsy, a conventional trial would have required patients to withdraw and washout from existing anti-cataplexy medications, [narcoleptics are typically treated with tricyclic antidepressants (TCAs) or serotonin selective reuptake inhibitors (SSRIs)] followed by establishment of baseline levels of cataplexy prior to being randomized into treatment groups. A trial using this conventional design would have presented several difficulties. First, participation would have caused severe hardship for the patients in the placebo group, who would have been without any treatment for cataplexy for the duration of the trial. Second, the potential of not receiving long-term therapy for cataplexy would have resulted in substantial difficulties in the recruitment of sufficient numbers of patients to make the trial statistically robust. These design difficulties necessitated the development of an alternative paradigm for assessing long-term efficacy. The new study paradigm, which became the OMC-SXB-21 protocol, was an adaptation of a design suggested by the Neuropharmacology Division of the FDA. The agency provided extensive input on both study conduct and statistical analysis issues. To assess long-term efficacy, patients in the OMC-SXB-21 trial were removed from stable, long-term, open-label Xyrem therapy in a double-blinded fashion and a return of cataplexy was assessed as the primary efficacy endpoint.

3.1.3.2 Trial Objectives and Design

3.1.3.2.1 Efficacy Objective

OMC-SXB-21 was a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial to assess the long-term efficacy of orally administered Xyrem, compared to placebo, for the treatment of narcolepsy. The primary objective of this trial was to provide evidence for the long-term efficacy of Xyrem (sodium oxybate) based on the return of cataplexy symptoms upon cessation of a minimum of 6 months of open-label treatment with sodium oxybate. The measure of efficacy was a comparison between the Xyrem and placebo groups, of the change in the number of cataplexy attacks from baseline (2-week single-blind lead-in active treatment phase) to endpoint (2-week double-blind active or placebo treatment phase).

3.1.3.2.2 Trial Design

The trial design is summarized in Table 3.15 and discussed below.

Table 3.15 OMC-SXB-21 Trial Design

Phase I Screening	**Phase II Lead-In**	**Phase III Double-Blind Treatment**
3 to 5 Days	**14 ± 2 Days (Week 1, Week 2)**	**14 ± 2 Days (Week 1, Week 2)**
Xyrem at established dosage	Single-blind Xyrem at established dosage	Xyrem at established dosage
		Placebo
Stimulant use permitted TCA/SSRI use not permitted		

↑ Visit 1 (Randomization) ↑ Visit 2 ↑ Visit 3 ↑ Visit 4

The trial consisted of 3 phases (4 visits). During Phases I and II, patients continued Xyrem at the same dosage they were taking in OMC-SXB-7 (3, 4.5, 6, 7.5, and 9g per night in divided doses). The period from Visit 1 to Visit 2 served to screen patients for inclusion and exclusion criteria and evaluate hematology and chemistry laboratory results. Patients were randomized immediately following Visit 1. During Phase II (lead-in), patients received single-blind Xyrem for 2 weeks (Visit 2 to Visit 3). In Phase III (double-blind), half the patients received Xyrem at their established dosage, and half received placebo in identical volume to their established Xyrem dose, for 2 weeks (Visit 3 to Visit 4). During Phases II and III, patients kept diaries to record the number of daily cataplexy attacks and adverse events. Patients who received placebo during the double-blind phase were predicted to have a higher incidence of cataplexy attacks than patients who received Xyrem.

3.1.3.2.3 Patient Selection Criteria

Patients were drawn from a pool of patients participating in OMC-SXB-7 (the open-label extension to OMC-GHB-3, OMC-SXB-6, and the Scharf trial). In addition to meeting the entry criteria for participating in the OMC-SXB-7 trial, patients were also required to meet the following criteria for inclusion in OMC-SXB-21:

- Had a history of at least 5 cataplexy attacks per week, confirmed through patient query or medical history, prior to receiving initial treatment (TCAs, SSRIs, and/or Xyrem) for cataplexy.
- Had been treated continuously for the symptoms of narcolepsy with sodium oxybate for a period of 6 months to 3.5 years. The patients must have been previously enrolled in Orphan Medical clinical trials OMC-GHB-3 or OMC-SXB-6.
- Had not been taking TCAs, SSRIs, or any other anti-cataplexy medications, other than Xyrem, within the 30-day period prior to Visit 1 of this trial.
- Stimulant medications were to be maintained at constant levels throughout the trial.

Enrollment of up to 80 patients was planned for this trial. Fifty-five (55) patients were actually treated; all completed the trial.

3.1.3.2.4 Treatments

The Xyrem trial medication was an oral aqueous solution with a concentration of 500 mg/mL of sodium oxybate. Placebo was a sodium citrate solution in equimolar concentration to the sodium in Xyrem oral solution. Placebo was shown to be similar to Xyrem in a blinded taste test (Orphan Medical Protocol OMC-SXB-16).

During the single-blind lead-in phase of the trial, each patient took the same dosage of Xyrem oral solution (3.0, 4.5, 6.0, 7.5, or 9.0 g/d in 2 divided doses) previously taken in the OMC-SXB-7 trial. During the double-blind phase of the trial, patients received either Xyrem at the same dosage as at Visit 2, or placebo at an equivalent volume to the dosage of Xyrem that the patient took during the single-blind phase.

Trial medication was self-administered. Patient compliance was calculated at Visits 2 and 3. Patients were considered non-compliant with trial medication if they missed or exceeded their prescribed doses by 30% or more.

3.1.3.2.5 Randomization and Blinding

Randomization was performed centrally and occurred following the completion of Visit 1. At the request of the FDA, the randomization code was developed to ensure that there was not dose stratification across the placebo and Xyrem treatment groups. Separate randomization code sequences were developed for the existing OMC-SXB-7 treatment doses of 4.5 (3 g/d included in this grouping), 6, 7.5, and 9g/d. Neither the Orphan Medical clinical development representatives nor the clinical site personnel knew the identity of the double-blind medication.

3.1.3.2.6 Efficacy Measurements

Patients were asked to complete a daily diary each night before bedtime during the single-blind and double-blind phases of the trial. The information captured in the diaries was the number of cataplexy attacks the patient had experienced during that day and any AEs or other relevant medical information. A cataplexy attack, episode, or event was defined as a sudden bilateral loss of voluntary muscle tone. To be classified as cataplexy for this trial, the event must have been bilateral, of sudden onset and localized to a specific muscle group(s) or part of the body, and the patient must have been aware of time and place during the event (ie, not a sleep attack or microsleep).

3.1.3.2.7 Statistical Analysis

Efficacy analyses were performed using the Intent-to-Treat Patients population, which included all patients who received 1 or more doses of double-blind trial medication, and had baseline and post-baseline cataplexy measurements.

The primary efficacy variable was the change in the number of cataplexy attacks between baseline (2-week, single-blind lead-in phase) and endpoint (double-blind treatment phase). If fewer or greater than 14 days were available for either treatment phase, then the average number of cataplexy attacks per day was calculated and multiplied by 14.

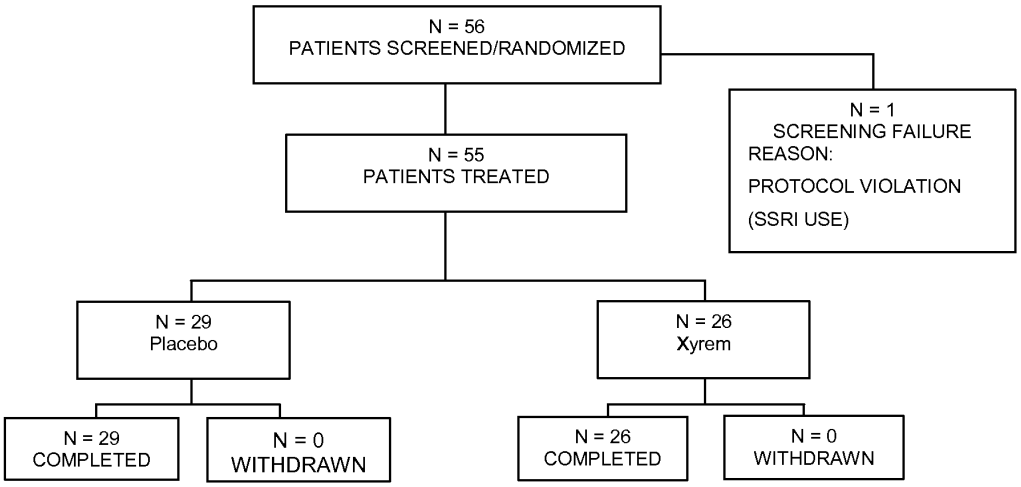
The change in the number of cataplexy attacks was analyzed using a nonparametric analysis of covariance (ANCOVA). Specifically, the baseline number of cataplexy attacks and the change from baseline in the number of cataplexy attacks were replaced by their corresponding ranks, where mean ranks were assigned in case of ties. The rank changes from baseline in the number of cataplexy attacks were analyzed using ANCOVA, including the rank baseline number of cataplexy attacks, treatment group, and baseline-by-treatment group interaction. The overall inference among treatments, placebo versus Xyrem, was presented. Two-sided p-values with a level of significance at 0.05 were used to determine statistical significance.

3.1.3.3 Patient Disposition and Demographics

3.1.3.3.1 Patient Disposition

Figure 3.12 presents the disposition of patients by treatment group. Fifty-six (56) patients were screened and randomized; 1 randomized patient failed screening due to concomitant use of an SSRI and was never treated. A total of 55 patients were treated; all completed the trial.

Figure 3.12 Disposition of Patients



3.1.3.3.2 Patient Demographics

Patient demographic data revealed no significant differences in patient age, gender, weight, height, race, or baseline number of cataplexy attacks between the treatment groups. Table 3.16 summarizes patient demographics and current dosage at screening by treatment group. Prior to trial entry, patients had been taking Xyrem (sodium oxybate) for 7 to 44 (mean = 21) months for the treatment of narcolepsy.

Table 3.16 Demographics and Baseline Characteristics by Treatment Group

Characteristics	Total (N=55)	Treatment Group		p-Value
		Xyrem (N=26)	Placebo (N=29)	
Age (years)				
Mean ± SD	47.7 ± 16.66	47.9 ± 17.06	47.6 ± 16.60	0.955
Range	16.3 – 82.6	19.1 – 82.6	16.3 – 70.0	
Gender (n, %)				
Male	23 (42%)	8 (31%)	15 (52%)	0.172
Female	32 (58%)	18 (69%)	14 (48%)	
Weight (kg)				
Mean ± SD	80.5 ± 20.09	83.8 ± 24.31	77.6 ± 15.22	0.250
Range	54.0 – 142.0	54.0 – 142.0	55.0 – 127.0	
Height (cm)				
Mean ± SD	170.1 ± 10.25	169.6 ± 10.42	170.6 ± 10.24	0.710
Range	152.0 – 188.0	152.0 – 188.0	155.0 – 188.0	
Race (n, %)				
Caucasian	52 (95%)	23 (88%)	29 (100%)	0.099
African-American	2 (4%)	2 (8%)	0	
Asian	0	0	0	
Hispanic	1 (2%)	1 (4%)	0	
Other	0	0	0	
Time on Xyrem (months)				
Mean ± SD	21.22 ± 12.28	23.27 ± 12.36	19.38 ± 12.13	ND
Range	7 – 44	8 – 38	7 – 44	

(continued)

Table 3.16 Demographics and Baseline Characteristics by Treatment Group

Characteristics	Total (N=55)	Treatment Group		p-Value
		Xyrem (N=26)	Placebo (N=29)	
Cataplexy attacks (2-week baseline)				
N	55	26	29	0.436
Mean	12.6	9.0	15.7	
SD	31.75	19.25	39.88	
Median	3.0	1.9	4.0	
Minimum	0.0	0.0	0.0	
Maximum	197.0	86.8	197.0	
Daily Dosage of Xyrem at Screening (n, %)				
3.0 g/d	2 (4%)	1 (4%)	1 (3%)	ND
4.5 g/d	9 (16%)	4 (15%)	5 (17%)	
6.0 g/d	15 (27%)	7 (27%)	8 (28%)	
7.5 g/d	15 (27%)	7 (27%)	8 (28%)	
9.0 g/d	14 (25%)	7 (27%)	7 (24%)	

3.1.3.4 Efficacy Evaluation

3.1.3.4.1 Treatment Compliance

Only 3 (5%) patients (1 placebo, 2 Xyrem) had compliance levels outside the protocol-acceptable range during one or both phases of the trial.

3.1.3.4.2 Efficacy Results

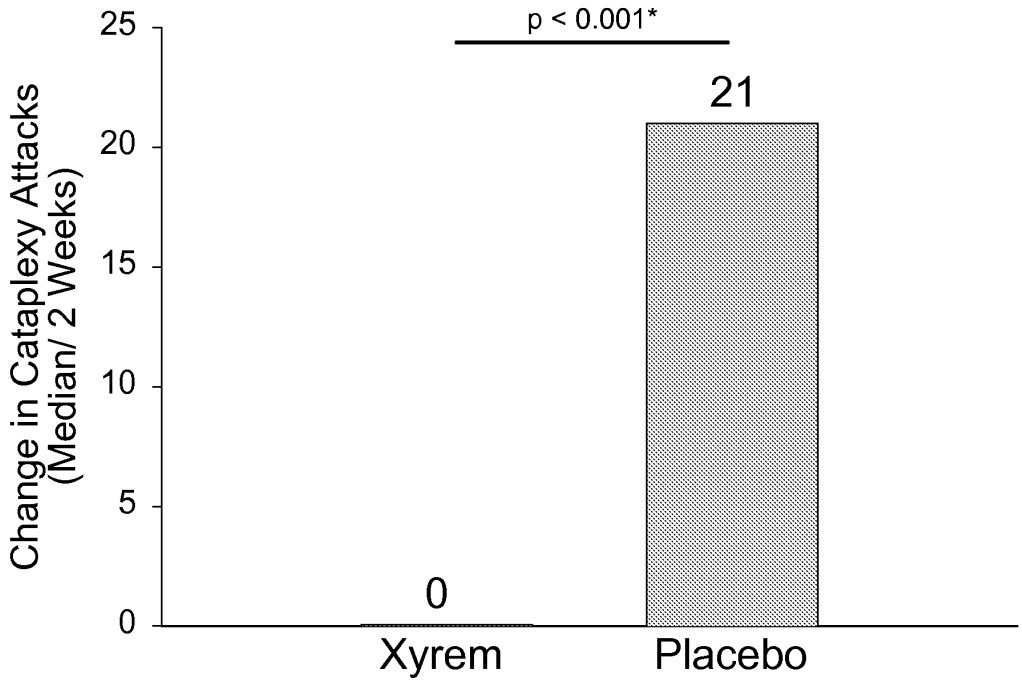
As shown in Table 3.17 and Figure 3.13, there was no change in the number of cataplexy attacks from baseline to endpoint in the Xyrem group (median change 0.0), while cataplexy attacks increased by a median of 21.0 in the placebo group. This difference was statistically significant ($p < 0.001$) when analyzed by an ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction, with a median rank change from baseline of 39.0 for the placebo group and 16.5 for the Xyrem group.

Table 3.17 Change From Baseline in Number of Cataplexy Attacks and Rank Change (Per 2 Weeks) by Treatment Group — Intent-to-Treat Patients

	Xyrem (N=26)			Placebo (N=29)		
	Phase II	Phase III	Change	Phase II[a]	Phase III	Change
Number of cataplexy attacks (per 2 weeks)						
Mean ± SD	9.0 ± 19.25	12.6 ± 30.34	3.6 ± 20.73	15.7 ± 39.88	50.4 ± 81.09	34.6 ± 55.72
Median	1.9	1.1	0.0	4.0	21.0	21.0
Minimum	0.0	0.0	-24.3	0.0	0.0	-15.0
Maximum	86.8	138.3	87.2	197.0	269.2	206.2
Rank change						
Mean ± SD			18.1 ± 12.65			36.9 ± 13.31*
Median			16.5			39.0
Minimum			1.0			3.0
Maximum			52.0			55.0

SD = standard deviation.
[a] Placebo group patients received Xyrem during Phase II.
* $p < 0.001$, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.

Figure 3.13 Median Change from Baseline in Number of Cataplexy Attacks



* p < 0.001, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.

As shown in Table 3.18 and Figure 3.14, change from baseline in the number of cataplexy attacks by week during the double-blind period mirrors the overall change from baseline: no change in the Xyrem group (median change 0.0, each week), while cataplexy attacks increased in the placebo group by a median of 4.2 in Week 1, and 11.7 in Week 2.

Table 3.18 Change from Baseline by Week During the Double-Blind Treatment Period in the Number of Cataplexy Attacks by Treatment Group — Intent-to-Treat Patients

Number of Cataplexy Attacks	Xyrem			Placebo		
	Phase II[a]	Phase III	Change	Phase II[a]	Phase III	Change
Week 1						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	5.3 ± 11.84	0.8 ± 7.48	7.9 ± 19.94	21.1 ± 35.13	13.2 ± 22.02
Median	0.9	1.0	0.0	2.0	7.0	4.2
Minimum	0.0	0.0	-15.4	0.0	0.0	-7.5
Maximum	43.4	50.8	25.2	98.5	126.0	87.5
Week 2						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	7.2 ± 18.66	2.7 ± 13.74	7.9 ± 19.94	29.7 ± 47.30	21.8 ± 35.16
Median	0.9	0.5	0.0	2.0	13.0	11.7
Minimum	0.0	0.0	-10.7	0.0	0.0	-7.5
Maximum	43.4	87.5	62.0	98.5	168.0	143.5

[a] Baseline (Phase II) was determined by normalizing the total number of cataplexy attacks during the 2-week Phase II period to 7 days.
Data Source: Appendix Section 14.2.4, Summary Tables 14.2.4.1 and 14.2.4.2.

Figure 3.14 Median Change from Baseline by Week During the Double-Blind Treatment Period in the Number of Cataplexy Attacks — Intent-to-Treat Patients

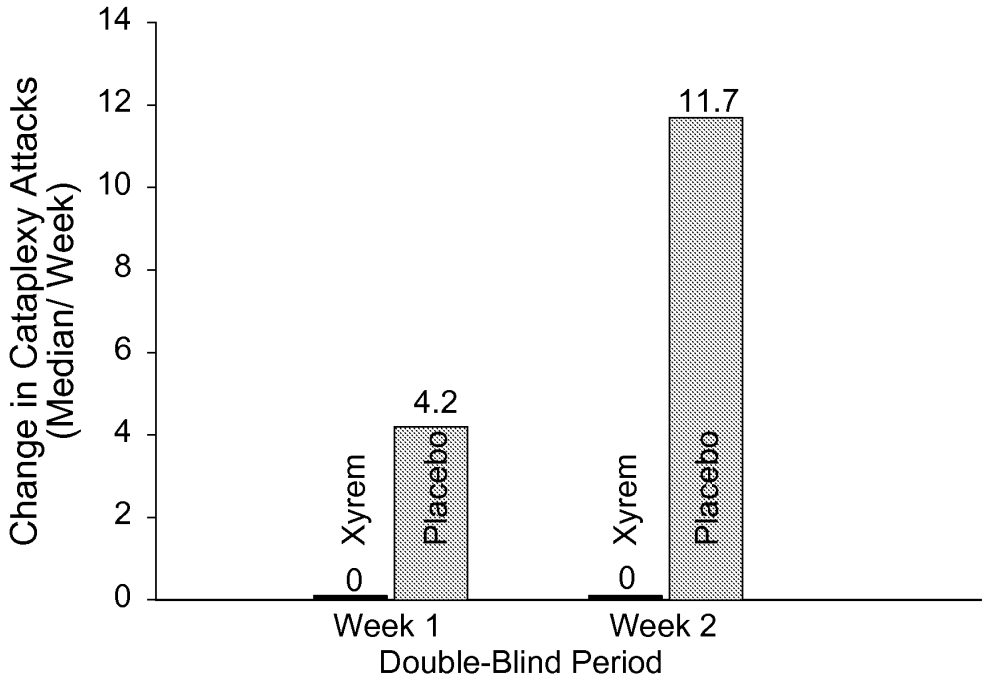
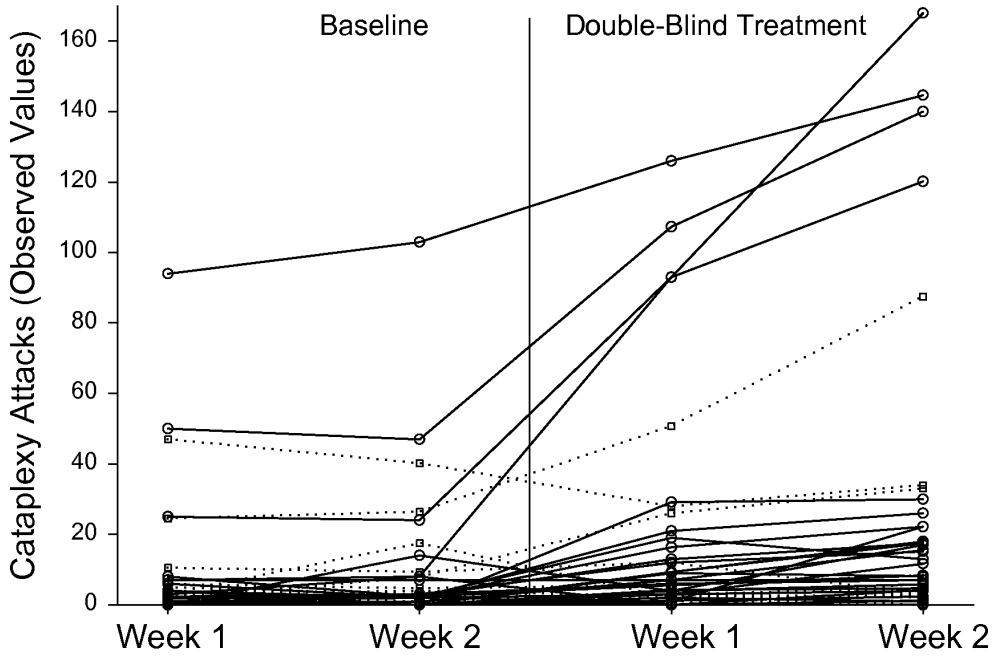


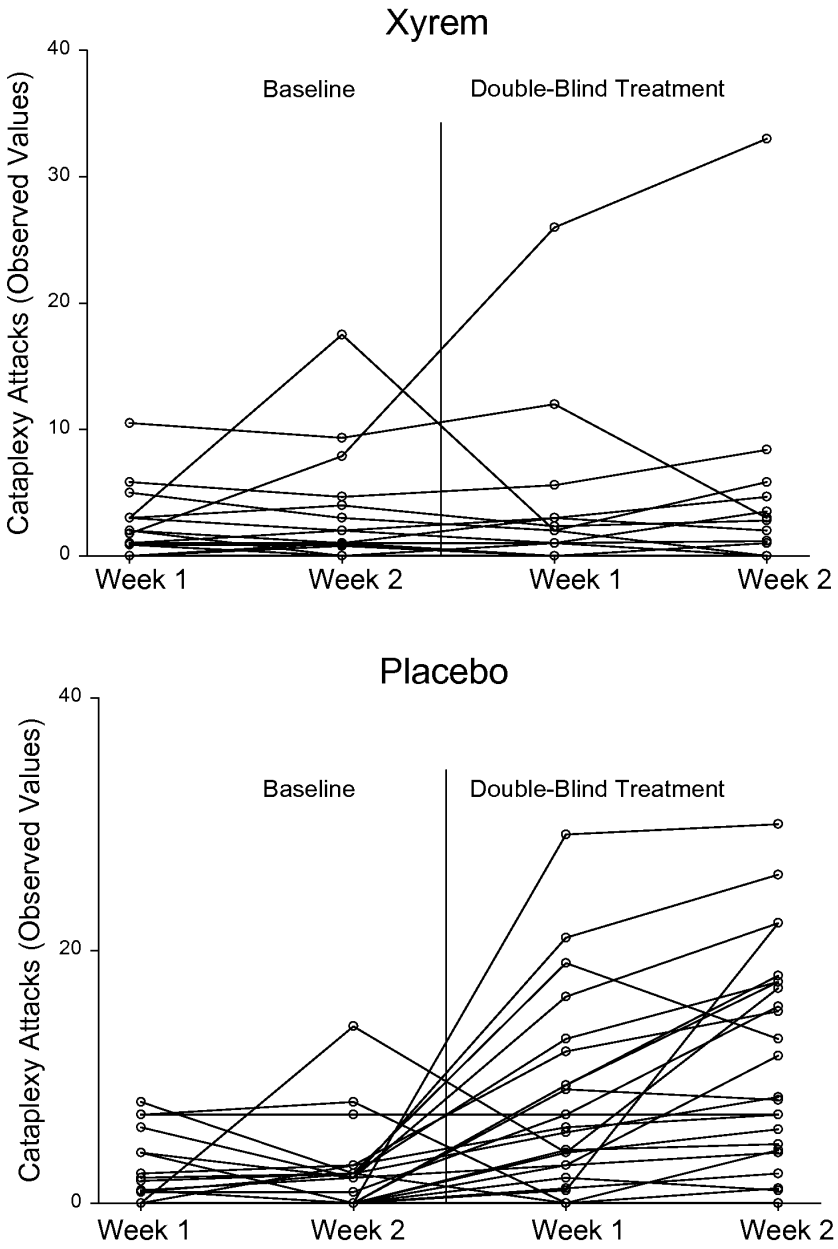
Figure 3.15 is a by-patient display of observed number of cataplexy attacks during Weeks 1 and 2 of the baseline period and during Weeks 1 and 2 of the double-blind treatment period. Solid lines are patients treated with placebo during double-blind treatment; dotted lines are patients treated with Xyrem. Because of the outliers (several patients had over 100 cataplexy attacks per week during Week 2 of the double-blind treatment period), it is difficult to discern a pattern among the data. Figure 3.16 is a by-patient display of observed number of cataplexy attacks over the course of the trial presented by treatment group. In this figure, for clarity, the 6 patients (4 placebo, 2 Xyrem) with values above 40 per week at any time are not displayed. It can be seen that patients who continued to receive Xyrem during double-blind treatment overwhelmingly maintained the low number of cataplexy attacks seen during the baseline period. In contrast, many patients who received placebo during the double-blind treatment phase showed increases at both Weeks 1 and 2, providing visual confirmation of the statistically significant increase (change from baseline) in median number of cataplexy attacks indicated by the summary statistics in Table 3.17 and Figure 3.13.

Figure 3.15 Observed Number of Cataplexy Attacks at Each Visit



Solid lines are patients treated with placebo during double-blind treatment; dotted lines are patients treated with Xyrem.

Figure 3.16 Observed Number of Cataplexy Attacks at Each Visit by Treatment Group



Six patients (4 placebo, 2 Xyrem) with values above 40 per week at any time are not displayed.

3.1.3.4.3 Efficacy Conclusions

OMC-SXB-21 was a randomized, double-blind, placebo-controlled, parallel group, multicenter trial to assess the long-term efficacy of orally administered Xyrem when compared to placebo. Patients entering this trial were using open-label Xyrem for the treatment of narcolepsy for a period of 7 to 44 months (mean = 21 months).

During the lead-in (baseline) phase of the trial, patients continued to take Xyrem in a single-blind fashion at their established effective dosage. The frequency of cataplexy attacks was measured during the 2-week baseline period by patient entries into daily diaries. There was no statistical difference ($p = 0.436$) between treatment groups in the mean number of cataplexy attacks during this period.

Following the baseline period, patients entered the 2-week double-blind treatment phase, where the frequency of cataplexy attacks was captured in daily diaries. Patients given placebo had significantly more cataplexy attacks (median change 21.0) than did patients who continued on active Xyrem treatment (median change 0.0). When the rank change was analyzed, a statistically significant difference was seen ($p < 0.001$), with a median rank change from baseline of 39.0 for the placebo group and 16.5 for the Xyrem group. As shown in Table 3.18 and Figure 3.14, change from baseline in the number of cataplexy attacks by week during the double-blind period mirrors the overall change from baseline: no change in the Xyrem group (median change 0.0, each week), while cataplexy attacks increased in the placebo group by a median of 4.2 in Week 1, and 11.7 in Week 2.

These data strongly indicate that Xyrem is an effective long-term treatment for the control of the narcolepsy symptom of cataplexy.

3.1.4 LAMMERS TRIAL

3.1.4.1 Design

The Lammers trial (The Netherlands) was a prospective, randomized, double-blind, placebo-controlled, 2-way crossover, single-center trial comparing the efficacy of 60 mg/kg (mean 4.7 g) sodium oxybate with placebo for the treatment of narcolepsy. The total nightly dose of trial medication was taken in 2 equal doses: just before going to sleep, and again 4 hours later. Each dose was administered orally in a solution containing sugar, citric acid, crème de cacao essence, and distilled water; placebo also contained trisodium citrate, and sodium chloride. The trial design is summarized in Table 3.19.

Table 3.19 Lammers Trial Design

Baseline 1	Treatment 1	Washout	Baseline 2	Treatment 2
1 Week	4 Weeks	3 Weeks	1 Week	4 Weeks
X	Sodium Oxybate (60 mg/kg)	X	X	Placebo
X	Placebo	X	X	Sodium Oxybate (60 mg/kg)
Continue concomitant treatment for cataplexy and EDS				

The trial consisted of two 5-week periods (1 week baseline observation, 4 weeks treatment) separated by a 3-week washout period. In each of the treatment periods, patients took randomly assigned trial medication (60 mg/kg [mean 4.7 g] sodium oxybate) or a similar placebo) in 2 divided doses at bedtime and 4 hours later as an added medication to existing therapy for narcolepsy. A total of 13 men and 12 women were treated; all completed the trial. One patient (patient 13) failed to keep his diary and was not evaluable.

To enter the trial, patients were required to have had a combination of sleep attacks during the day, and at least 1 of the "REM dissociation phenomena" (cataplexy, hynagogic hallucinations, and sleep paralysis); or, in case of clinical doubt, a positive multiple sleep latency test as recorded with a 24-hour EEG was required.

Patients were allowed to continue taking anti-cataplectic medications (TCAs/SSRIs) they had been using prior to enrollment in the trial; hence, sodium oxybate (or placebo) treatment was taken in addition to the patients' ongoing anti-cataplectic regimen (in contrast to OMC-GHB-2 and the Scrima trial, where anti-cataplectic medication was withdrawn prior to treatment with sodium oxybate). As in the OMC-GHB-2 trial and the Scrima trial, patients were allowed to continue on their stimulant medication for excessive daytime sleepiness at a constant dosage. Patients with cataplexy of relatively mild severity (approximately 5 attacks per week at baseline) were enrolled into the trial.

3.1.4.2 Objectives

Primary efficacy parameters were:

- The opinion of the patients on the benefit of the medication (global therapeutic impression [GTI])
- The opinion of the physician (global clinical impression; [GCI]) was not performed
- The number of cataplexy attacks per day

Secondary efficacy parameters were:

- The number of sleep attacks during the day
- The feeling of sleepiness during the day
- MSLT improvement of the two shortest latencies

- The stability of alertness during the day
- The duration of the nocturnal slow wave sleep on PSG
- The number of stage-shifts at night

The tolerability and safety of the medication was assessed by interviewing the patients. Comments with respect to tolerability were recorded on the patient questionnaires.

3.1.4.3 Statistical Analysis

In the published report (Lammers *et al* [1993]) intragroup differences were analyzed using Wilcoxon's signed-rank test. As a post-hoc reanalysis, an analysis of covariance was used employing a model appropriate for a crossover design. The significance of the covariate was (also) examined. Residuals were analyzed using the Shapiro-Wilk test and non-parametric methods (Wilcoxon).

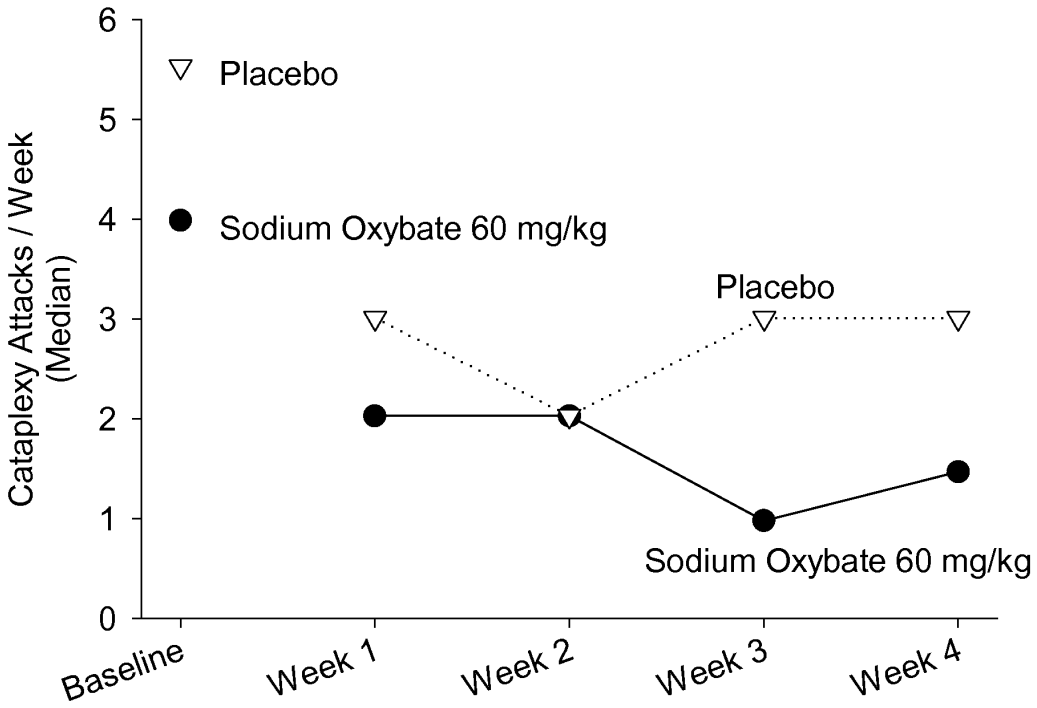
3.1.4.4 Efficacy Results

In the primary efficacy analysis reported in the publication derived from this study (Lammers *et al* [1993]), statistically significant differences between placebo and sodium oxybate-treated groups in the number of cataplexy attacks were not seen. Although the primary endpoint as analyzed according to the original statistical analysis plan did not reach statistical significance, it should be noted that patients enrolled in this trial presented with a much lower rate of cataplexy than seen in either OMC-GHB-2 or the Scrima trial (Lammers patients reported about one-fourth the rate of cataplexy attacks at baseline as did patients in either OMC-GHB-2 or the Scrima trial). In addition to this much lower rate of cataplexy, patients were allowed to continue using anti-cataplectic medication (TCAs/SSRIs) throughout the course of the trial. With such a low severity of disease at baseline, and in the presence of concomitant anti-cataplectic therapy, a robust treatment effect might prove difficult to demonstrate.

In addition, this non-significant p-value (reported in Lammers et al 1993) was obtained using a statistical model that treated each of the two drug administration periods as though they comprised two *independent* samples of patients. When these data were reanalyzed using a statistical model more appropriate for a crossover design (ANCOVA) that included treatment order, patient, period, and baseline cataplexy rate, the difference between placebo and sodium oxybate-treated groups was highly statistically significant ($p = 0.002$).

The number of cataplexy attacks/week by treatment group are presented in Figure 3.17.

Figure 3.17 Number of Cataplexy Attacks by Treatment Group — Lammers Trial



In the Lammers trial (publication), the Global Therapeutic Impression of Change (GTI) as rated by the patients was significantly more often in favor of sodium oxybate; 15/24 (62.5%) patients reported a beneficial effect during sodium oxybate treatment compared to 2/24 (8.3%) patients during placebo treatment (p =<0.001).

Marked improvements in excessive daytime sleepiness were evident. Statistically significant between treatment reductions in daytime sleepiness (p = 0.028) (based on the patient's assessment of the feeling of sleepiness recorded on a visual analogue scale), inadvertent naps/sleep attacks (p = 0.001) (recorded on the patient diary) resulted following 60 mg/kg (mean 4.7 g) sodium oxybate.

Reanalysis of the data using a statistical model more appropriate for a crossover design also revealed a highly significant (p = 0.002) reduction in the number of cataplexy attacks.

Among polysomnographic variables, the number of awakenings during REM sleep and the percentage of wakefulness during REM sleep (p = 0.016 and 0.007, respectively) were also improved. There were also statistically significant between treatment changes in hypnagogic hallucinations (p = 0.008).

3.1.4.5 Conclusions

The Lammers *et al* (1993) publication reported that sodium oxybate is an effective and well-tolerated treatment for symptoms of narcolepsy. Statistically significant between treatment reductions in daytime sleepiness ($p = 0.028$), inadvertent naps/sleep attacks ($p = 0.001$), and the patient GTI ($p<0.001$) following 60 mg/kg (mean 4.7 g) sodium oxybate. The number of awakenings during REM sleep, the percentage of wakefulness during REM sleep, and the frequency of hypnagogic hallucinations were also improved. Reanalysis of the data using a statistical model more appropriate for a crossover design also revealed a highly significant ($p = 0.002$) reduction in the number of cataplexy attacks.

3.2 Uncontrolled Studies

3.2.1 OMC-GHB-3

3.2.1.1 Trial Objectives and Design

3.2.1.1.1 Objectives

OMC-GHB-3 was an open-label, long-term extension of the OMC-GHB-2 double-blind trial. The primary objective of this study was to evaluate the safety of sodium oxybate when used in patients with narcolepsy for up to 24 months at doses of 3g, 4.5g, 6g, 7.5, or 9g daily. The secondary objective of this study was to evaluate the following measures of efficacy:

- Incidence of cataplexy attacks
- Daytime sleepiness as measured by the Epworth Sleepiness Scale and number and duration of inadvertent naps
- Quality of nighttime sleep as measured by the number of awakenings during the night and the total amount of sleep
- Incidence of hypnagogic hallucinations
- Incidence of sleep paralysis
- Clinical Global Impressions of Change in Severity
- Ability to Concentrate
- Quality of Sleep
- Level of Alertness

3.2.1.1.2 Trial Design

Visit 1 occurred concurrently with Visit 7 of OMC-GHB-2. Patients were not randomized to dose. All patients were to begin the study on 6g daily and investigators were required to titrate the patients to the optimum dose (3g, 4.5g, 6g, 7.5g, or 9g sodium oxybate) based on safety and efficacy. Patients made study site visits every 2 weeks during the first month of the trial, (Visits 2 and 3); one month later (Visit 4); then at 2-month

intervals (Visits 5 – 12) for months 4 - 18; then at 3-month intervals (Visits 13 and 14) for months 21 and 24. Primary clinical endpoints were the two week intervals immediately preceding Visits 3, 4, 5, 6, 7, 8 and 9.

Efficacy information was collected using patient diaries through Month 18; for the Month 21 and 24 assessments it was collected via a patient questionnaire completed by the patient during the study site visit.

During these visits the following procedures were performed:

Visit 1
- Administration of Epworth Sleepiness Scale
- Administration of Clinical Global Impressions of Change in Severity

Visits 2 - 12
- Collection and review of all diaries
- Administration of Epworth Sleepiness Scale
- Administration of Clinical Global Impressions of Change in Severity

Visits 13 and 14
- Narcolepsy Symptom Assessment administration

3.2.1.1.3 Patient Selection Criteria

Participation was offered to all patients completing OMC-GHB-2, if they so wished and their physician concurred. They were still required to meet all the same entry criteria with the exception of a minimum incidence of cataplexy of 3 times per week. In addition, patients could not be taking medication for their disease other than a stable dose of stimulant medication.

3.2.1.1.4 Treatments

Patients entering OMC-GHB-3 were to begin the trial with 6g of sodium oxybate nightly. The total nightly dose was divided into 2 equal doses. If indicated, the sodium oxybate dose could be decreased to 3g or 4.5g per night, or increased to 7.5g or 9g per night. After the individualized dose of sodium oxybate was established, patients were to maintain that dose from Visit 2 through the completion of the trial, although dose changes after Visit 2 were permitted if clinically indicated. Patients were considered non-compliant if they missed more than 30% of their expected doses during any period between scheduled visits.

3.2.1.1.5 Efficacy Measurements and Analysis

Patients were instructed to complete diaries on several efficacy measures. These measures included:

- Total number of cataplexy attacks
- Number of complete cataplexy attacks
- Number of partial cataplexy attacks
- Number of inadvertent naps and sleep attacks
- Number of planned naps
- Duration of planned naps
- Number of times patient woke up during the night
- Total amount of sleep
- Number of episodes of hypnagogic hallucinations
- Number of episodes of sleep paralysis
- Ability to Concentrate
- Quality of Sleep
- Level of alertness in morning

Non-diary measures of efficacy included the following:

- Epworth Sleepiness Scale
- Severity of the patient's symptoms as measured by the Clinical Global Impression of Change

The primary efficacy parameter was the change in the total number of cataplexy attacks (TNCA) from baseline (from OMC-GHB-2 trial) to endpoint. Change in TNCA was evaluated based on the weekly average of the TNCA. Since diary entries were not always completed for an assessment period (2 weeks), the completed TCNA data were normalized by calculating the daily average of the endpoint two-week interval and multiplying by 7.

Other efficacy parameters collected during the study were considered secondary measures.

3.2.1.1.6 Statistical and Analytical Plans

The following definitions were used for the planned analyses of this study:

Baseline = the Baseline period in the OMC-GHB-2 trial as defined in the protocol. Baseline for "Overall Ability to Concentrate, Quality of Sleep, and Level of Alertness", was taken from Visit 2 in OMC-GHB-3.

Endpoints = the two week intervals immediately preceding Visits 3, 4, 5, 6, 7, 8 and 9 in the 12-month OMC-GHB-3 trial. The two week intervals immediately preceding Visits 10, 11, and 12 for the 12 month follow-up period.

Statistical analysis was performed on an intent-to-treat population. All patients who received a single dose of study medication during the trial were included. Treatment groups were developed by calculating the average dose used over the course of the study and rounding to the nearest dose category.

The average total number of cataplexy attacks was the primary efficacy measure. Overall treatment group comparison of the log mean change from baseline for TCNA was determined using analysis of covariance (ANCOVA) using the model:

$$\log(TNCA+1) - \text{Baseline } \log(TNCA+1) = \text{Treatment} + \text{Baseline Log}(TNCA+1)$$

No pairwise comparisons were performed. Within-group and All Patient analyses were performed using Wilcoxon Sign Rank Test.

For the secondary efficacy measures, selected statistical testing was performed. For continuous measures, ANCOVA was used to examine overall treatment effect. Within-group comparisons were performed using paired t-tests. For dichotomous secondary efficacy measures, Fisher's Exact test was utilized to examine overall treatment effect.

3.2.1.2 Patient Disposition and Demographics

3.2.1.2.1 Patient Disposition

By protocol amendment, patients could continue the study for up to 24 months, however, data were analyzed in detail only for the 12-month study duration indicated in the original protocol. Efficacy and safety were analyzed in summary for up to 18 months and 24 months, respectively.

The disposition of patients through 12 months of the study from the combined dose categories is shown in Figure 3.18. Disposition of patients through 24 months is presented in Table 3.20.

Figure 3.18 Disposition of Patients in OMC-GHB-3 Through 12 Months

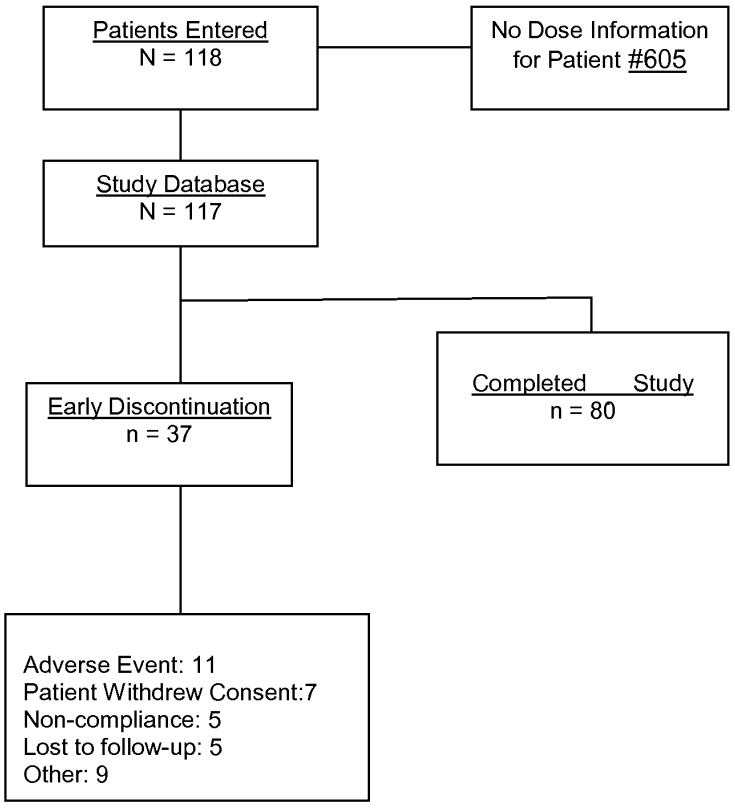


Table 3.20 Disposition of Patients in OMC-GHB-3 Months 12 to 24

	Visit (Month)				
Reason For Withdrawal	9 (12 M)	10 (14 M)	11 (16 M)	12 (18 M)	14 (24 M)
AE	0	1	0	0	0
LOST TO FOLLOW-UP	2	1	0	0	0
NON-COMPLIANCE	2	1	2	2	0
PROTOCOL VIOLATION	0	1	0	0	0
WITHDREW CONSENT	1	1	1	0	2
OTHER	0	1	0	3	1
COMPLETED STUDY	0	2	6	7	39
TOTAL	5	8	9	12	42
Visit	9	10	11	12	14
Active Patients	76	71	63	54	42

3.2.1.2.2 Patient Demographics

The demographic characteristics of the 117 patients who received study medication are summarized in Table 3.21 below.

Table 3.21 Baseline Demographic Characteristics of Study Population (OMC-GHB-3)

Characteristic	All Patients	GHB dose (g) 3	4.5	6	7.5	9	p-value*
	N (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Age (years)							0.262
N	117	15	20	37	25	20	
MEAN	43.4	44.9	48.7	44.3	39.5	40.2	
SD	15.1	14.1	14.7	14.5	17.0	14.1	
MIN	18.0	20.0	25.0	22.0	18.0	24.0	
MAX	79.0	73.0	71.0	67.0	79.0	65.0	
Gender							0.002
Male	51 (43.6)	1 (6.7)	7 (35.0)	15 (40.5)	15 (60.0)	13 (65.0)	
Female	66 (56.4)	14 (93.3)	13 (65.0)	22 (59.5)	10 (40.0)	7 (35.0)	
Race							1.000
Caucasian	108 (92.3)	14 (93.3)	19 (95.0)	33 (89.2)	23 (92.0)	19 (95.0)	
African-American	7 (6.0)	1 (6.7)	1 (5.0)	2 (5.4)	2 (8.0)	1 (5.0)	
Asian	1 (0.9)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	
Other	1 (0.9)	0 (0.0)	0 (0.0)	1 (2.7)	0 (0.0)	0 (0.0)	
Height (cm)							0.017
N	99	12	16	28	24	19	
Mean	172.3	164.9	171.4	172.5	176.2	172.5	
SD	9.4	6.1	10.8	9.9	7.5	9.3	
Weight (kg)							0.003
N	106	13	17	32	24	20	
Mean	83.7	67.0	80.6	85.4	89.5	87.6	
SD	18.0	14.7	16.9	17.1	20.6	12.6	
MIN	48.5	49.4	57.2	48.5	60.8	66.2	
MAX	134.3	93.0	116.1	113.0	134.3	118.0	

*p-value: Age based on ANOVA (GLM);
Sex and Race based on Fisher's Exact Test.
Baseline = the Baseline period in Study OMC-GHB-02.

Statistically significant differences across treatment groups were noted for sex. Additional statistically significant differences across treatment groups were noted for height and weight, consistent with the differences in distribution by sex. The majority of the 3g, 4.5g, and 6g sodium oxybate groups were female, and the majority of the 7.5g and 9g sodium oxybate groups were male.

3.2.1.3 Efficacy Evaluation

3.2.1.3.1 Treatment Compliance

At each study visit through 18 months, the overall patient population was 94% compliant with study medication through 18 months of the study.

3.2.1.3.2 Efficacy Results

By protocol amendment, patients could continue the study for up to 24 months, however, data were analyzed only for the 12-month study duration indicated in the original protocol.

For all efficacy parameters, change from baseline evaluations at specific visits represented comparison to the same measures from the OMC-GHB-2 trial end of baseline period (Visit 4).

Total number of cataplexy attacks. The results presented in Table 3.22, a summary of mean change from baseline to all endpoints for total number of cataplexy attacks per week by visit, show the significant effect produced by all combined dose groups on this primary efficacy parameter. Graphical display for cataplexy attacks per week by visit through 18 months for the median percent change from baseline, are presented in Figure 3.19. Figure 3.19 shows that that majority of the reduction in cataplexy attacks occurred during the first month of sodium oxybate treatment; there was a greater than 75% median reduction in cataplexy attacks at Visit 3 (month 2 from Baseline, month 1 of OMC-GHB-03 study treatment) and an almost 90% median reduction in cataplexy attacks at Visit 4 (month 3 from Baseline, month 2 of OMC-GHB-03 study treatment).

Graphical display for cataplexy attacks per week by dose through 12 months for the median percent change from baseline, are presented in Figure 3.20. Values were calculated from the distribution of change values for each individual. Figure 3.20 displays that there are no dose differences for change in cataplexy attacks with sodium oxybate treatment when patients are titrated to clinical effect. Greater than 90% median reduction was maintained through 18 months of study treatment (19 months from Baseline).

Table 3.22 Change and Percent Change From Baseline to Endpoints for Total Number of Cataplexy Attacks per Week by Visit Through 18 Months (OMC-GHB-3)

	Visit Number (month)									
	3 (1 m)	4 (2 m)	5 (4 m)	6 (6 m)	7 (8 m)	8 (10 m)	9 (12 m)	10 (14 m)	11 (16 m)	12 (18 m)
Change from baseline to Visit										
N[1]	103	102	93	89	83	77	75	71	62	52
Mean[2]	-23.65	-27.50	-30.91	-32.24	-34.70	-34.51	-35.48	-36.79	-35.47	-36.14
SD	33.04	36.89	41.92	42.73	43.22	43.68	43.49	45.92	39.27	43.18
Median	-15.08	-18.25	-18.67	-19.00	-22.56	-22.17	-23.00	-23.60	-25.08	-20.08
1st Quart.	-27.00	-32.17	-34.35	-35.00	-37.83	-38.00	-38.00	-41.46	-41.00	-44.49
3rd Quart.	-5.50	-7.39	-10.00	-9.13	-11.00	-11.00	-10.50	-10.84	-11.81	-11.07
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
% Change from baseline to Visit										
Mean[2]	-61.09	-72.24	-77.93	-81.89	-86.40	-73.12	-80.05	-84.03	-85.38	-83.19
SD	60.02	46.63	35.53	29.75	25.14	79.29	42.04	30.92	22.91	25.40
Median	-76.67	-88.24	-89.53	-92.50	-96.96	-92.19	-93.08	-94.35	-95.28	-92.68
1st Quart	-93.91	-98.37	-98.00	-100.00	-100.00	-100.00	-99.73	-100.00	-100.00	-99.60
3rd Quart	-50.39	-68.07	-77.42	-80.96	-84.87	-79.03	-77.78	-83.20	-79.76	-78.61
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[1]N reflects all patients with available data for number of cataplexy attacks at that visit.
[2]Weekly average total number of cataplexy attacks (TNCA) assessed as: (Daily average of the endpoint two week interval)*7
*p-value(Within Group) based on Wilcoxon Sign Rank test for change from baseline.

Figure 3.19 Median Percent Change from Baseline for Total Number of Cataplexy Attacks Per Week through 18 Months (OMC-GHB-3)

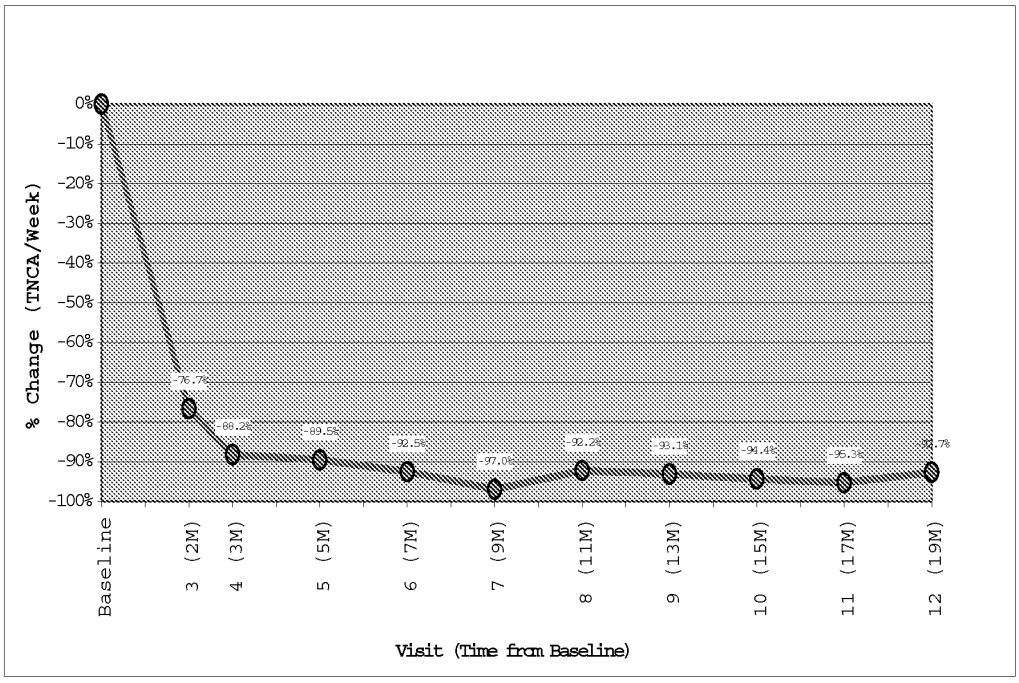


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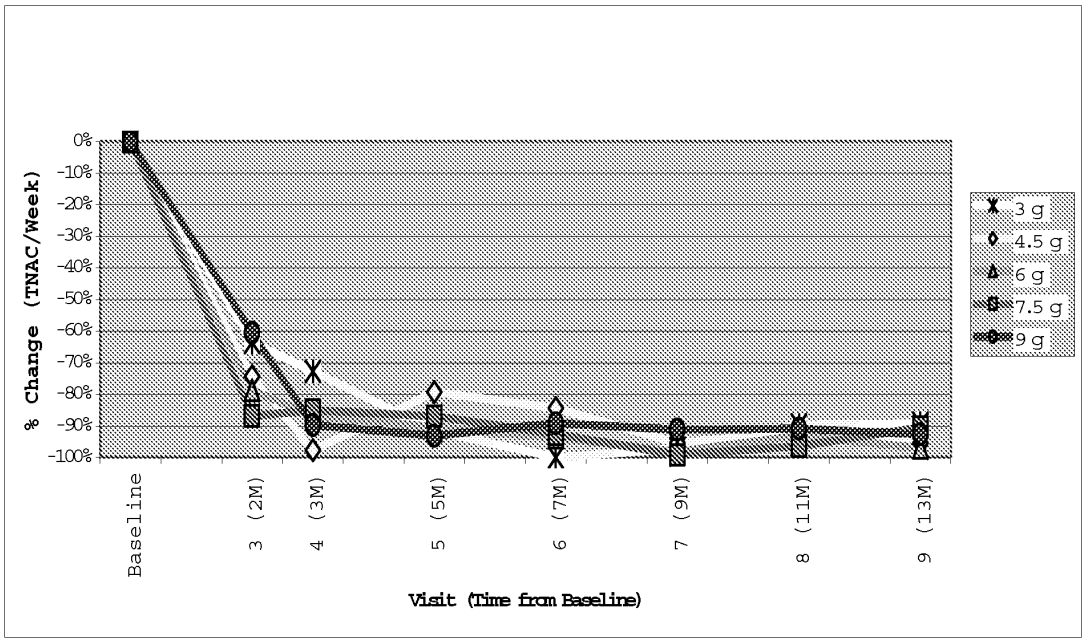
Figure 3.20 Median Percent Change from Baseline for Total Number of Cataplexy Attacks Per Week by Dose through 12 Months (OMC-GHB-3)



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Daytime Sleepiness. The results presented in Table 3.23, a summary (through 12 months of the study) of change from baseline to overall endpoints in daytime sleepiness by visit as measured by the Epworth Sleepiness Scale (ESS), show the significant effect produced by the combined dose groups on this secondary efficacy parameter. There was statistically significant improvement observed at all visits, but there was little or no change in the daytime Epworth Sleepiness Scale values with successive visits. The overall mean change from baseline was -4.47 (SD = 5.05) at Visit 3 (1 month) and -5.30 (SD = 4.57) at Visit 9 (12 months). The mean change from baseline in Epworth Daytime Sleepiness was statistically significant ($p<0.001$) at all study visits.

Table 3.23 Change from Baseline to Endpoints in Daytime Sleepiness as Measured by the Epworth Sleepiness Scale by Visit

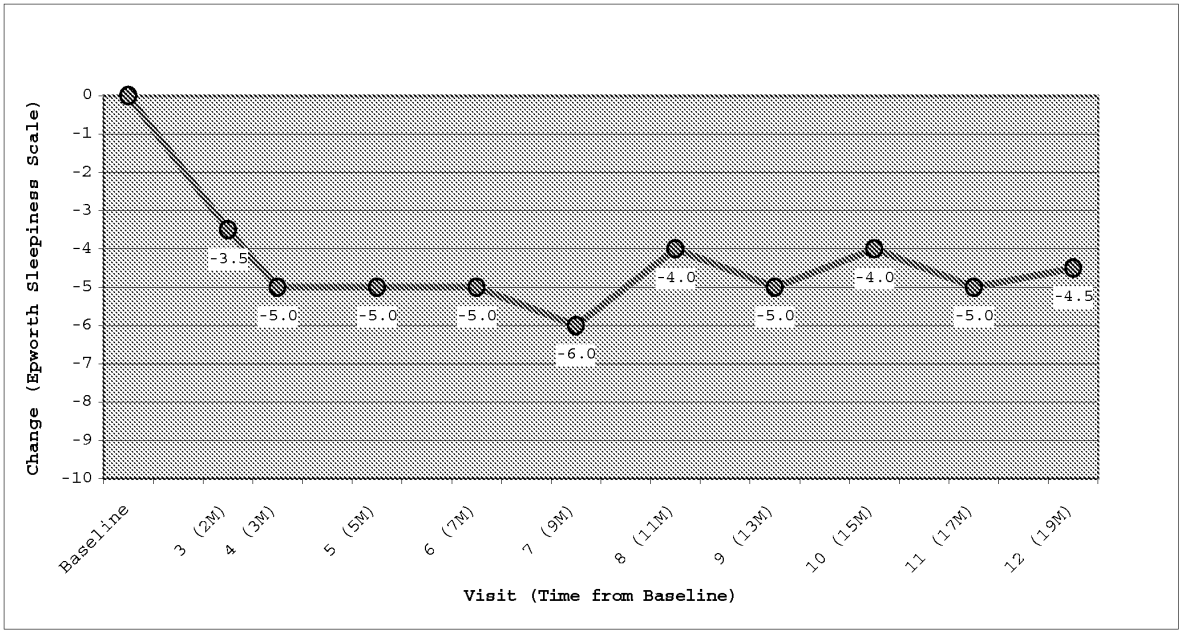
	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline* to Visit							
N[1]	106	99	91	87	83	75	74
Mean	-4.47	-5.56	-6.02	-5.76	-6.30	-5.23	-5.30
SD	5.05	5.44	5.53	4.82	5.05	4.81	4.57
Median	-3.50	-5.00	-5.00	-5.00	-6.00	-4.00	-5.00

[1]N reflects all patients with available data for Epworth Sleepiness scale at that visit.
*Baseline taken from OMC-GHB-2.

Graphical display for daytime sleepiness by visit through 18 months for the median change from baseline is presented in Figure 3.21. Visit times (months) for Figure 3.21 time intervals are measured from the Baseline (Baseline, taken from OMC-GHB-02, was 1 month prior to Visit 1 of OMC-GHB-03) rather than time since Visit 1, and, therefore, do not reflect the exact amount of time in study OMC-GHB-3. These values were calculated from the distribution of change values for each individual. The maximum effect was achieved by Visit 4 (month 3 from Baseline, month 2 of OMC-GHB-03 study treatment). The maximum decrease in daytime sleepiness was an approximate 35% median decrease in the Epworth Sleepiness scale. Clinical benefit in diminished daytime sleepiness appeared to be maintained through 18 months of study treatment (19 months from Baseline). Statistical assessment across treatment groups (3, 4.5, 6, 7.5, and 9 g/d) demonstrated that there were no significant dose differences for change in the Epworth Sleepiness Scale values.

It is important to note that the changes in EDS in response to Xyrem treatment show an identical temporal response as was seen in cataplexy, with maximum change occurring in about 8 weeks from start of treatment, and then maintained response over the remainder of the 12 months.

Figure 3.21 Median Change from Baseline in Daytime Sleepiness (Epworth Sleepiness Scale) through 18 Months (OMC-GHB-3)



Inadvertent Naps/Sleep Attacks. Table 3.24 presents change from baseline to endpoints in total number and duration of inadvertent naps and sleep attacks/day by visit. These data demonstrate a slight decline (increased negative change from baseline) in the number of inadvertent naps and a general trend towards continued decline (increased negative change from baseline) in the duration of inadvertent naps with successive visits. There was no statistically significant Xyrem effect on this parameter.

Table 3.24 Change from Baseline to Endpoints in Total Number and Duration of Inadvertent Naps (Sleep Attacks/day) by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline to Visit							
Total number of inadvertent naps (sleep attacks) (N/day)							
N[1]	103	102	93	89	83	77	75
Mean	-0.77	-0.84	-0.91	-1.03	-1.04	-0.93	-1.03
SD	1.28	1.41	1.36	1.36	1.39	1.36	1.29
Median	-0.64	-0.63	-0.71	-0.85	-0.84	-0.85	-0.60
Total duration of inadvertent naps and sleep attacks (min)							
N[1]	102	101	92	88	82	77	75
Mean	-20.27	-24.29	-25.59	-26.27	-26.05	-28.35	-29.64
SD	39.00	42.45	40.60	44.32	52.21	46.26	47.74
Median	-9.96	-12.31	-11.36	-11.69	-14.32	-14.87	-10.86

[1]Patients with non-missing assessments.

Number and Duration of Planned Naps. Table 3.25 presents change from baseline to endpoints in total number and duration of planned naps by visit. These data demonstrate a decrease from baseline to Visit 3 in the number of planned naps with no change at subsequent visits and a decrease in the duration of planned naps at Visit 3 with continued improvement at successive visits. There was no statistically significant Xyrem effect on this parameter.

Table 3.25 Change From Baseline to Endpoints in Total Number and Duration of Planned Naps by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline to Visit							
Total number of planned naps (N/day)							
N[1]	102	101	93	88	82	76	74
Mean	-0.21	-0.23	-0.24	-0.29	-0.24	-0.20	-0.25
SD	0.50	0.56	0.68	0.68	0.74	0.83	0.74
Median	-0.14	-0.14	-0.10	-0.14	-0.12	-0.16	-0.15
Total duration of planned naps (min)							
N[1]	100	100	92	87	81	76	74
Mean	-12.63	-13.26	-14.94	-16.96	-15.60	-14.49	-17.17
SD	34.41	40.64	44.81	46.01	51.50	53.57	52.63
Median	-5.45	-7.77	-7.28	-12.77	-7.47	-9.74	-10.14

[1]Patients with non-missing assessments.

Nighttime sleep. Improvement in nighttime sleep was measured by collecting the number of reported awakenings during each night and the total amount of sleep each night preceding the visit to the research center. Improvement in nighttime sleep recorded in the patient diaries was evaluated and compared to the same measures from the OMC-GHB-2 trial end of baseline visit (Visit 4).

The results for the number of awakenings and total amount of sleep are shown in Table 3.26. These data demonstrate improvement from baseline at successive visits for number of awakenings per night and improvement from baseline in the total duration of sleep per night. There was little change at successive visits in the total duration of sleep per night.

Table 3.26 Change From Baseline to Endpoints for the Number of Awakenings Each Evening and the Total Amount of Sleep by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline to Visit for:							
Number of awakenings (N/night)							
N[1]	103	102	93	89	83	77	75
Mean	-0.64	-0.71	-0.82	-0.95	-0.86	-0.95	-0.92
SD	1.51	1.62	1.66	1.59	1.58	1.65	1.60
Median	-0.48	-0.64	-0.57	-0.79	-0.71	-0.67	-0.54
Total amount of sleep (min)							
N[1]	102	101	92	88	81	76	75
Mean	18.45	14.09	21.97	18.32	26.33	22.86	19.60
SD	68.80	66.97	73.08	75.14	76.33	97.45	80.68
Median	16.39	9.75	15.31	17.50	24.07	13.60	13.72

[1]Patients with non-missing assessments.

Hypnagogic hallucinations and Sleep paralysis. Not all patients with narcolepsy report either hypnagogic hallucinations or sleep paralysis. However, in this study, 102 patients (87.2%) and 103 patients (88.0%), reported hypnagogic hallucinations or sleep paralysis symptoms, respectively, at Visit 3. The number of occurrences of these symptoms as recorded in the patient diaries were evaluated and compared to the same measures from the
OMC-GHB-2 trial end of baseline visit (GHB-2 Visit 4).

The results for the number of hypnagogic hallucinations and number of episodes of sleep paralysis are summarized in Table 3.27. A trend towards diminished symptoms was evident, at Visit 3 compared to Baseline and at subsequent visits.

Table 3.27 Change From Baseline to Endpoints for the Number of Hypnagogic Hallucinations and Number of Episodes of Sleep Paralysis by Visit

	Visit Number						
	3 (mo.1)	4 (mo.2)	5 (mo.4)	6 (mo.6)	7 (mo.8)	8 (mo.10)	9 (mo.12)
Change from baseline to Visit for:							
Number of hypnagogic hallucinations (N/day)							
N[1]	102	101	93	88	82	76	74
Mean	-0.48	-0.58	-0.64	-0.71	-0.71	-0.78	-0.78
SD	1.83	1.89	2.07	2.17	2.23	2.36	2.38
Median	-0.18	-0.22	-0.23	-0.30	-0.28	-0.30	-0.29
Number of episodes of sleep paralysis (N/day)							
N[1]	103	102	93	89	83	77	75
Mean	-0.38	-0.43	-0.44	-0.48	-0.49	-0.54	-0.51
SD	0.95	1.11	1.16	1.21	1.23	1.30	1.29
Median	-0.07	-0.08	-0.08	-0.09	-0.14	-0.14	-0.12

[1]Patients with non-missing assessments.

Clinical Global Impression of Change (CGI-c). Table 3.28 displays the results for the CGI-c assessments for each visit by individual treatment group. For the purposes of this report, patients are categorized as “responders” or “non-responders”. Approximately 80% of all patients were categorized as responders at Visit 3, however, there appeared to be a trend towards continued improvement (increased percentage of responders) at successive visits.

The response was relatively uniform across doses; there was a statistically significant difference across treatment groups at Visits 4 (p=0.017) and 6 (p=0.016) only. This difference by dose was most probably due to the variability inherent in any group with a relatively small number of patients (n = 14 for the 3g sodium oxybate dose group at Visit 4 and n = 15 for the 4.5g sodium oxybate dose group at Visit 6) and not a true reflection of a real dose-effect.

Table 3.28 Change from Baseline to Endpoints for Clinical Global Impression of Change (CGI-c) by Visit

	Visit Number						
	3 (mo.1)	**4 (mo.2)**	**5 (mo.4)**	**6 (mo.6)**	**7 (mo.8)**	**8 (mo.10)**	**9 (mo.12)**
N[1] Total Patients	108	101	95	89	83	77	74
Change from baseline to Visit							
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Very much improved	36 (33.3)	38 (37.6)	40 (42.1)	40 (44.9)	40 (48.2)	35 (45.5)	34 (45.9)
Much improved	48 (44.4)	50 (49.5)	41 (43.2)	44 (49.4)	40 (48.2)	38 (49.4)	33 (44.6)
Minimally improved	15 (13.9)	9 (8.9)	7 (7.4)	3 (3.4)	2 (2.4)	3 (3.9)	6 (8.1)
No change	3 (2.8)	1 (1.0)	4 (4.2)	1 (1.1)	1 (1.2)	1 (1.3)	0 (0.0)
Minimally changed	5 (4.6)	3 (3.0)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Much worse	1 (0.9)	0 (0.0)	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Responder*	84 (77.8)	88 (87.1)	81 (85.3)	84 (94.4)	80 (96.4)	73 (94.8)	67 (90.5)
Non-responder	24 (22.2)	13 (12.9)	14 (14.7)	5 (5.6)	3 (3.6)	4 (5.2)	7 (9.5)

[1]N reflects all patients with available data for CGI-c scores at that visit.

*Responder = "Very much improved" or "Much improved" on CGI-c scale. Non-responder = all other categories except "Not assessed".

Ability to Concentrate, Quality of Sleep, and Level of Alertness. The efficacy measures of ability to concentrate, quality of sleep, and level of alertness are summarized in Table 3.29. The Baseline for Ability to Concentrate was Visit 2 of the OMC-GHB-3 Study; for other variables Baseline was the Baseline (Visit 4) of the OMC-GHB-2 Study. At Visit 3 all dose groups provided statistically significant improvement in the three efficacy parameters. The only exceptions were in Quality of Sleep (p=0.056) and Level of Alertness (p=0.068), both in the 4.5g treatment group. Similar statistical significance was observed for the three efficacy parameters at Visit 9. The only exception was in Level of Alertness (p=0.055), in the 3g sodium oxybate treatment group. These p-values, just above the level of statistical significance, were probably due to variability inherent in the small number of patients (n=6) in the 4.5g group, and did not reflect a true treatment failure. There were no statistically significant values across-treatments.

Table 3.29 Change from Baseline to Endpoints for the Overall Ability to Concentrate, Quality of Sleep, and Level of Alertness by Treatment Group

		GHB dose (g)					
	All Patients	**3**	**4.5**	**6**	**7.5**	**9**	**p-value***
Measure[1] of change from baseline[2] to **visit 3**							
Ability to Concentrate							
N[3]	104	14	6	55	8	21	0.719
Mean	0.66	0.81	0.56	0.66	0.76	0.56	
SD	0.59	0.69	0.37	0.58	0.58	0.61	
Median	0.69	0.93	0.41	0.69	0.79	0.44	
p-value**	<0.001	0.001	0.013	<0.001	0.007	<0.001	
Quality of Sleep							
N[3]	105	14	6	55	9	21	0.720
Mean	0.76	0.74	0.48	0.80	0.84	0.74	
SD	0.56	0.46	0.48	0.59	0.59	0.57	
Median	0.79	0.94	0.43	0.78	0.87	0.86	
p-value**	<0.001	<0.001	0.056	<0.001	0.003	<0.001	
Level of Alertness							
N[3]	105	14	6	55	9	21	0.463
Mean	0.65	0.67	0.37	0.70	0.74	0.53	
SD	0.58	0.49	0.39	0.63	0.67	0.48	
Median	0.65	0.56	0.33	0.67	0.81	0.52	
p-value**	<0.001	<0.001	0.068	<0.001	0.011	<0.001	

[1]Weighted Average of Measure (WAM) = $(1xN_{POOR} + 2xN_{FAIR} + 3xN_{GOOD} + 4xN_{EXCEL})/N$, where N_{POOR}, N_{FAIR}, N_{GOOD}, N_{EXCEL} = number of days with poor, fair, good, and excellent level of measure, respectively. $N = N_{POOR} + N_{FAIR} + N_{GOOD} + N_{EXCEL}$ = total number of days reported.

[2]Baseline for Ability to Concentrate was the Visit 2 of Study OMC-GHB-3; for other measures, Baseline was the Baseline period in Study OMC-GHB-2.

[3]Patients with non-missing assessments.

*p-value for overall treatment group based on ANOVA (GLM)

**p-value within treatment group based on paired t-test for change from baseline.

3.2.1.4 Conclusions

Eighty-six patients (73.5%) reached dose stabilization in this open-label, long-term study. For all patients who reached dose stabilization, the mean was 3.38 weeks. As displayed in Table 3.30, there was an increased distribution of patients in the higher dose groups by last reported dose.

Table 3.30 Distribution of Patients by the Last Reported Dose (OMC-GHB-3)

	GHB dose (g)				
All Patients	**3**	**4.5**	**6**	**7.5**	**9**
	n	n	n	n	n
	(%)	(%)	(%)	(%)	(%)
117	16	11	42	13	35
	(13.7)	(9.4)	(35.9)	(11.1)	(29.9)

Overall clinical improvement, assessed as change from baseline, was evident at the earliest endpoint (Visit 3), and was maintained at all endpoints throughout the study. Patients were titrated to achieve maximum clinical benefit. In general, there appeared to be no compelling evidence of enhanced benefit with increasing dose. The data from this 12-month, open-label study demonstrate that 3g to 9g doses of sodium oxybate taken in divided doses before bedtime and 2.5-4 hours later produced significant and long-term clinical improvement in the symptoms of narcolepsy.

For the overall population, there was highly statistically significant improvement from baseline at all visits for the primary efficacy parameter, number of cataplexy attacks. There appeared to be continued improvement at successive visits; the mean change from baseline for overall treatment was a decrease of 23.65 cataplexy attacks at Visit 3 and a decrease of 35.48 cataplexy attacks at Visit 9.

Except for the 3g and 4.5g sodium oxybate dose groups at Visit 3 (p=0.122 and p=0.074, respectively), the change from baseline in number of cataplexy events was highly statistically significant for all dose groups at all visits. Statistical assessment across treatment groups demonstrated that there was no significant dose differences for change in this primary efficacy parameter. It is important to note that patients in study OMC-GHB-3 began the study on 6g daily and investigators were required to titrate the patients to an individualized dose (3g, 4.5g, 6g, 7.5g, or 9g sodium oxybate) based on safety and efficacy. Therefore, p-values for comparisons across dose groups were not expected to show statistical significance as doses represented the patients' average dose throughout the study and were not randomized groups.

Except for the 4.5g sodium oxybate dose group at Visit 3 (p=0.104) and Visit 6 (p=0.087), the decrease from baseline in daytime sleepiness as measured by the

Epworth Sleepiness Scale was statistically significant for all dose groups at all visits. There was little or no additional improvement, however, beyond Visit 3.

A trend towards diminished symptoms was evident for all secondary efficacy parameters including: frequency and duration of inadvertent naps and sleep attacks; frequency and duration of planned naps; frequency of awakenings that occurred during the night; and frequency of hypnagogic hallucinations and episodes of sleep paralysis. However, the statistical design did not provide definitive statistical support for the clinical benefit of sodium oxybate for these secondary efficacy parameters.

For all patients the overall response to treatment, as assessed by the Clinical Global Impression of Change, was clear and positive. Responders ranged from 78.5% at Visit 3 to 96.4% at Visit 7. There was a slight trend towards a dose relationship in the CGI-c at the earlier visits, and there was no statistically significant difference across treatment groups.

3.2.2 OMC-SXB-20

3.2.2.1 Rationale

Nocturnal polysomnography provides an objective means to determine the neurological and physiological changes in response to treatment, and would provide an opportunity to obtain a broader understanding of the overall effects of Xyrem on sleep. Previous polysomnographic studies of the effects of sodium oxybate have been published in normal subjects (Lapierre 1990), non-narcoleptic depressive patients (Mamelak 1977) and in surgical patients with intravenous infusion to produce sedation (Entholzner 1995), all indicating that sodium oxybate increased delta wave sleep.

Medications used for cataplexy (TCAs and SSRIs) and for improved sleep (hypnotics and barbiturates) are known to cause a decrease in REM sleep. For example, the reductions in REM sleep have been noted for, but are not limited to, the benzodiazepine hypnotics flunitrazepam, flurazepam, and triazolam (Borbely 1985), fluvoxamine and other SSRIs (Wilson 2000, Oberndorfer 2000), the TCA imipramine (Kupfer 1989), and the imidazopyridine hypnotic Zolpidem (Brunner 1991). Since sodium oxybate has been described to produce improvement of sleep and cataplexy symptoms, it was of interest for this NDA to characterize the effects of this drug on narcoleptic sleep architecture in relation to dose.

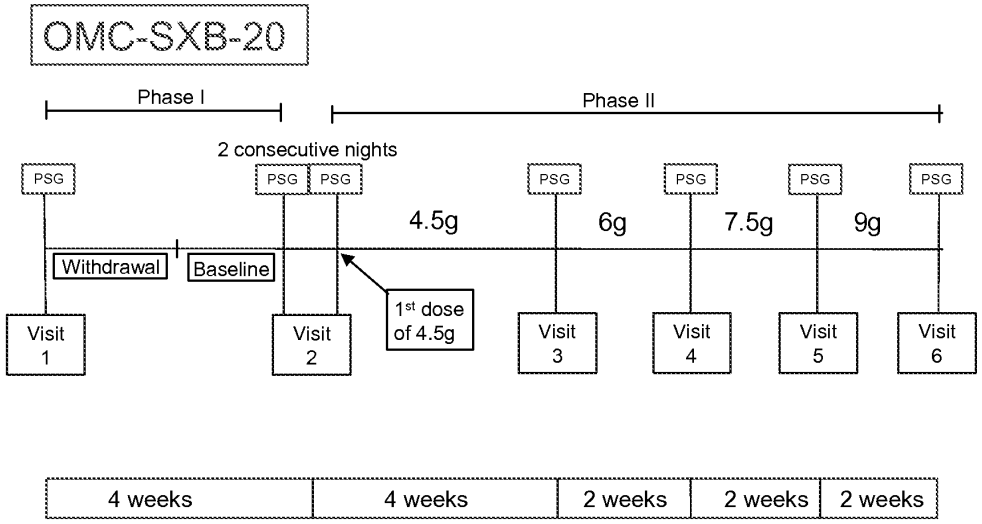
The effects of sodium oxybate on objective measures of nocturnal sleep in narcoleptic patients have been studied in six previous clinical studies (Broughton and Mamelak 1976,1980; Scharf 1985; Bedard 1989; Scrima 1990; Lammers 1993). These six studies have examined the non-comparative effects of doses of sodium oxybate ranging from 2.25 g up to 6.75 g. In general, these previous PSG studies demonstrated that sodium oxybate produces a modest decrease in Stage 1 sleep, no changes in Stage 2 sleep, a marked increase in Stages 3 and 4 sleep (delta sleep or slow wave sleep), and a decrease in the number of awakenings. Several of the trials also documented a decrease in the number of stage shifts and a decrease in REM latency. No change in

REM stage sleep duration was reported. Since the dosing regimen of sodium oxybate in these studies was different from Xyrem, it was of interest for this NDA to characterize the effects of Xyrem on the sleep architecture profile of narcoleptic patients across the doses proposed in the therapeutic regime.

3.2.2.2 Trial Objectives/Design

The primary objective of this trial design (Figure 3.22) was to characterize the polysomnographic (PSG) sleep architecture in narcoleptic patients at four escalating doses (4.5 g, 6.0 g, 7.5 g, and 9.0 g) of Xyrem, encompassing a 10-week exposure to Xyrem. In addition, parameters relating to daytime function were also evaluated for possible corresponding relationship to PSG effects.

Figure 3.22 OMC-SXB-20 Trial Design



The OMC-SXB-20 clinical trial was designed as an open-label trial using patients diagnosed with narcolepsy and with a history of cataplexy. The patients were required to be currently treated with TCAs or SSRIs, so as to be able to determine the profile of the effects of removal of these anti-cataplectic medications. The first phase of the trial was the withdrawal and washout from pre-existing medications of stable TCAs, SSRIs, and hypnotics. In the last two weeks of this phase, all patients were free of TCAs, SSRIs, and hypnotics. At the beginning of the first phase, an overnight PSG was performed to assess PSG status resulting from TCA, SSRI, and/or hypnotic therapy and again at the end of phase I (baseline, prior to first dose of Xyrem) as a baseline measure. Stimulant medication was maintained at constant dose throughout all phases of the trial.

The second phase of the trial began with the patient receiving the first night dosing of 4.5 g Xyrem (sodium oxybate) and ended after a 10-week escalation to a final 9 g dose. An overnight PSG was performed on the night of the first dose of 4.5g Xyrem to measure any acute changes in the PSG produced by Xyrem. Each patient remained on a stable 4.5 g dose of Xyrem for 4 weeks. After the 4-week stable dosing period, another PSG was performed, and Xyrem was increased to 6.0 g, 7.5 g, and 9.0 g in successive two-week intervals (see Figure 3.22). An overnight PSG was performed on the last night of each dose of Xyrem to measure the effects of each dose of Xyrem on the PSG, and to define any dose-response on sleep architecture for each patient. For all PSG nights, Xyrem dose was administered in divided dosing just prior to lights out and again 4.0 hours later.

Subjective determinations of the effects of Xyrem on daytime sleepiness were measured by the Epworth Sleepiness Scale (ESS), and changes in common symptoms of narcolepsy were assessed by the Narcolepsy Symptoms Assessment (NSA). In addition to these subjective measures, an objective measure of the effects of Xyrem on daytime sleepiness were evaluated by the well-established procedure, the Maintenance of Wakefulness Test (MWT). The ESS Questionnaire and the NSA were administered at each visit. The Maintenance of Wakefulness Test (MWT) was administered four times: while still on TCA, SSRI, and/or hypnotics (Visit 1), after washout of these medications (Visit 2; baseline), after 4 weeks at 4.5 g Xyrem (Visit 3), and after 2 weeks at 9 g Xyrem (Visit 6).

3.2.2.2.1 Primary Measures

The primary measures consisted of a set of objective clinical PSG parameters in relation to dose of Xyrem, recorded overnight in a sleep laboratory setting. The set of objective PSG parameters for each study night included the following:

- Total Sleep Time (TST) in minutes following the first and second dose of Xyrem and a summation. Total Sleep Time is the duration of time during which the patient was recorded to be in any of the sleep stages. (Total time in bed for this trial was 8.0 hours.)
- Sleep latency in minutes following the first and second dose of Xyrem. Sleep latency is the period of time in minutes between the epoch when the lights were turned off in the room where the nocturnal PSG was being performed and the first epoch that was scored as Stage 1, 2, 3, 4 or REM.
- Stage 1 sleep time in minutes following the first and second dose of Xyrem and a summation. Stage 1 sleep time is the duration of time in minutes in which the EEG recording was scored as Stage 1 sleep. Stage 1 sleep is defined as a relatively low voltage, mixed frequency EEG without rapid eye movements (REMs).
- Stage 2 sleep time in minutes following the first and second dose of Xyrem and a summation. Stage 2 sleep time is the duration of time in minutes in which the EEG recording is scored as Stage 2 sleep. Stage 2 sleep time is defined as 12 to 14 cycles per second (cps) sleep spindles and K-complexes on a background of relatively low voltage, mixed frequency EEG activity. Sleep spindles are a spindle-shaped cluster of waves.

- Stage 3 & 4 sleep time in minutes following the first and second dose of Xyrem and a summation. Stage 3 and 4 sleep time is the duration of time in minutes in which the EEG recording was scored as Stage 3 or Stage 4 sleep. Stage 3 sleep is defined as a form of slow wave sleep, and is used when between 20 to 50 percent of the epoch (30 seconds) is occupied by delta waves of peak-to-trough voltage equal to or greater than 75 microvolts. Stage 4 sleep is the slow wave sleep during which at least 50 percent of the epoch is occupied by delta waves of peak-to-trough voltage equal to or greater than 75 microvolts. Stage 3 and 4 sleep thus represents the slow wave sleep during which at least 20 percent of the epoch is occupied by delta waves of peak-to-trough voltage equal to or greater than 75 microvolts (Rechschaffen and Kales 1968).
- Delta power in microvolts^2/Hz following the first and second dose of Xyrem and an average. Delta power is the accumulated index of EEG signal power for frequencies between 0.5 to 4.0 Hz that occur during sleep stages 1, 2, 3, or 4 all divided by the number of fast Fourier transforms (FFTs) performed in those stages and 3.5 Hz (Guilleminault 1998).
- Rapid Eye Movement (REM) Sleep time in minutes following the first and second dose of Xyrem and a summation. REM Sleep time is the duration of time in minutes in which the EEG recording was scored as Stage REM. Stage REM sleep is defined as rapid eye movement sleep, a relatively low voltage, mixed frequency EEG in conjunction with episodic REMs and low amplitude electromyogram.
- REM sleep latency in minutes following the first and second dose of Xyrem and a summary. REM sleep latency is the duration of time in minutes between the first epoch of sleep and the first epoch scored as REM.
- Wake After Sleep Onset (WASO) in minutes following the first and second dose of Xyrem and a summation. WASO is the duration of time in minutes that the patient was wakeful (Stage W) after sleep onset had initially occurred; sleep onset was defined as the time after which a 30 second epoch scored as Stage 1, 2, 3, 4, or REM occurred. This is defined as the duration of time that is staged as awake that occurs between sleep onset and “Lights On” at the end of the sleep period.
- Stage shifts per hour following the first and second dose of Xyrem and an average. Stage shifts per hour is the number of times that an epoch (30 seconds) was scored as having a different EEG sleep stage than the previous epoch all divided by the total time between lights out and lights on.
- Total awakenings following the first and second dose of Xyrem and a summation. Awakenings is a term defined by the number of occurrences of wake epochs immediately following a sleep epoch.

3.2.2.2.2 Secondary Measures

Secondary measures consisted of both subjective and objective tools to ascertain the effects of Xyrem on daytime symptoms of narcolepsy. The set of parameters included:

- The ESS Questionnaire (Johns 1991) was used as an indication of daytime sleepiness. It was performed at each visit prior to the overnight PSG. The ESS Questionnaire instructed patients to rate their "chance of dozing" on a scale of 0-3 (never, slight, moderate, and high chance of dozing) in each of eight standard possible situations.

- The initial NSA, at Visit 1, asked the patients to historically rate their common narcolepsy symptoms for the week prior to starting the clinical trial, while the follow-up NSA evaluations (Visits 2 – 6) rated qualitative changes in narcolepsy symptoms for the previous week in comparison to the time before entry into the trial.
- The MWT is a standardized 40-minute EEG to determine the patient's daytime wakefulness under specified soporific conditions (quiet, darkened room and semi-recumbent position) at four times during the day, spaced two hours apart (Mitler 1982, 1998). The MWT trials were used to assess average sleep latency time and to determine whether or not a sleep-onset REM Period (SOREMP) had occurred. For the MWT trials, the patient was instructed to keep to the same schedule of stimulant medications for the day of each of the MWT tests during the trial, as well as caffeine and nicotine consumption. MWT sleep latency was defined as the duration of time in minutes (up to 40-minutes) between the time when the room where the EEG was being performed was darkened and either the first epoch that was scored as Stage 2, 3, 4, or REM, or the first of 3 consecutive stages of Stage 1 sleep. For the MWT, determination of sleep latency required 10 minutes of subsequent sleep whether continuous or intermittent. The individual trial was stopped once sleep onset had been determined, or after 40 minutes if no sleep occurred.

Baseline and endpoints are defined as follows:

- Baseline consisted of the data collected on Visit 2a for PSG, ESS, and MWT; the baseline for the NSA was Visit 1. Visit 2a represents the period when patients had discontinued TCAs, continued stimulants, and was just prior to Xyrem dosing.
- Endpoints for this trial consisted of Visit 1, the first night of Xyrem administration (Visit 2b), and subsequent visits (Visit 3, 4, 5, 6)

3.2.2.3 Patient Demographics

Twenty-seven narcoleptic patients were enrolled into the trial; twenty-five patients were treated at four investigative sites; and 21 patients completed the trial. In the patient population, there was a trend towards older (average 52.6 years old),female (72%), overweight (average 84.2 kg), and Caucasian (92%) patients. It is known that age of the patient population will have an impact on sleep architecture, specifically a reduction in Stages 3 and 4 sleep are seen with increasing age. Recent literature indicates that older males exhibit markedly reduced levels of slow-wave sleep (Stage 3 and 4) (Van Cauter, 2000).

During the withdrawal period, patients withdrew from pre-existing medications of TCAs, SSRIs, and hypnotics. In the last two weeks of this phase, all patients were free of TCAs, SSRIs, and hypnotics. Stimulant medications were continued at stable dosing throughout the trial. Eighty-eight percent (88%) of patients took TCAs, SSRIs, or hypnotics prior to the start of treatment. The most frequently used medications were venlafaxine, taken by 24% of patients, fluoxetine, taken by 20% of patients, and sertraline, taken by 16% of patients.

3.2.2.4 Efficacy Evaluation

3.2.2.4.1 Primary Variables

The primary efficacy analysis — Polysomnography Variables – (Table 3.31) provides an overall summary of total sleep time (TST), sleep latency, time in Stage 1, time in Stage 2, time in Stage 3 and 4 (also see Figure 3.23), REM sleep time, delta power, REM sleep latency, wake time after sleep onset (WASO), number of stage shifts per hour, and number of total awakenings.

Table 3.31 Overall Summary of Changes from Baseline in Nocturnal Polysomnography Variables by Dosage — Intent-to-Treat Patients

Visit	1	2a	2b	3	4	5	6
Variable	Anti-Cataplexy Medications	Baseline[a]	1st dose 4.5 g	4.5 g	6.0 g	7.5 g	9.0 g
N	20	21	18	20	21	20	20
Stage 1 Time (min)							
Sum							
Mean (SD)	13.3 (27.63)	74.8 (31.43)	-19.8 (23.56)	-2.5 (31.61)	-6.7 (27.02)	-5.4 (39.12)	-12.2 (32.04)
P-value from baseline[b]	0.044	-	0.002	0.733	0.268	0.544	0.106
Stage 2 Time (min)							
Sum							
Mean (SD)	-1.8 (62.17)	217.8 (45.45)	-4.3 (37.40)	-0.9 (51.46)	-0.9 (62.67)	6.3 (54.05)	20.2 (58.11)
P-value from baseline[b]	0.898	-	0.636	0.938	0.947	0.607	0.137
Stage 3 and 4 Time (min)							
Sum							
Mean (SD)	0.6 (13.29)	3.5 (8.38)	5.0 (17.08)	0.6 (8.71)	5.4 (20.16)	10.7 (21.02)	23.2 (39.80)
P-value from baseline[c]	0.636	-	0.296	0.771	0.296	0.056	0.012
Delta Power (microvolts^2/Hz)							
Average							
Mean (SD)	3417.3 (31189.26)	69708.6 (19296.87)	12482.3 (10438.58)	4771.3 (13806.55)	12598.9 (25627.51)	22208.8 (17940.01)	32629.3 (27165.27)
P-value from baseline[b]	0.630	-	<0.001	0.139	0.036	<0.001	<0.001

(continued)

Table 3.31 Overall Summary of Changes from Baseline in Nocturnal Polysomnography Variables by Dosage — Intent-to-Treat Patients

Visit	1	2a	2b	3	4	5	6
Variable	Anti-Cataplexy Medications	Baseline[a]	1st dose 4.5 g	4.5 g	6.0 g	7.5 g	9.0 g
N	20	21	18	20	21	20	20
REM Sleep Time (min)							
Sum							
Mean (SD)	-37.5 (43.21)	87.2 (28.93)	16.6 (32.66)	-15.8 (30.43)	-18.1 (29.16)	-21.0 (34.07)	-33.8 (36.23)
P-value from baseline[b]	0.001	-	0.046	0.032	0.010	0.013	<0.001
REM Sleep Latency (min)							
1st half							
Mean (SD)	60.5 (98.32)	44.0 (52.21)	-18.1 (62.32)	-0.5 (70.04)	2.6 (60.69)	7.0 (83.35)	33.6 (91.71)
P-value from baseline[c]	0.010	-	0.424	0.668	0.545	0.776	0.057
2nd half							
Mean (SD)	39.3 (82.38)	47.3 (47.69)	-6.3 (40.89)	-1.2 (80.02)	-18.8 (52.36)	13.0 (75.07)	-3.3 (72.98)
P-value from baseline[c]	0.070	-	0.640	0.735	0.162	0.568	0.791
WASO (min)							
Sum							
Mean (SD)	19.2 (45.89)	79.0 (28.37)	-0.3 (34.61)	12.4 (30.70)	7.8 (42.02)	-4.4 (41.96)	-5.2 (36.79)
P-value from baseline[b]	0.078	-	0.973	0.088	0.406	0.644	0.533
TST (min)							
Sum							
Mean (SD)	-25.4 (58.19)	383.4 (29.15)	-2.5 (42.04)	-18.6 (37.79)	-20.4 (55.05)	-9.3 (51.58)	-2.6 (42.84)
P-value from baseline[b]	0.066	-	0.804	0.041	0.105	0.430	0.789

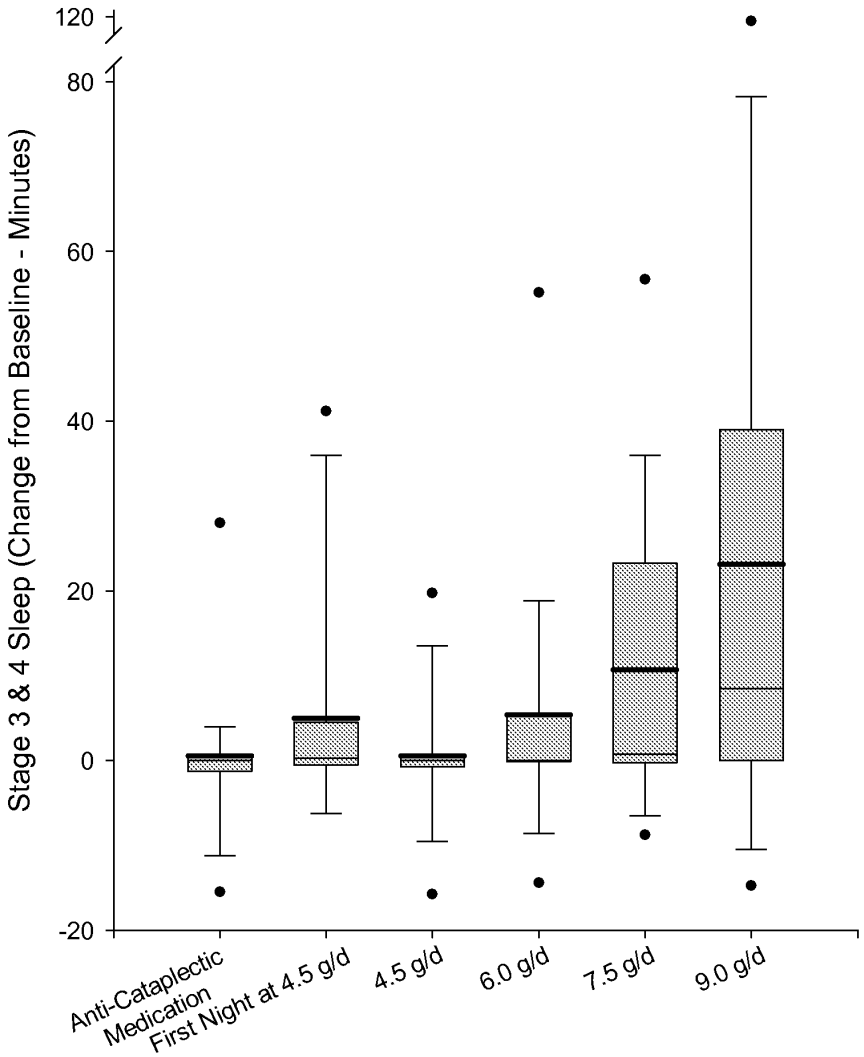
(continued)

Table 3.31 Overall Summary of Changes from Baseline in Nocturnal Polysomnography Variables by Dosage — Intent-to-Treat Patients

Visit	1	2a	2b	3	4	5	6
Variable	Anti-Cataplexy Medications	Baseline[a]	1st dose 4.5 g	4.5 g	6.0 g	7.5 g	9.0 g
N	20	21	18	20	21	20	20
Sleep Latency (min)							
1st half							
Mean (SD)	3.4 (6.39)	2.2 (2.16)	0.1 (1.89)	1.4 (2.48)	4.1 (10.76)	2.6 (3.79)	3.9 (5.35)
P-value from baseline[c]	0.022	-	0.693	0.048	0.042	0.005	0.003
2nd half							
Mean (SD)	2.7 (5.33)	2.5 (2.84)	2.4 (5.46)	3.8 (7.12)	3.8 (6.95)	6.1 (9.85)	3.9 (5.54)
P-value from baseline[c]	0.053	-	0.058	0.020	0.012	0.005	0.005
Stage Shifts Per Hour							
Average							
Mean (SD)	1.5 (5.22)	21.0 (5.28)	-3.2 (3.72)	0.3 (4.59)	-0.8 (3.92)	-3.1 (4.00)	-1.5 (4.86)
P-value from baseline[b]	0.217	-	0.002	0.792	0.364	0.002	0.185
Total Awakenings							
Sum							
Mean (SD)	4.5 (16.04)	50.2 (13.67)	-9.1 (14.22)	-0.2 (14.83)	-5.1 (14.82)	-12.9 (13.21)	-12.4 (16.34)
P-value from baseline[b]	0.230	-	0.015	0.964	0.131	<0.001	0.003

[a] Visit 2a (Baseline) is the actual value, all other visits are changes from baseline.
[b] Within treatment p-values:t-test
[c] Within treatment p-values:Wilcoxon signed rank test

Figure 3.23 Changes in Stage 3 and 4 Sleep (From Baseline) — Intent-to-Treat Patients



In this box plot, the median is depicted by the horizontal line within the box, the mean is depicted by the bold horizontal line, the limits of the box are the 1st and 3rd quartiles, the whiskers are the 10th and 90th percentiles, and the upper and lower circular symbols denote the 95th and 5th percentiles, respectively.

3.2.2.4.2 Secondary Variables

The secondary efficacy analysis are presented in the accompanying tables, and provides a complete, overall summary of the results from Epworth Sleepiness Score, Narcolepsy Symptoms Assessment, and Maintenance of Wakefulness Test.

Epworth Sleepiness Score (Table 3.32)
There were marked dose-related decreases in the mean ESS across all doses, incremental beyond the continued stable dosing of stimulants. These mean decreases in the ESS, a subjective measure of daytime sleepiness, also support changes seen in previous Xyrem studies (OMC-GHB-2; OMC-GHB-3). Changes in the ESS seen in the SXB-20 study are comparable to results of recent placebo-controlled stimulant studies with modafinil, a well-established stimulant for narcoleptics, in which mean ESS scores decreased 4 to 5 points in the modafinil group. A minimal decrease was observed in the placebo control (US Modafinil in Narcolepsy Study Group, 2000), indicating that ESS scores on narcoleptics in an open-label trial, such as OMC-SXB-20, may constitute real changes, as opposed to perceived changes.

Narcolepsy Symptom Assessment (Table 3.33)
There were improvements in narcolepsy symptoms of cataplexy attacks, hypnagogic hallucinations, number of sleep paralysis episodes, number of inadvertent naps/sleep attacks during the day, number of awakenings at night, and the severity of daytime sleepiness beginning with Visit 3, after 4 weeks on the 4.5 g dosage. Greater reductions in narcolepsy symptoms were seen with increasing Xyrem dosage. Quality of sleep at night, ability to concentrate, and overall condition also improved beginning with Visit 3, after 4 weeks on the 4.5 g dosage. In general, improvement in symptoms was observed with increasing doses of Xyrem, relative to the condition of the patient prior to starting the trial (when on TCA/SSRI/hypnotics).

Table 3.32 Summary of Changes from Baseline in the Epworth Sleepiness Scale by Dosage — Intent-to-Treat Patients

Visit Condition	1 Anti-Cataplexy Medica-tions	2a Baseline	2b 1st dose 4.5 g	3 4.5 g	4 6.0 g	5 7.5 g	6 9.0 g
N	21	21	21	21	21	20	21
Mean	-1.9	19.8	0.5	-2.4	-3.8	-4.8	-5.8
SD	1.92	2.66	2.11	2.75	3.62	4.02	4.55
Median	-2.0	20.0	0.0	-2.0	-3.0	-4.0	-7.0
Minimum	-6.0	12.0	-3.0	-9.0	-12.0	-13.0	-14.0
Maximum	3.0	24.0	5.0	2.0	0.0	1.0	2.0
P-value from baseline	<0.001	-	0.341	<0.001	<0.001	<0.001	<0.001
Inference with 4.5 g	-	-	-	-	0.042	<0.001	<0.001
Inference with 6.0 g	-	-	-	-	-	0.076	0.006
Inference with 7.5 g	-	-	-	-	-	-	0.317

Visit 2a (baseline) is the actual value, all other visits are changes from baseline.
Within treatment p-values: Wilcoxon signed rank test. Between treatment p-values: ANOVA on rank changes from baseline.

Table 3.33 Summary of Follow-up Narcolepsy Symptoms Assessment by Dosage — Intent-to-Treat Patients

Visit Condition	2a Pre-treatment	3 4.5 g	4 6.0 g	5 7.5 g	6 9.0 g
Number of Patients	**21**	**21**	**21**	**21**	**21**
Number of Cataplexy Attacks	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	13 (62%)	3 (14%)	0	0	0
Decreased	0	11 (52%)	17 (81%)	18 (86%)	18 (86%)
About the same	8 (38%)	7 (33%)	4 (19%)	2 (10%)	3 (14%)
Number of Hypnagogic Hallucinations	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	8 (38%)	3 (14%)	1(5%)	0	0
Decreased	0	6 (29%)	10(48%)	15 (71%)	16 (76%)
About the same	13 (62%)	12 (57%)	10(48%)	5 (24%)	5 (24%)
Number of Sleep Paralysis Episodes	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	8 (38%)	1(5%)	0	0	0
Decreased	0	8 (38%)	14 (67%)	15 (71%)	16 (76%)
About the same	13 (62%)	12 (57%)	7 (33%)	5 (24%)	5 (24%)
Number of Inadvertent Naps/Sleep Attacks During the Day	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	13 (62%)	1(5%)	0	0	0
Decreased	0	11 (52%)	16 (76%)	16 (76%)	16 (76%)
About the same	8 (38%)	9 (43%)	5 (24%)	4 (19%)	5 (24%)
Number of Awakenings at Night	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	8 (38%)	2 (10%)	1(5%)	0	3 (14%)
Decreased	3 (14%)	11 (52%)	11 (52%)	13 (62%)	12 (57%)
About the same	10(48%)	8 (38%)	9 (43%)	7 (33%)	6 (29%)

(continued)

Table 3.33 Summary of Follow-up Narcolepsy Symptoms Assessment by Dosage — Intent-to-Treat Patients

Visit Condition	2a Pre-treatment	3 4.5 g	4 6.0 g	5 7.5 g	6 9.0 g
Number of Patients	**21**	**21**	**21**	**21**	**21**
Severity of Daytime Sleepiness	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Increased	12 (57%)	1(5%)	1(5%)	0	0
Decreased	0	14 (67%)	14 (67%)	14 (67%)	16 (76%)
About the same	9 (43%)	6 (29%)	6 (29%)	6 (29%)	5 (24%)
Quality of Sleep at Night	21 (100%)	21 (100%)	21 (100%)	21 (100%)	21 (100%)
Much improved	0	4 (19%)	5 (24%)	5 (24%)	5 (24%)
Somewhat improved	3 (14%)	12 (57%)	14 (67%)	13 (62%)	12 (57%)
Unchanged	9 (43%)	4 (19%)	2 (10%)	2 (10%)	2 (10%)
Somewhat worse	4 (19%)	1(5%)	0	0	2 (10%)
Much worse	5 (24%)	0	0	0	0
Ability to Concentrate	21(100%)	21(100%)	21(100%)	21(100%)	21(100%)
Much improved	0	0	3 (14%)	3 (14%)	1 (5%)
Somewhat improved	0	9 (43%)	10 (48%)	11 (52%)	13 (62%)
Unchanged	11 (52%)	9 (43%)	7 (33%)	6 (29%)	7 (33%)
Somewhat worse	9 (43%)	3 (14%)	1 (5%)	0	0
Much worse	1 (5%)	0	0	0	0
Overall Condition	21(100%)	21(100%)	21(100%)	21(100%)	21(100%)
Much improved	0	1 (5%)	5 (24%)	7 (33%)	9 (43%)
Somewhat improved	0	16 (76%)	12 (57%)	12 (57%)	8 (38%)
Unchanged	5 (24%)	3 (14%)	4 (19%)	1 (5%)	3 (14%)
Somewhat worse	8 (38%)	1 (5%)	0	0	1 (5%)
Much worse	8 (38%)	0	0	0	0

The number of patients reported does not equal the total patients treated if data was missing.

Maintenance of Wakefulness Test (Table 3.34)
Polysomnographic measurement of daytime wakefulness indicated a dose related increase in sleep latency. Mean (SD) sleep latency time in minutes was 4.5 (6.01) minutes at Visit 2a (baseline). Mean (SD) change at Visit 3 on 4.5 g Xyrem was 3.7 (7.68) minutes and mean change (SD) at Visit 6 on 9.0 g Xyrem was 6.1 (6.82) minutes. There were statistically significant changes from baseline at Visit 3 ($p = 0.038$), and Visit 6 ($p<0.001$).

These increases in sleep latency were incremental beyond current stimulant therapy. The magnitude of these changes for the 9 g Xyrem dose group (6.1 min) was larger than that shown for all dosages of Modafinil in recent controlled studies compared to placebo, a well-established stimulant medication for daytime sleepiness in narcoleptics. In one study, changes from baseline were only 2.1 min for 200 mg modafinil and 1.9 min for 400 mg modafinil (US Modafinil in Narcolepsy Study Group, 2000) and, in another study, changes from placebo were 4.5 min for 200 mg modafinil and 6.0 min for 400 mg modafinil (Broughton 1997).

There was a dose-related decrease in the percentage of patients with one or more sleep-onset REM period (SOREMP). At Visit 2a (baseline), 18 of 21 patients (86%) had SOREMP. At Visit 3 on 4.5 g Xyrem, 13 of 21 patients (62%) had SOREMP, and 6 of 20 patients (30%) on 9.0 g Xyrem had SOREMP. Patients on anti-cataplexy medications (Visit 1 in Table 3.34) also had decreases in SOREMPs, but not as profound as those on 9.0 g Xyrem. Prior research has shown that decreases in SOREMPs are positively associated with a reduction in cataplexy attacks (Amira 1985; Hishikawa 1995).

Table 3.34 Summary of Maintenance of Wakefulness Test by Visit — Intent–to-Treat Patients

Visit	1	2a	3	6
	Anti-Cataplexy Medica-tions	Baseline	4.5 g	9.0 g
Number of Patients	**21**	**21**	**21**	**20**
Sleep Latency (minutes)				
N	21	21	21	20
Mean	1.0	4.5	3.7	6.1
SD	5.69	6.01	7.68	6.82
Median	0.6	2.3	1.0	3.3
Minimum	-10.8	0.5	-8.0	-5.0
Maximum	16.6	27.1	30.2	21.9
p-value from baseline	0.441	—	0.038	<0.001
Inference with Visit 3	—	—	—	0.286
SOREMP				
Yes	11 (52%)	18 (86%)	13 (62%)	6 (30%)
No	10 (48%)	3 (14%)	8 (38%)	14 (70%)

SOREMP = Sleep-onset rapid eye movement period.
Visit 2a (baseline) is the actual visit, all other visits are changes from baseline.
Within treatment p-values: t-test. Between treatment p-values: ANOVA on rank changes from baseline.
For SOREMP: Frequencies are actual counts at each visit.

3.2.2.5 Conclusions and Discussion

3.2.2.5.1 Conclusions

With respect to the effect of four dosages of Xyrem on overnight polysomnography (PSG) recordings in narcoleptic patients, the following conclusions can be derived from the present data:

1. Xyrem treatment resulted in a dose related increase in slow wave sleep (SWS, delta sleep, Stage 3 & 4) across all 4 doses reaching significance at the 9.0 g/night regimen.
2. Delta power, a derived index of all slow wave signals, showed a dose related increase that was highly significant on the first night following 4.5 g as well as after 2 weeks of dosing at 6.0 g, 7.5 g and 9.0 g/night.
3. A dose related decrease in the number of nocturnal awakenings was recorded, which was significant at the 7.5 g and 9.0 g/night Xyrem doses.
4. Across doses a non-significant decrease in Stage 1 sleep was observed, while the amount of Stage 2 sleep remained unchanged.
5. An acute increase in REM sleep was demonstrated with the initial 4.5 g treatment, with subsequent dose related significant decreases in total REM sleep duration at all 4 doses.
6. No significant change in REM latency was observed among the 4 doses studied.
7. No dose related change in total sleep time (TST) was observed; however, a significant decrease in TST was found following 4.5 g/night dosing for 4 weeks.
8. The number of shifts in sleep stage demonstrated a decreasing trend at doses greater than 4.5 g/night but a significant decrease was recorded only following 7.5 g/ night Xyrem.
9. The total time spent awake after the onset of sleep (WASO) was not significantly altered by any of the Xyrem doses.
10. A significant dose-dependent increase in sleep latency was observed across all 4 doses.

Consistent with the objective PSG findings, the subjective report by the patients on the Narcolepsy Symptom Assessment indicated a dose related improvement in the overall quality of sleep and the perceived number of nighttime awakenings as compared to the patient's self assessment at study entry while still on their anti-cataplectic and stimulant medications. The nocturnal symptoms of hypnogogic hallucinations and sleep paralysis likewise were decreased appreciably in 16 of 21 (76%) patients.

The following are the conclusions derived from the objective and subjective measures of daytime sleepiness:

1. The administration of Xyrem produced a significant increase in sleep latency as measured by the MWT. This dose-dependant increase averaged 3.7 minutes ($p = 0.038$) after 4 weeks of 4.5 g nightly that further increased to a mean improvement of 6.1 minutes ($p < 0.001$) following the nightly 9.0 g dose. This measured response is additive to that produced by concomitant stimulant dosing.

2. The presence of SOREMPs during MWT, which occurred in of 18 of 21 patients (86%) at baseline, decreased to 13 of 21 (62%) following 4 weeks of 4.5 g Xyrem nightly. SOREMPs further decreased to 6 of 20 patients (30%) following the 9.0 g dose.
3. The ESS total score significantly decreased in a dose-dependent manner by the nightly administration of Xyrem. The median total score of 20 at baseline improved by 2 points following the 4.5 g dose regimen ($p < 0.001$) and by 7 points after the 9.0 g dose ($p < 0.001$).
4. The patients in the current trial reported substantial improvements in subjectively determined (by NSA recording of) daytime narcolepsy symptoms including the incidence of cataplexy attacks, the number of inadvertent naps as well as decreased daytime sleepiness, and increased the ability to concentrate and a perception of overall improvement in their narcolepsy while taking nightly doses of Xyrem.

3.2.2.5.2 Discussion

This study was designed to allow descriptive comparison of standard parameters of sleep architecture in a group of narcoleptic patients initially on stimulant and anti-cataplectic medications (TCAs, SSRIs, and hypnotics) and to assess changes when these anti-cataplectic medications were discontinued (down-titration over two weeks, followed by two weeks of no medication) to provide a baseline recording with only stimulant medications continued. This allowed measurement of the PSG effects attributed to these medications and a proximate comparison with sodium oxybate effects. Dosing with Xyrem in an escalating dose regimen provided the basis for assessment of both the acute PSG effects (during first night of dosing at 4.5 g) and across the dose range from 4.5 to 9.0 g/night, representing the principal dosing regimens for Xyrem in the treatment of narcolepsy. Collection of the parameters representative of daytime sleepiness by objective (MWT) and subjective (ESS, NSA) measures allowed consideration of the relationship between nighttime sleep characteristics, Xyrem dose (or time-on-drug), and daytime clinical effect.

3.2.2.5.2.1 Stage 3 and 4 Sleep

The most important finding of this report is that of the dose-dependent increase in the restorative Stage 3 and 4 sleep time (delta sleep, slow wave sleep) following treatment with Xyrem (sodium oxybate). The increase in slow wave sleep following treatment with sodium oxybate has been repeatedly reported in the literature (Broughton 1976, 1980; Scharf 1985; Bedard 1989; Scrima 1990; Lammers 1993). The relatively small amount of slow-wave sleep recorded across the entire trial (e.g. 3.5 minutes at baseline) was attributed to the presence of strict scoring criteria which required that the slow-wave EEG amplitude be at least 75 micro-volts (peak-to-trough) (Rechtschaffen 1968), a voltage that would be expected to be low in this trial due to the high average age of the patient population (Van Cauter 2000). Slow-wave sleep for the initial polysomnograph when the patients were on TCAs, SSRIs, or hypnotics was not significantly different from baseline, confirming that these medications lack the ability to increase slow wave sleep (Borbely 1985, Kupfer 1994, Wilson 2000, Oberndorfer 2000).

3.2.2.5.2.2 Delta Power

This increase in slow wave sleep is coincident with an increase in delta power. Delta power was determined by spectral analysis (using fast Fourier transformation) of the digital EEG signals from electronic PSG recordings so as to determine the index of all slow waves occurring during non-REM sleep between 0.5 and 4 Hz (Guilleminault 1998, Pivik 1993). As dose increases, the corresponding increase in delta power supports the increase in Stage 3 and 4 sleep. Stage 3 and 4 sleep only represents those sleep epochs containing greater than 20% and 50%, respectively, of slow waves with amplitudes of 75 microvolts or higher. Delta power differs in that it measures the total EEG signal in the delta wave range during all stages of NREM sleep. Slow wave sleep and delta wave signals in general (delta power) constitute that component of sleep that has been found to have restorative properties as demonstrated by correlation with measures of daytime performance and alertness (Jurado 1989, Schneider-Helmert 1987, Crenshaw 1999, Edinger 2000, Takahashi 1994).

3.2.2.5.2.3 REM Sleep

The effects on REM sleep time in this study were particularly interesting, and not entirely in keeping with the published literature. The expected decrease in REM sleep that was associated with TCA/SSRI/hypnotic treatment was supported by these data, with a highly significant (p=0.001) mean reduction of 37.5 minutes from the baseline mean total REM sleep time of 87.2 minutes. The acute pharmacologic response to Xyrem dosing at 4.5 g on the first night was a significant increase in total REM sleep time (p=0.046), which was followed by dose-dependent significant reductions in total REM sleep time across the 4.5, 6.0, 7.5, and 9.0 g dose groups. Previous literature had reported either no change in the proportion of REM sleep (Scrima 1990, Bedard 1989, Lammers 1993, Scharf 1985, Mamelak 1981) in narcoleptics, or a marked increase in REM sleep in the patients with depression (Broughton 1976). Further consideration of REM efficiency and REM density measures could be usefully applied to these recordings to assist in the interpretation of this unexpected data. There is a suggestion of a reciprocal relationship between REM and non-REM (NREM) sleep in humans (Merica 1998, Toussaint 1997, Uchida 1992, Takahashi 1994) and in rats (Benington 1994, Borbely 1984). Thus, the subsequent reduction in total REM sleep time beyond the pharmacologic increase produced by the initial dose of 4.5 g Xyrem may be an outcome of the drug-mediated increase in slow wave sleep.

3.2.2.5.2.4 REM Latency

Although often associated with decreases in REM latency in narcoleptics at lower doses of sodium oxybate (Broughton 1976, 1980; Scharf 1985; Bedard 1989; Scrima 1990; Lammers 1993), REM latency in the patient population in OMC-SXB-20 has not shown a decrease in REM latency, nor any dose effects. In contrast, the chronic dosing of TCA/SSRI/hypnotic medication present at the start of the trial lead to a marked increase in REM latency, relative to that recorded after their withdrawal and washout (baseline). Based on the distinctly different effects on REM latency between TCA/SSRI/hypnotic

medications at the start of the trial and escalating Xyrem dosing, the difference in effects could represent different neuropharmacological mechanisms.

As this is a small, open-label study, definitive conclusions cannot be established from any of these independent measures. However, the uniform changes in all subjective assessments and the objective measure as provided by the MWT in daytime sleepiness provides strong support for the therapeutic response to Xyrem treatment across the range of doses studied. This provides further consistent support for the previously submitted subjective data from the OMC-GHB-2 and OMC-GHB-3 studies.

In this single-arm trial, there is a confounding of effects between time-on-drug and dose-escalation. In all findings that exhibit an increase in extent of effect across the study, a definite statement regarding the dose-dependency of these effects must be qualified by the fact that these increases in extents of effects may be caused in part by the duration of time on drug (10 weeks of exposure while escalating dose up to 9 g at Visit 6). This is an unmitigatable feature of the trial. However, the source of the effect (time and/or dose level) does not diminish the impact of the drug on PSG parameters and narcolepsy symptoms.

3.2.2.5.2.5 Maintenance of Wakefulness Test (MWT)

The incremental improvement in sleep latency for the MWT, over-and-above that which was already present with current stimulant treatment, provides an opportunity to strongly suggest that Xyrem improved daytime alertness by a large magnitude.

3.3 Efficacy Summary

Based on the results of two adequate and well-controlled studies (OMC-GHB-2 and the Scrima trial), a supporting controlled study (Lammers trial) and supportive data from 2 uncontrolled studies (OMC-GHB-3 and OMC-SXB-6), dosages of between 3 g/d and 9 g/d of sodium oxybate are effective in the treatment of narcolepsy (reducing the frequency of cataplexy attacks and excessive daytime sleepiness [reduction in the Epworth Sleepiness Scale and the number of inadvertent naps or sleep attacks] associated with narcolepsy).

The findings of OMC-GHB-2 and OMC-GHB-3 taken together support the conclusion that, while the therapeutic benefit of sodium oxybate is clearly evident within 4 weeks of nightly therapy, the full benefit is not achieved until the patient has been treated for 2 to 3 months.

A blinded, randomized trial, OMC-SXB-21, provided evidence for the long-term efficacy of Xyrem. In this trial, patients abruptly discontinued from long-term (7 to 44 months) Xyrem therapy, had a recurrence of cataplexy.

Results of the long-term open-label dose-titration studies (OMC-GHB-3 and OMC-SXB-6) also shows long-term effectiveness of dosages from 3 g/d to 9 g/d when titrated to optimal clinical effectiveness for individual patients.

Overall, clinical improvement and benefit of sodium oxybate in the treatment of patients with narcolepsy is documented by both the physician-based (CGIc) and patient-based (Global Therapeutic Impression of Benefit) assessments.

Evidence (OMC-SXB-6) suggests that patients can safely decrease or discontinue other anti-cataplectic therapy (TCAs/SSRIs) once treatment with sodium oxybate is initiated, with continuing clinically satisfactory reduction in frequency of cataplectic attacks. There is no evidence of rebound cataplexy or other withdrawal effects (other than a return of narcolepsy symptoms) when patients are removed from sodium oxybate after 4 weeks of therapy at dosages up to 9 g/d.

In addition, sodium oxybate further improves daytime sleepiness when used adjunctively in narcoleptic patients already maintained on stimulant medications to treat their daytime sleepiness.

OMC-SXB-20 was an open-label pharmacological study that evaluated the effect of Xyrem on sleep architecture using objectively-measured nocturnal polysomnography at four escalating doses (4.5 g, 6 g, 7.5 g, 9 g) over a 10-week dosing period. The most important finding of this study is that of the increase in slow-wave sleep across all four doses of Xyrem compared to baseline in narcoleptic patients, with statistically significant increases in Stage 3&4 sleep reached at the 9.0 g per night dose as well as statistically significant increases in Delta Power at all four doses. Another important finding was the dose-related improvement in daytime sleepiness, as measured by the Maintenance of Wakefulness Test (MWT), which objectively quantifies the sleep latency of patients who are trying to remain awake while experiencing defined, soporific conditions. The increase in MWT sleep latency, relative to baseline, averaged 3.7 minutes ($p = 0.038$) after 4 weeks of 4.5 g per night of Xyrem that further increased to a mean improvement of 6.1 minutes ($p < 0.001$) following the nightly 9.0 g Xyrem dose. This vigorous response is additive to that already produced by concomitant stimulant dosing, supporting the reasons to conclude that Xyrem can be used to markedly improve daytime sleepiness in narcoleptics.

SECTION 4
SAFETY

4.0 SAFETY

4.1 Overview of Sodium Oxybate Trials

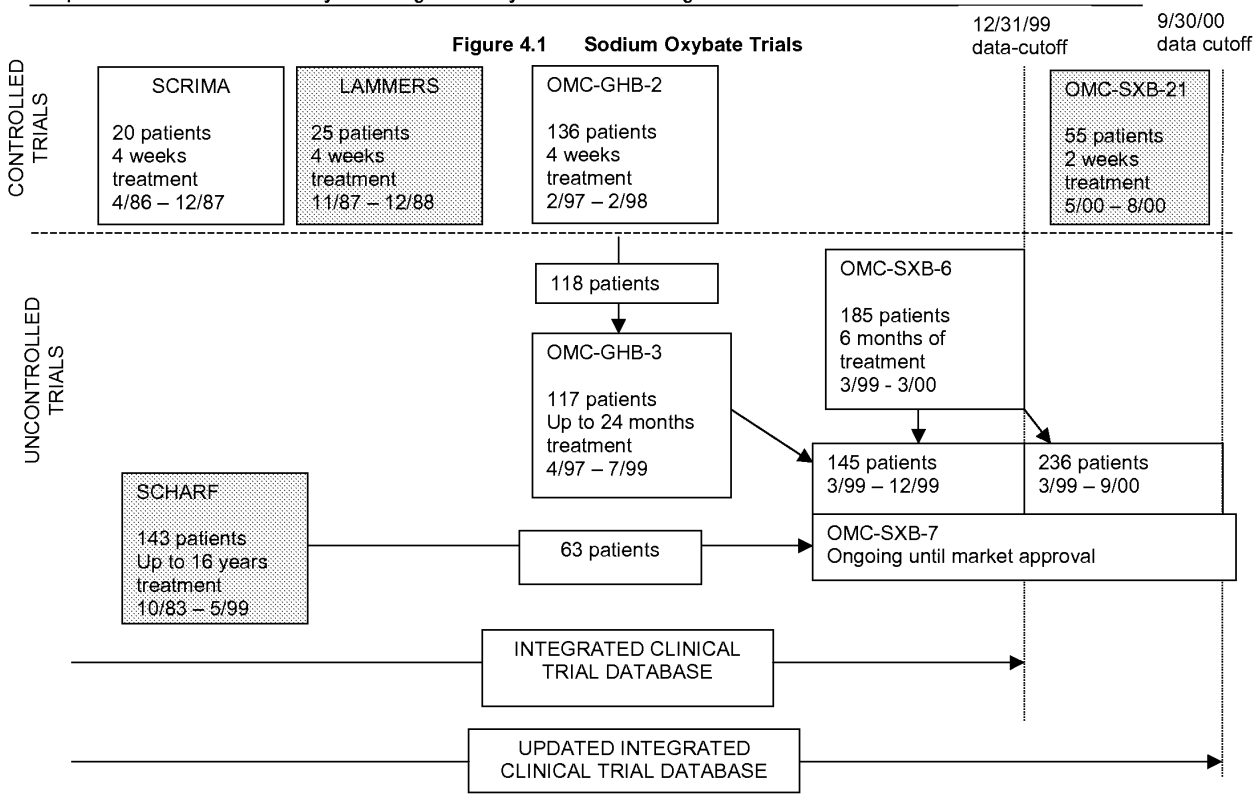
The following represents a summary of all available safety information for Xyrem (sodium oxybate). The safety data were carefully collected and reported by independent investigators conducting the clinical trials that make up the safety database in the Xyrem New Drug Application. The comprehensive database was reviewed by medical experts and summarized in individual clinical trial reports and in an Integrated Summary of Safety (submitted to FDA October 2, 2000). Safety data submitted subsequently included the Clinical Trial Report for controlled trial OMC-SXB-21 (submitted December 16, 2000) and a 4-Month Safety Update for the ongoing open-label trial (OMC-SXB-7, submitted February 2, 2001).

Four databases were used in compiling this analysis of safety:

- The updated integrated clinical trial database – this was a merge of the original integrated clinical trial database used for the Integrated Summary of Safety in the NDA and the 4-Month Safety Update database
  - The original integrated clinical trial database included two 4-week, placebo-controlled trials (Scrima and OMC-GHB-2) and 3 open-label, long-term trials (OMC-GHB-3, OMC-SXB-6, and OMC-SXB-7, the last through December 31, 1999), with a total of 402 patients, 148 of whom participated in more than 1 trial.
  - The 4-Month Safety Update database included 236 patients in the OMC-SXB-7 trial (with an additional 51 patients that transferred from OMC-SXB-6 to OMC-SXB-7 after the December 31, 1999 data cut-off).
- The Lammers trial, a 4-week, placebo-controlled trial, which was also included in the Integrated Summary of Safety as a separate database (this was not integrated in the statistical database due to its simplified method of data collection), with 25 patients
- The Scharf trial, an open-label, long-term trial, which was also included in the Integrated Summary of Safety as a separate database (this was not integrated in the statistical database due to the trial design and its history), with 143 patients, 63 of whom also participated in OMC-SXB-7 and are therefore included in the updated integrated clinical trial database
- The OMC-SXB-21 trial, a 4-week, placebo-controlled trial with 55 patients, all of whom also participated in OMC-SXB-7 (however, their safety data during OMC-SXB-21 are not included in the updated integrated clinical trial database; they were reported in the OMC-SXB-21 clinical trial report)

Figure 4.1 shows the trials included in this safety analysis. Shaded boxes represent the 3 trials (Lammers, Scharf, and OMC-SXB-21) not included in the updated integrated clinical trial database.

Figure 4.1 Sodium Oxybate Trials



Only Adverse Events (AEs) occurring during treatment were included in the analysis of the updated integrated clinical trial database and the Scharf trial.

Of the 402 narcolepsy patients included in the updated integrated clinical trial database, 331 (82%) experienced at least 1 AE. As expected, a higher incidence (95%) was seen in the long-term clinical trial (Scharf). Related AEs were seen for 247(61%) of the 402 patients in the updated integrated clinical trial database. Severe AEs were seen for 82 (20%) of the 402 patients In the Scharf trial, severe AEs were seen for 21 (15%) of the 143 patients during the first 6 months on sodium oxybate.

Serious Adverse Events (SAEs) were experienced by 27 (7%) of the 402 patients in the updated integrated clinical trial database and 54 (38%) of the 143 patients in the Scharf trial. Two (<1%) deaths were reported in the updated integrated clinical trial database (both in the OMC-SXB-7 trial, including patient 0936, who died 5 months after the September 30, 2000, data cutoff), and 11 (8%) deaths were reported in the Scharf trial over 16 years. None of these deaths was considered related to trial medication. Fifty-three patients (13%) discontinued due to 1 or more AEs in the updated integrated clinical trial database, and 23 (16%) patients did so in the long-term (Scharf) trial. Of the discontinued patients, 42 (10%) in the updated integrated clinical trial database and 6 (4%) in the Scharf trial discontinued due to AEs considered to be related to trial medication.

For purposes of analysis, patients who had Xyrem oral solution dosages other than the protocol specified dosages were assigned a dosage according to the algorithm shown in Table 4.1.

Table 4.1 Algorithm for Assigning Dosages Other Than Those Specified by Protocol

Dosage (g/d)	Dosage Assignment(g/d)
≤ 0.00	Missing
> 0.00 to < 3.75	3.0
≥ 3.75 to < 5.25	4.5
≥ 5.25 to < 6.75	6.0
≥ 6.75 to < 8.25	7.5
≥ 8.25	9.0

4.2 Drug Exposure

In 4 of the clinical trials, patients were treated with sodium oxybate for 6 months or longer, including OMC-SXB-6 (6-month trial), OMC-GHB-3 (2-year trial), OMC-SXB-7 (2-year trial [amended to 30 months] and ongoing), and Scharf (16-year trial).

Table 4.2 provides an overview of duration of exposure for the 399 patients who received sodium oxybate in the updated integrated clinical trial database (up to September 30, 2000). Three patients received placebo in OMC-GHB-2, and did not

continue into an open-label trial; they are therefore not included in this table. The overall patient exposure was 296 patients with ≥ 6 months, 223 patients with ≥ 1 year, and 48 patients with an exposure of ≥ 2 years.

Table 4.2 Updated Integrated Clinical Trial Database — Cumulative Duration of Sodium Oxybate Exposure, by Patient Dosage

Duration of Exposure[b]	Total	Sodium Oxybate Patient Dosage[a] (g/d)				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
≥ 6 mo (168 d)	296 (74%)	9 (9%)	50 (19%)	115 (40%)	59 (44%)	62 (48%)
≥ 1 y (336 d)	223 (56%)	5 (5%)	27 (10%)	60 (21%)	26 (20%)	34 (26%)
≥ 2 y (672 d)	48 (12%)	2 (2%)	4 (1%)	13 (4%)	9 (7%)	13 (10%)

[a] Patient Dosage: the number of patients who took the specified dosage at any time during the trial. Patients could be counted for more than 1 dosage; alternatively, patients may not have taken any 1 dosage for the specified time period but did take sodium oxybate overall for that period. Therefore, the sum of patients exposed to specific dosages does not equal the total number of patients.

[b] Duration was calculated based on a 28-day month. Duration of exposure was not calculated for the 3 patients who received placebo only.

Table 4.3 provides the duration of exposure for the 479 patients in the combined experience from the updated integrated clinical trial database and the Scharf trial. With the experience from the long-term Scharf trial included, the overall patient exposure was 360 patients with ≥ 6 months, 286 patients with ≥ 1 year, and 150 patients with an exposure of ≥ 2 years.

Table 4.3 Updated Integrated Clinical Trial Database Plus Scharf Trial — Cumulative Duration of Sodium Oxybate Exposure, by Patient Dosage

Duration of Exposure[b]	Total	Sodium Oxybate Patient Dosage[a] (g/d)				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	**479 (100%)**	**198 (100%)**	**377 (100%)**	**383 (100%)**	**184 (100%)**	**159 (100%)**
≥ 6 mo (168 d)	360 (75%)	25 (13%)	87 (23%)	171 (45%)	83 (45%)	70 (44%)
≥ 1 y (336 d)	286 (60%)	12 (6%)	55 (15%)	114 (30%)	50 (27%)	42 (26%)
≥ 2 y (672 d)	150 (31%)	6 (3%)	26 (7%)	66 (17%)	34 (18%)	23 (14%)

[a] Patient Dosage: the number of patients who took the specified dosage at any time during the trial. Patients could be counted for more than 1 dosage; alternatively, patients may not have taken any 1 dosage for the specified time period but did take sodium oxybate overall for that period. Therefore, the sum of patients exposed to specific dosages does not equal the total number of patients.

[b] Duration was calculated based on a 28-day month. Duration of exposure was not calculated for the 3 patients who received placebo only.

Both with and without the experience from the Scharf trial, the most frequently administered dosage for all 3 durations of exposure (≥ 6 months, ≥ 1 year, and ≥ 2 years) was 6.0 g/d.

Total exposure to sodium oxybate (calculated based on twelve 28-day months) was 330 patient-years in the updated integrated clinical trial database, 2 patient-years in the Lammers trial, and 996 patient-years in the Scharf trial, or a total of 1,328 patient-years.

4.3 Updated Integrated Clinical Trials

The updated integrated clinical trial database is composed of a merge of the original integrated clinical trial database used for the Integrated Summary of Safety in the NDA and the 4-Month Safety Update database.

In the OMC-GHB-3 trial, 34 patients received placebo and all but 3 of these continued into open-label trials with sodium oxybate. Since all data in the updated integrated clinical trial database are presented by last dosage, only the 3 patients who did not go on to treatment with sodium oxybate are included in the placebo group. Since the 20 patients in the Scrima trial received both placebo and sodium oxybate, they are included in the sodium oxybate group.

As shown in Table 4.4, a majority of patients in the updated integrated clinical trial database had completed treatment (48/402, 12%) or were still enrolled in OMC-SXB-7 as of the September 30, 2000, data cutoff (210/402, 52%). Of the 144 patients who discontinued treatment, 52 (13%) did so due to AEs.

Table 4.4 Patient Disposition — Updated Integrated Clinical Trial Database

Patient Disposition	Total	Placebo	Sodium Oxybate
Patients treated	402 (100%)	3 (100%)	399 (100%)
Completed treatment	48 (12%)	2 (67%)	46 (12%)
Ongoing treatment	210 (52%)	0	210 (52%)
Discontinued treatment	144 (36%)	1 (33%)	143 (36%)
AE[a]	53 (13%)	1 (33%)	52 (13%)
Patient request/withdrew consent	34 (8%)	0	34 (9%)
Patient non-compliance	19 (5%)	0	19 (5%)
Other	18 (4%)	0	18 (5%)
Lost to follow-up	11 (3%)	0	11 (3%)
Lack of efficacy	5 (1%)	0	5 (1%)
Protocol deviation/violation	4 (<1%)	0	4 (<1%)
Death[a]	2 (<1%)	0	2 (<1%)

[a] Count includes patient 0936, who died on 2/24/01, 5 months after data cutoff, but is included here for completeness.

4.3.1 INCIDENCE OF ADVERSE EVENTS

Table 4.5 summarizes the AEs by sodium oxybate dosage at onset for the updated integrated clinical trial database.

- The majority of the 402 patients (331, 82%) experienced at least 1 AE.
- Approximately half of the patients (247, 61%) experienced related AEs.
- Severe AEs were reported for 82 patients (20%).
- Only 24 patients (6%) experienced SAEs.
- 53 patients (13%) discontinued due to AEs.
- There were 2 deaths (1%).

A higher incidence of AEs was seen with the 9.0 g/d sodium oxybate group compared with the other 4 dosage groups. This was true for:

- Patients with at least 1 AE (78% for 9.0 g/d, compared with 51% to 62% for the other 4 dosage groups)
- Patients with SAEs (6% for 9.0 g/d, vs. 1% to 3% for the other 4 dosage groups)
- Patients with related AEs (55% for 9.0 g/d, vs. 28% to 40% for the other 4 dosage groups)
- Patients with severe AEs (16% for 9.0 g/d, vs. 3% to 12% for the other 4 dosage groups)
- Discontinuations due to AEs (14% for 9.0 g/d, vs. 3% to 6% for the other 4 dosage groups)

However, the incidence for each category was lower for 7.5 g/d than for 6.0 g/d, making it difficult to infer a true dose-response relationship. Interestingly, the incidence for the placebo group was similar to that for the 9.0 g/d group for patients with at least 1 AE (70%) and patients with related AEs (50%).

Table 4.5 AEs by Dosage at Onset — Updated Integrated Clinical Trial Database

	Total[a]	Place-bo	Sodium Oxybate Dosage at Onset (g/d)					
			Total[a]	3.0	4.5	6.0	7.5	9.0
Number of patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
At least 1 AE	331 (82%)	38 (70%)	326 (82%)	58 (60%)	138 (51%)	181 (62%)	72 (54%)	101 (78%)
SAEs	27 (7%)	0	27 (7%)	0	5 (2%)	11 (4%)	3 (2%)	10 (8%)
Related AEs	247 (61%)	27 (50%)	241 (60%)	37 (38%)	92 (34%)	115 (40%)	37 (28%)	71 (55%)
Severe AEs	82 (20%)	3 (6%)	80 (20%)	3 (3%)	25 (9%)	35 (12%)	6 (5%)	20 (16%)
Discontinu-ations due to AEs	53 (13%)	1 (2%)	52 (13%)	5 (5%)	15 (6%)	14 (5%)	4 (3%)	18 (14%)
Deaths	2 (1%)	0	2 (1%)	0	0	2 (1%)	0	0

[a] Patients are counted only once in each category. However, patients could have had more than 1 AE with different dosages at onset, so the sum of the patients in the dosage at onset groups may exceed the total number of patients in each event category.

Table 4.6 summarizes the incidence of AEs occurring in ≥ 5% of patients in the updated integrated clinical trial database. The most frequently reported AEs included headache (116 patients, 29%), nausea (94 patients, 23%), dizziness (76 patients, 19%), and pain (71 patients, 18%). The most frequently affected body systems were body as a whole (225 patients, 56%) and the nervous system (206 patients, 51%). There were no apparent differences in incidence of headache and pain among the 6 dosage at onset groups, including placebo and the 5 sodium oxybate groups. There was a higher incidence (23%) of nausea in the 9.0 g/d group, compared with 7% for placebo and 8% to 11% for the other 4 sodium oxybate groups. A higher incidence of dizziness was seen in the 3.0 g/d and 9.0 g/d groups (16% and 17%, respectively), compared with 4% for placebo and 6% to 12% for the other 3 sodium oxybate groups.

Approximately half of the patients (247, 61%) experienced a related AE. The great majority of these patients reported AEs that were mild (99 patients, 40% of those with related AEs, 25% of the total population) or moderate (112 patients, 45% of those with related AEs, 28% of the total population). Severe related AEs were experienced by 36 patients (15% of those with related AEs, 9% of the total population). A higher incidence of both moderate and severe AEs overall was seen in the 9.0 g/d group. Moderate AEs were seen in 28% of the 9.0 g/d group, compared with 11% for placebo and 13% to 15% for the other 4 sodium oxybate groups; severe AEs were seen in 8% of the 9.0 g/d group, vs. 2% for placebo and 1% to 4% for the other 4 sodium oxybate groups. The incidence of severe related AEs for the most frequently reported AEs listed above was 1% (5/402) for headache, 1% (3/402) for nausea, 1% (4/402) for dizziness,

and 0 for pain. A higher incidence of mild headache was seen for placebo (11%), compared with 2% to 6% for the 5 sodium oxybate groups. No apparent differences were seen in the other AEs among the 6 groups, including placebo and the 5 sodium oxybate dosage at onset groups.

Table 4.6 AEs Occurring in ≥ 5% of Any Group, by Body System, COSTART Preferred Term, and Dosage at Onset — Updated Integrated Clinical Trial Database

Body System COSTART Preferred Term	Total[a]	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total[a]	3.0	4.5	6.0	7.5	9.0
Number of patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
Body as a Whole	225 (56%)	25 (46%)	221 (55%)	39 (40%)	81 (30%)	106 (37%)	41 (31%)	57 (44%)
Abdominal pain	25 (6%)	1 (2%)	24 (6%)	4 (4%)	6 (2%)	9 (3%)	3 (2%)	4 (3%)
Accidental injury	38 (9%)	0	38 (10%)	4 (4%)	6 (2%)	17 (6%)	6 (5%)	9 (7%)
Asthenia	36 (9%)	1 (2%)	35 (9%)	5 (5%)	6 (2%)	17 (6%)	5 (4%)	9 (7%)
Back pain	28 (7%)	2 (4%)	27 (7%)	2 (2%)	4 (1%)	13 (4%)	6 (5%)	8 (6%)
Chest pain	21 (5%)	0	21 (5%)	2 (2%)	4 (1%)	9 (3%)	5 (4%)	4 (3%)
Flu syndrome	41 (10%)	2 (4%)	39 (10%)	6 (6%)	7 (3%)	14 (5%)	10 (8%)	7 (5%)
Headache	116 (29%)	12 (22%)	112 (28%)	19 (20%)	40 (15%)	42 (14%)	13 (10%)	25 (19%)
Infection	42 (10%)	1 (2%)	41 (10%)	5 (5%)	2 (1%)	19 (7%)	7 (5%)	8 (6%)
Malaise	10 (2%)	3 (6%)	9 (2%)	1 (1%)	1 (<1%)	1 (<1%)	4 (3%)	3 (2%)
Pain	71 (18%)	4 (7%)	70 (18%)	12 (12%)	18 (7%)	33 (11%)	8 (6%)	16 (12%)
Viral infection	40 (10%)	0	40 (10%)	2 (2%)	6 (2%)	18 (6%)	5 (4%)	12 (9%)
Cardiovascular System	47 (12%)	2 (4%)	45 (11%)	6 (6%)	5 (2%)	17 (6%)	8 (6%)	11 (9%)
Digestive System	157 (39%)	9 (17%)	150 (38%)	23 (24%)	43 (16%)	62 (21%)	21 (16%)	42 (33%)
Diarrhea	38 (9%)	1 (2%)	37 (9%)	4 (4%)	6 (2%)	15 (5%)	7 (5%)	9 (7%)
Dyspepsia	32 (8%)	5 (9%)	27 (7%)	7 (7%)	8 (3%)	7 (2%)	2 (2%)	7 (5%)
Nausea	94 (23%)	4 (7%)	90 (23%)	9 (9%)	21 (8%)	31 (11%)	13 (10%)	30 (23%)
Vomiting	34 (8%)	1 (2%)	33 (8%)	1 (1%)	6 (2%)	14 (5%)	3 (2%)	10 (8%)
Metabolic and Nutritional System	53 (13%)	2 (4%)	53 (13%)	6 (6%)	8 (3%)	19 (7%)	14 (11%)	14 (11%)
Weight loss	12 (3%)	0	12 (3%)	0	0	4 (1%)	3 (2%)	6 (5%)

(continued)

Table 4.6 AEs Occurring in ≥ 5% of Any Group, by Body System, COSTART Preferred Term, and Dosage at Onset — Updated Integrated Clinical Trial Database

Body System COSTART Preferred Term	Total[a]	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total[a]	3.0	4.5	6.0	7.5	9.0
Number of patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
Musculoskeletal System	74 (18%)	2 (4%)	72 (18%)	8 (8%)	19 (7%)	33 (11%)	9 (7%)	12 (9%)
	21(5%)	2(4%)	19(5%)	2(2%)	7(3%)	10(3%)	1(1%)	2(2%)
Nervous System	206 (51%)	17 (31%)	201 (50%)	31 (32%)	66 (25%)	98 (34%)	31 (23%)	63 (49%)
Abnormal dreams	20 (5%)	0	20 (5%)	2 (2%)	8 (3%)	7 (2%)	4 (3%)	1 (1%)
Confusion	30 (7%)	1 (2%)	29 (7%)	4 (4%)	6 (2%)	11 (4%)	6 (5%)	10 (8%)
Depression	28 (7%)	1 (2%)	27 (7%)	5 (5%)	2 (1%)	12 (4%)	4 (3%)	6 (5%)
Dizziness	76 (19%)	2 (4%)	74 (19%)	16 (16%)	15 (6%)	34 (12%)	9 (7%)	22 (17%)
Emotional lability	13 (3%)	3 (6%)	10 (3%)	2 (2%)	2 (1%)	2 (1%)	1 (1%)	3 (2%)
Insomnia	25 (6%)	1 (2%)	24 (6%)	1 (1%)	8 (3%)	11 (4%)	3 (2%)	3 (2%)
Nervousness	35 (9%)	6 (11%)	31 (8%)	3 (3%)	9 (3%)	14 (5%)	3 (2%)	8 (6%)
Sleep disorder	47 (12%)	2 (4%)	45 (11%)	4 (4%)	15 (6%)	21 (7%)	5 (4%)	12 (9%)
Somnolence	60 (15%)	8 (15%)	55 (14%)	11 (11%)	14 (5%)	23 (8%)	5 (4%)	14 (11%)
Respiratory System	127 (32%)	6 (11%)	125 (31%)	16 (16%)	34 (13%)	61 (21%)	20 (15%)	18 (14%)
Cough increased	24 (6%)	2 (4%)	22 (6%)	5 (5%)	6 (2%)	10 (3%)	2 (2%)	1 (1%)
Pharyngitis	48 (12%)	3 (6%)	47 (12%)	5 (5%)	8 (3%)	23 (8%)	10 (8%)	2 (2%)
Rhinitis	36 (9%)	1 (2%)	35 (9%)	4 (4%)	12 (4%)	11 (4%)	7 (5%)	5 (4%)
Sinusitis	32 (8%)	0	32 (8%)	5 (5%)	6 (2%)	16 (6%)	4 (3%)	4 (3%)
Skin	61 (15%)	4 (7%)	58 (15%)	4 (4%)	9 (3%)	27 (9%)	5 (4%)	19 (15%)
Sweating	18 (4%)	0	18 (5%)	2 (2%)	2 (1%)	6 (2%)	1 (1%)	10 (8%)
Special Senses	52 (13%)	3 (6%)	49 (12%)	8 (8%)	10 (4%)	16 (6%)	7 (5%)	12 (9%)

(continued)

Table 4.6 AEs Occurring in ≥ 5% of Any Group, by Body System, COSTART Preferred Term, and Dosage at Onset — Updated Integrated Clinical Trial Database

Body System COSTART Preferred Term	Total[a]	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total[a]	3.0	4.5	6.0	7.5	9.0
Number of patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
Urogenital System	94 (23%)	6 (11%)	90 (23%)	7 (7%)	18 (7%)	43 (15%)	10 (8%)	25 (19%)
Incontinence urine	8 (2%)	0	8 (2%)	0	0	2 (1%)	0	6 (5%)
Urinary incontinence	28 (7%)	0	28 (7%)	2 (2%)	8 (3%)	9 (3%)	6 (5%)	6 (5%)

[a] Patients are counted only once in each category. However, patients could have had more than 1 instance of the same AE with different dosages at onset, so the sum of the patients in the dosage at onset groups may exceed the total number of patients in each event category or body system summary.

4.3.2 SERIOUS ADVERSE EVENTS

SAEs during treatment were experienced by 27 (7%) of the 402 patients in the updated integrated clinical trial database. Sodium oxybate dosage at onset was 3g for 1 patient 4.5 g/d for 5 patients, 6.0 g/d for 13 patients, 7.5 g/d for 2 patients, and 9.0 g/d for 8 patients (2 patients [1433 and 1630] had SAEs with different dosages at onset, and are counted twice).

Treatment-related SAEs were seen in only 11 of the 27 patients (1 in OMC-GHB-2, 1 in OMC-GHB-3, 3 in OMC-SXB-6, and 6 in OMC-SXB-7), resulting in an overall incidence of 3% (11 of 402) of SAEs possibly, probably, or definitely related to sodium oxybate treatment in the updated integrated clinical trial database.

Nine of the 11 treatment-related SAEs noted in the database resulted in inpatient hospitalization (1 SAE [23230] was originally classified as definitely related by the Investigator and upon further evaluation was determined to be not related: Therefore there are 10 treatment related SAEs.

- Patient 0207 (OMC-GHB-2) experienced confusion (severe, probably related) on Day 7 at a sodium oxybate dosage of 6.0 g/d, and was permanently discontinued from the trial. The patient recovered normal mental status following initial treatment with Haldol on the day of hospital admission. There have been no recurrences since study discontinuation.

- Patient 0232 (OMC-SXB-7) experienced acute paranoid delusional psychosis (severe, probably related) on Day 476 at a sodium oxybate dosage of 9.0 g/d, and was permanently discontinued from the trial. The SAE resolved approximately 2 months after discontinuing trial medication.

- Patient 0238 (OMC-SXB-6) fell and struck his head, proceeding to apnea, thinking abnormal, and coma (severe, probably related) on Day 170 at a sodium oxybate dosage of 4.5 g/d, and was permanently discontinued from the trial. The event resolved with no sequelae or recurrence following removal from trial medication.

- Patient 1131 (OMC-SXB-7) intentionally overdosed with Xyrem (approximately 150 g) (severe, definitely related to study medicine) on Day 280 while on a sodium oxybate maintenance dosage of 9.0 g/d, and was permanently discontinued from the trial. The patient had a history of treatment for depression and a previous suicide attempt. The patient was given psychiatric and medical referrals.

- Patient 1305 (OMC-GHB-3) experienced agitation (severe, possibly related) on Day 678 at a sodium oxybate dosage of 9.0 g/d, and trial medication was temporarily stopped. The patient later experienced an AE of “movement disorder” (Periodic Leg Movement in Sleep) and was discontinued from the trial on day 982.

- Patient 1735 (OMC-SXB-6) experienced abortion (mild, possibly related) on Day 108, previously at a sodium oxybate dosage of 6.0 g/d; however, she had been

permanently discontinued from the trial on Day 66 when she became pregnant (protocol violation, failing the inclusion criteria).

- Patient 2030 (OMC-SXB-7) began experiencing intermittent brief reactive psychosis (severe, possibly related) on Day 207 at a sodium oxybate dosage of 9.0 g/d, and was permanently discontinued from the trial. The patient was treated with Zyprexa and Trazadone and the event resolved with no recurring psychosis.

- Patient 23230 (OMC-SXB-7) began experiencing intermittent chest pain (originally severe, and definitely related, later determined to be not related) on Day 119. The patient was hospitalized for atypical chest pain, was treated and was discharged with the diagnosis of esophageal spasms. Patient participation is ongoing in trial OMC-SXB-7.

- Patient 2536 (OMC-SXB-7) fractured her ankle (severe, possibly related) on Day 228 at a sodium oxybate dosage of 9.0 g/d, and was permanently discontinued from the trial. The patient was discharged from the hospital on day 235 and referred to the rehabilitation clinic.

The remaining 2 treatment-related SAEs did not require inpatient hospitalization:

- Patient 0231 (OMC-SXB-6) experienced dizziness, confusion, nausea, vomiting, vertigo, and asthenia (all severe, possibly related) on Day 119 at a sodium oxybate dosage of 9.0 g/d, and was permanently discontinued from the trial. All events resolved within 24 hours of occurrence.

- Patient 14043 (OMC-SXB-7) attempted suicide by buspirone overdose (severe, possibly related) on Day 216 at a sodium oxybate dosage of 7.5 g/d, and was permanently discontinued from the trial. In current follow-up, patient's family state that the patient is doing well since her release from psychiatric treatment.

4.3.3 DISCONTINUATIONS AND OTHER SIGNIFICANT ADVERSE EVENTS

Fifty-three patients in the updated integrated clinical trial database withdrew due to 1 or more AEs, including 52 patients receiving sodium oxybate and 1 patient receiving placebo (0818).

Sodium oxybate dosage at onset was 3.0 g/d for 5 patients, 4.5 g/d for 15 patients, 6.0 g/d for 14 patients, 7.5 g/d for 4 patients, and 9.0 g/d for 18 patients.

Of the 53 patients discontinued due to AEs, 42 experienced AEs considered related to trial medication by the investigator (Table 4.7).

Table 4.7 Related AEs Causing Discontinuation — Updated Integrated Clinical Trial Database

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0204	OMC-GHB-3	6.0	33	51	Insomnia	Insomnia	No	Moderate
0207	OMC-GHB-2	6.0	7	9	Acute confusional state	Confusion	Yes	Severe
0213	OMC-GHB-3	9.0	90	135	Depressed mood	Depression	No	Moderate
		9.0	90	135	Excessive tiredness	Asthenia	No	Moderate
0221	OMC-GHB-2	9.0	13	15	Dizzy	Dizziness	No	Moderate
		9.0	13	15	Increased sleepiness	Somnolence	No	Moderate
		9.0	13	15	Nauseated	Nausea	No	Moderate
		9.0	13	15	Weakness (had trouble standing)	Asthenia	No	Moderate
	OMC-GHB-3	3.0	30	108	Lethargic all day	Somnolence	No	Mild
0231	OMC-SXB-6	9.0	119	119	Dizziness	Dizziness	Yes	Severe
		9.0	119	119	Confusion	Confusion	Yes	Severe
		9.0	119	119	Nausea	Nausea	Yes	Severe
		9.0	119	119	Vomiting	Vomiting	Yes	Severe
		9.0	119	119	Vertigo	Vertigo	Yes	Severe
		9.0	119	119	Weakness	Asthenia	Yes	Severe
0232	OMC-SXB-7	9.0	476	489	Acute paranoid delusional psychosis	Paranoid reaction	Yes	Severe
0238	OMC-SXB-6	4.5	170	170	Respiratory failure	Apnea	Yes	Severe
		4.5	170	170	Non-responsive	Coma	Yes	Severe
0409	OMC-GHB-3	9.0	61		Weight loss	Weight loss	No	Mild
0509	OMC-GHB-2	6.0	1	2	Restless leg syndrome increased	Hyperkinesia	No	Severe
0533	OMC-SXB-6	4.5	10		Swelling in legs	Peripheral edema	No	Severe

(continued)

Table 4.7 Related AEs Causing Discontinuation — Updated Integrated Clinical Trial Database

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0605	OMC-GHB-2	9.0	9	12	Daytime sedation feeling; "drugged feeling"	Somnolence	No	Mild
		9.0	9	12	Poor concentration	Thinking abnormal	No	Mild
0637	OMC-SXB-6	7.5	93[b]		Restless legs	Hyperkinesia	No	Moderate
		7.5	93[b]		Anxiety	Anxiety	No	Moderate
0701	OMC-GHB-3	6.0[c]	32		Decreased sexual libido	Libido decreased	No	Moderate
		6.0[c]	32		Decreased initiative to start any activity by gradual progression	Apathy	No	Mild
0702	OMC-GHB-2	9.0	20	25	Confusion	Confusion	No	Moderate
		9.0	20	25	Forgetfulness	Amnesia	No	Moderate
		9.0	20	23	Hallucinations	Hallucinations	No	Moderate
		9.0	21	21	Nausea	Nausea	No	Mild
		9.0	22	24	Paranoia	Paranoid reaction	No	Mild
0801	OMC-GHB-3	9.0	147	178	Chest pain, patient on drug, no hospitalization, no concomitant medication	Chest pain	No	Moderate
0802	OMC-GHB-3	9.0	49	55	Nervousness	Nervousness	No	Moderate
		9.0	49	51	Metallic taste	Taste perversion	No	Mild
		9.0	49	51	Upset stomach	Dyspepsia	No	Moderate
0809	OMC-GHB-3	3.0	332	332	Inability to control body 1 hr after taking medicine	Incoordination	No	Mild
0818	OMC-GHB-2	Placebo	23		Insomnia	Insomnia	No	Moderate
0821	OMC-GHB-3	6.0	39	51	Headaches	Headache	No	Moderate
		6.0	40	51	Irritable	Nervousness	No	Moderate

(continued)

Table 4.7 Related AEs Causing Discontinuation — Updated Integrated Clinical Trial Database

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0824	OMC-GHB-2	9.0[c]	5	5	Difficulty breathing	Dyspnea	No	Severe
	OMC-GHB-3	3.0	25	29	Difficulty breathing	Dyspnea	No	Moderate
0836	OMC-SXB-6	4.5	1		Headache	Headache	No	Moderate
0844	OMC-SXB-6	4.5	1	42	Nausea	Nausea	No	Moderate
		4.5	1	42	Vomiting	Vomiting	No	Moderate
		4.5	1	42	Headaches	Headache	No	Severe
0901	OMC-GHB-2	3.0	2	18	Lethargy	Somnolence	No	Mild
		3.0	2	18	Nausea	Nausea	No	Moderate
		3.0	3	18	Chest pressure	Chest pain	No	Mild
1131	OMC-SXB-7	9.0	280	280	Conscious overdose	Intentional overdose	Yes	Severe
1134	OMC-SXB-6	4.5	3		Urinary incontinence	Urinary incontinence	No	Moderate
1142	OMC-SXB-6	7.5	31	34	Left eye exposure keratitis	Keratitis	No	Mild
1201	OMC-GHB-2	9.0	5	5	Patient lost bowel control while asleep	Incontinence, fecal	No	Moderate
14043	OMC-SXB-7	7.5	216	216	Attempted suicide	Suicide attempt	Yes	Severe
1504	OMC-GHB-2	9.0	2	2	Nausea	Nausea	No	Severe
		9.0	2	2	Vertigo	Vertigo	No	Severe
		9.0	2	2	Vomiting	Vomiting	No	Severe
1631	OMC-SXB-6	6.0	23	59	Sleepwalking	Sleep disorder	No	Moderate
		4.5	44	59	Fragmented sleep	Sleep disorder	No	Severe
		4.5	44	60	Involuntary limb movements in sleep	Sleep disorder	No	Moderate
1735	OMC-SXB-6	6.0	108[d]	108[d]	Miscarriage	Abortion	Yes	Mild
2030	OMC-SXB-7	9.0	207	214	Brief reactive psychosis	Psychosis	Yes	Severe

(continued)

Table 4.7 Related AEs Causing Discontinuation — Updated Integrated Clinical Trial Database

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
2532	OMC-SXB-6	4.5	16	43	Sleepwalking	Sleep disorder	No	Mild
		4.5	16	43	Dizziness	Dizziness	No	Mild
		4.5	39	43	Arms and legs numb	Paresthesia	No	Mild
2533	OMC-SXB-6	4.5	25	81	Nausea	Nausea	No	Moderate
		6.0	74	81	Morning grogginess	Somnolence	No	Moderate
2536	OMC-SXB-7	9.0	228	228	Fractured ankle	Fractured ankle	Yes	Severe
2537	OMC-SXB-6	4.5	12		Increased headaches	Headache	No	Moderate
2633	OMC-SXB-6	4.5	2	4	Increased awakenings	Sleep disorder	No	Mild
		4.5	2	4	Tongue paresthesia	Paresthesia	No	Mild
2933	OMC-SXB-6	4.5	29		"Phlegm/knot" in throat	Pharyngitis	No	Moderate
3231	OMC-SXB-6	6.0	56		Exacerbation of colitis (Crohn's disease)	Colitis	No	Moderate
3830	OMC-SXB-6	7.5	52	62	Nausea	Nausea	No	Moderate
		7.5	58	58	Vomiting	Vomiting	No	Moderate
3831	OMC-SXB-6	3.0	12	24	Itching and swelling of extremities	Pruritus	No	Moderate
		3.0	12	24	Itching and swelling of extremities	Edema	No	Moderate
3930	OMC-SXB-6	4.5	2	3	Sleep paralysis	Sleep disorder	No	Moderate

[a] Day relative to start of treatment.
[b] Whole or partial data imputed from start of trial medication.
[c] Dosage carried forward.
[d] Patient discontinued study drug on study day 66, and the event of miscarriage occurred on day 108.

4.3.4 DEATHS

Two deaths, both suicides (0531 and 0936), were recorded among the 402 patients in the updated integrated clinical trial database. One (0531, coded as death) was due to multiple drug toxicity that included toxic levels of 6 psychotropic drugs other than sodium oxybate. The second patient (0936) had a history of depression and a subsequent suggested diagnosis of bipolar disease. This event was officially ruled as a death due to cardiovascular disease (without autopsy by the Medical Examiner), but later evidence pointed to a possible overdose that included lithium, Paxil, and Percocet as well as sodium oxybate. This event occurred on 2/24/01, which was 5 months after the data cutoff (9/30/00), but is included here for completeness. Both deaths were considered unrelated to study drug.

4.3.5 LABORATORY RESULTS

Laboratory evaluations for the original integrated clinical trial database (laboratory results were not analyzed for the 4-Month Safety Update for OMC-SXB-7) included blood chemistry, hematology, and urinalysis. Mean changes from baseline to last observation were small and similar across all 6 groups (placebo and 5 sodium oxybate last dosage groups) for all parameters.

4.3.5.1 Blood Chemistry

Shifts in ≥ 10% of the patients were only seen for calcium and total bilirubin. A shift from normal to low calcium was seen in 14 of 132 patients (11%) in the OMC-GHB-2 and OMC-GHB-3 trials (duration of up to two years); this ranged from 0 in the placebo group (for a 4 week treatment period) and the 7.5 g/d sodium oxybate last dosage group to 25% in the 3.0 g/d sodium oxybate last dosage group (treatment duration of up to two years). A shift from normal to low total bilirubin was seen in 32 of 314 patients (10%); this ranged from 4% in the 7.5 g/d sodium oxybate last dosage group (duration of up to two years) to 33% in the placebo group (4-week treatment period).

4.3.5.2 Hematology

Shifts in ≥ 10% of the patients were only seen for basophils, with a shift from high to normal in 30 of 310 patients (10%); this ranged from 0 in the placebo group (4-week treatment period) to 20% in the 3.0 g/d sodium oxybate last dosage group (duration of up to two years).

4.3.5.3 Urinalysis

Shifts in ≥ 10% of the patients were only seen for protein, with a shift from positive to negative in 42 of 307 patients (14%); this ranged from 6% in the 4.5 g/d sodium oxybate last dosage group (duration of up to two years) to 33% in the placebo group (4-week treatment period).

4.3.6 VITAL SIGNS AND ECG

Vital signs (pulse, respiration, blood pressure, body temperature, body weight) and ECG were analyzed for the original integrated clinical trial database (vital signs and ECG were not analyzed for the 4-Month Safety Update for OMC-SXB-7). Mean changes for all vital sign parameters were small, and were similar across all 6 groups (placebo group and 5 sodium oxybate last dosage groups).

Shifts from baseline to last observation in ECG results were analyzed. No shifts in ≥ 10% of the patients were seen overall or in any patient group for either abnormal to within normal limits or within normal limits to abnormal.

4.3.7 SAFETY SUMMARY – UPDATED INTEGRATED CLINICAL TRIALS

In dosages between 3 and 9g nightly in divided doses, sodium oxybate was generally well tolerated in the 5 trials comprising the Updated Integrated Clinical Trials. The side effects were usually mild in severity and most frequently included nausea, dizziness, and headache, and less frequently urinary incontinence (enuresis) and somnambulism (sleepwalking).

In the Updated Integrated Clinical Trials, a total of 296 patients have taken sodium oxybate for at least 6 months; of these, 223 patients have taken sodium oxybate for at least 1 year and 48 patients have taken sodium oxybate for at least 2 years. Total exposure to sodium oxybate was 329.89 patient years.

Of the 402 narcolepsy patients in this data base, 331 (82%) reported at least 1 AE. Adverse events considered to be possibly, probably, or definitely related to treatment with sodium oxybate were reported in 247 (61%) patients. Severe AEs were reported in 82 (20%) of the patients. Serious AEs were reported for a total of 27 (7%) patients, 10 whom had SAEs that were considered related to trial medication. Two deaths were reported (both suicides and both unrelated to trial medication).

Laboratory evaluations included blood chemistry, hematology, and urinalysis. The only potentially significant laboratory abnormality was hypocalcemia, which was present in 23 (17%) of 132 patients. It was a variable measure in 15 of these patients, with a return to normal during sodium oxybate treatment. In all cases, the reduction in calcium levels was minor and deemed not of clinical significance.

4.4 Lammers Trial

The Lammers trial was a double-blind, placebo-controlled, crossover trial in 25 patients to assess the effects of 60 mg/kg sodium oxybate or placebo in narcolepsy.

Sodium oxybate was well tolerated. AEs during the Lammers trial were few and mild, and were experienced by 6 (24%) of the 25 patients, as follows:

- 2 patients during the washout period (1 patient with frequent headache, and 1 patient with severe dreaming)
- 1 patient on placebo (kidney problems, urination problems/stranguria)
- 3 patients on sodium oxybate:
  - 1 patient with severe perspiration, influenza/common cold, sore throat, headache, and frequent micturition
  - 1 patient with bladder infection, sore throat, and flickering in the eyes
  - 1 patient with terrible dreaming, dry mouth, paralysis in legs and arms, anxious, and insecure

No SAEs or deaths were reported during the trial, and no patient withdrew due to an AE.

4.5 Scharf Trial

From the time of study initiation in 1983 to the time of study closure in 2000, a total of 143 patients participated in the Scharf open-label trial. Table 4.8 summarizes the disposition of the 143 patients in the Scharf trial. As of the NDA cutoff date of May 31, 1999, 63 of these patients transferred into the Orphan Medical Treatment IND protocol OMC-SXB-7. Of the remaining 80 patients, 8 continued to participate in the Scharf open-label trial, and 71 patients had discontinued from the Scharf open-label trial prior to the cutoff date. The reasons for discontinuation were: non-compliance (24); adverse events (23); cost of study participation (13); patient request (5); lack of efficacy (4); protocol deviation and other (1 each). The patient listed as “other” for reason for discontinuation, entered Dr. Scharf’s GHB fibromyalgia trial. One patient was a screen failure.

Table 4.8 Summary of Patient Disposition in Scharf Clinical Trial

Patient Disposition	Number of Patients
Patients screened	143
Patients treated	142
Ongoing treatment (OMC-SXB-7)	63
Ongoing treatment (Scharf)	8
Discontinued treatment	71
Non-compliance	24
Failure to provide diaries	22
Failure to follow dosing instructions	2
AEs	23
Death (coded as an SAE)	10[a]
Other AE	13
Cost of medication	13
Patient request/withdrawal of consent	5
Lack of efficacy	4
Protocol deviation	1
Other (transfer to fibromyalgia study)	1

[a]In the initial Scharf Report, 11 deaths were reported, however, one patient (202)died in a boating accident seven months following discontinuation of study medication. The case report form lists patient request as the reason for discontinuation.

This open-label, long-term (up to 16 years) clinical trial was developed under the investigator's IND following consultation with the FDA in 1983. These data were collected by Dr. Scharf more as a matter of clinical record than for drug development research and, hence, there are some differences from the other trials (eg, laboratory results were generated from many different laboratories, dose titration extended to dosages as high as 12.5 g/d). These data, do, however, provide experience in long-term treatment exposure. A total of 143 patients were enrolled in this trial, with 85% (121/143), 73% (104/143), 52% (74/143), and 32% (46/143) receiving sodium oxybate for > 6 months, > 1 year, > 5 years, and > 10 years, respectively.

The FDA and Orphan Medical, Inc agreed to a compilation of the Scharf data on the premise that it would potentially provide a profile of long-term clinical experience with sodium oxybate. Orphan Medical performed a retrospective compilation of the data for all 143 patients treated for up to 16 years.

4.5.1 INCIDENCE OF ADVERSE EVENTS – SCHARF TRIAL

In the Scharf trial, Adverse Events were recorded retrospectively on CRFs from information reported by patients in daily diaries (sleep logs) and from investigator-maintained medical records. These data included any untoward events noted by the patients, including possible side effects and effects of concomitant medications, as well as intercurrent illnesses, injuries, or accidents.

The majority of the 143 patients (136, 95.1%) experienced at least 1 AE. This is to be expected, given the unusually long duration of the trial (16 years, with 32% of patients on sodium oxybate for > 10 years). For this reason, it is difficult to compare these results with those given for the updated integrated clinical trial database, the Lammers trial, and the OMC-SXB-21 trial. To provide an easier basis for comparison, AEs over the first 6 months were analyzed for OMC-SXB-6, OMB-GHB-3, and Scharf.

Over the course of the Scharf trial, AEs reported by only 1 or 2 patients accounted for 44% of the AEs, which does not support a strong association with sodium oxybate.

Severe AEs were reported by 21 patients (14.7%) during their first 6 months in the trial. Over the course of the trial, one third of the patients (54, 37.8%) experienced SAEs, and 23 patients (16.1%) discontinued due to AEs. Eleven deaths (7.7%) were reported. No apparent differences were seen among the 5 sodium oxybate dosage of longest duration groups.

The most frequently reported AEs (nearly all of which were to be expected in a long-term trial and were associated with common intercurrent illnesses) included viral infection (56.6%), headache (52.4%), pain (48.3%), accidental injury (42.0%), nausea (40.6%), flu syndrome (38.5%), pharyngitis (37.8%), rhinitis (36.4%), increased cough (34.3%), sleep disorder (sleepwalking; 31.5%), diarrhea (28.0%), dizziness (27.3%), fever (26.6%), abdominal pain (26.6%), sinusitis (26.6%), dyspepsia (25.2%) and enuresis (23%).

Many of the most frequently reported AEs were considered not related to trial medication. During the first 6 months of treatment, the proportion of the reported AEs that were related to trial medication was 100% for sleep disorder (sleepwalking) and urinary incontinence, 48% for dizziness, 24.2% for nausea, 10.8% for pain, 7.7% for dyspepsia, and 5.9% for abdominal pain. No related AEs were seen for accidental injury, diarrhea, fever, flu syndrome, increased cough, pharyngitis, rhinitis, or sinusitis.

The frequency of cardiovascular AEs (arrhythmias and ventricular extrasystoles) appeared to be higher in the Scharf trial (26%) than in the other 2 trials (1% for OMC-SXB-6, 15% for OMC-GHB-3). This higher incidence probably reflects the higher incidence (approximately 20%) of prior history of cardiovascular disease in the Scharf trial population at baseline, and the expected age-related progression and presentation of cardiovascular morbidities in this long-term trial. Consistent with this observation is the fact that 5 of the 11 deaths in the Scharf trial were from cardiovascular causes and were unrelated to sodium oxybate treatment (as were the other 6 deaths).

4.5.1.1 Adverse Events Over the First 6 Months

To more easily compare the results from the Scharf trial with those from the other clinical trials, the incidence of AEs over the first 6 months of treatment with sodium oxybate was compared in the OMC-SXB-6, OMC-GHB-3, and Scharf trials.

The incidence of frequently occurring AEs including headache, nausea, pain, dizziness, and pharyngitis was similar in all 3 studies, except for pain (9% in OMC-SXB-6, 20% in

OMC-GHB-3, and 26% in Scharf). The incidence of patients reporting 1 or more AEs was similar in the 3 trials (78% for OMC-SXB-6, 91% for OMC-GHB-3, and 87% for Scharf).

4.5.2 SERIOUS ADVERSE EVENTS – SCHARF TRIAL

A total of 205 SAEs were reported for 54 of the 143 patients (37.8%) in the Scharf trial. Sodium oxybate dosage at onset was 3.0 g/d for 1 patient, 4.5 g/d for 17 patients, 6.0 g/d for 21 patients, 7.5 g/d for 7 patients, and 9.0 g/d for 5 patients. Dosage at onset was unknown for 3 patients.

Only 6 of the 54 patients had SAEs considered to be related to trial medication. In addition, relationship to trial medication was missing for 7 patients with SAEs: patient 012 (disorientation, stupor, weakness), patient 047 (ulcerated colon), patient 054 (skin cancer), patient 070 (back pain), patient 241 (severe headaches), patient 273 (tumors in neck-parotid glands), and patient 277 (hospital readmission after uvulopalatopharyngoplasty surgery).

Table 4.9 Patients with Serious Adverse Events Judged Related to the Study Medication

Patient Number	Age Sex	COSTART Term	Verbatim Term	Unexpected/ Expected	Dose[1]	Time on Drug (yr)
017[2]	68, M	Overdose	Overdose	Unexpected	18g	1.6
017	68, M	Coma	Comatose	Unexpected	18g	1.6
017	68, M	Stupor	Unresponsive	Unexpected	18g	1.6
019[3]	41, M	Suicide Attempt	Suicide Attempt	Unexpected	UNK	2.0
048[2]	27, F	Convulsion	Convulsive-like seizure	Unexpected	8.3g	5.3
048	27, F	Incontinence Urine	Urinary Incontinence	Expected	8.3g	5.3
257[2]	32, M	Reaction Unevaluable	Potential overdose	Unexpected	12g	2.6
257	32, M	Apnea	Hypoxemia	Unexpected	11.3g	8.0
267[3]	61, F	Overdose	Overdose	Unexpected	UNK	4.6
281[2]	59, M	Injury Accidental	Contusion from fall (over right eye)	Unexpected	7.5g	1.0
281	59, M	Injury Accidental	Contusion from fall (right arm)	Unexpected	7.5g	1.0
281	59, M	Injury Accidental	Head injury from fall	Unexpected	7.5g	1.0

[1]The dose listed is the dose associated with the SAE, not the patient's most common dose during the study.
[2]Patients who had more than one SAE as part of a single event except for patient 257 which represents two events.
[3]Patient reported to have taken an overdose of sodium oxybate although the exact dose is not known.

A relationship between higher dosages of trial medication and SAEs was found in this trial, although not in any other trial. Possible contributory factors affecting the frequency of SAEs include the length of the trial (16 years), the individual patients' increased age during the course of the trial (from a mean age of 45.3 years at entry to approximately 61 years at last observation), the SAEs that would be expected to occur in patients with narcolepsy, the baseline rate of cardiovascular abnormalities, and, for some patients, the continued use of TCAs.

4.5.3 DISCONTINUATIONS AND OTHER SIGNIFICANT ADVERSE EVENTS

Twenty-three patients withdrew from the Scharf trial because of AEs. Sodium oxybate last dosage was 3.0 g/d for 5 patients, 4.5 g/d for 2 patients, 6.0 g/d for 9 patients, 7.5 g/d for 5 patients, and 9.0 g/d for 2 patients. Eight of these patients subsequently died; the reasons for discontinuation in these 8 patients were the same as the causes of death with the exception of patient 243, who withdrew from the trial because of weight loss, and died 4 months later because of a heart attack.

AEs leading to withdrawal were considered to be related to trial medication in 6 of the 23 patients:

- Patient 019 was hospitalized following a suicide attempt (SAE) using an overdose of sodium oxybate on an unspecified date. This SAE was believed to be definitely related to treatment (intentional overdose) with sodium oxybate, and the patient was discontinued from the trial. The patient was started on sodium oxybate 5.3 g/d on July 12, 1987; his last recorded dosage of sodium oxybate (9.0 g/d) was July 30, 1989.

- Patient 259 discontinued sodium oxybate due to AEs of "feeling like a zombie," stiffness in legs and chest, and excessive crying (COSTART terms delirium, hypertonia, and emotional lability). These AEs, which were considered to be probably related to trial medication, were first reported on June 6, 1987 (sodium oxybate was begun June 3,1987at a dose of 5.3g/d), at which time the dosage of sodium oxybate was decreased to 3.0 g/d. The dosage was further reduced over the next 11 days to 0.8 g/d. The problem did not resolve, and the patient was discontinued on July 15, 1987.

- Patient 271 began taking sodium oxybate (5.3 g/d) in October 1994. He reported an AE of swollen ankles and feet (COSTART term edema) on January 18, 1995. This AE was considered to be possibly related to trial medication. Initial action was to reduce salt intake, with no change in sodium oxybate dosage. The event did not resolve, and the patient discontinued the trial on April 30, 1995. The last recorded dosage of sodium oxybate was 4.3 g/d.

- Patient 066 began taking sodium oxybate on March 25, 1985. She was discontinued from 7.5g sodium oxybate treatment on 4/20/91 due to possible drug-induced lupus. The patient presented rheumatoid-like symptoms accompanied by a series of sustained high anti-nuclear antibody (ANA) titers over a period of five months preceding her discontinuation. Titers for ANA continued to be elevated for the 6 months following the discontinuation of sodium oxybate. Anti-histone antibody titer reported on 10/5/92 was negative. No symptoms consistent with lupus accompanied the elevated ANA titers and no diagnosis of drug-induced lupus or systemic lupus erythematosus was made.

- Patient 244 began taking sodium oxybate on June 21, 1988. The patient was discontinued due to high ANA titer (possible drug-induced lupus) on May 3, 1989.

The dose at discontinuation was 2.3g. No symptoms consistent with lupus accompanied the elevated ANA titers and no diagnosis of drug-induced lupus or systemic lupus erythematosus was made. Follow-up notes of November 1992 indicated that the patient was negative for both ANA and anti-histone antibodies. The patient also informed the site that she was participating in a sodium oxybate trial under Dr. Scrima's IND. Dr. Scrima reported that the patient participated in his trial until termination in 2000 with good efficacy and no symptoms of lupus.

- Patient 254 began taking sodium oxybate on May 2, 1988. The patient discontinued due to a serious adverse event of pulmonary interstitial infiltrate, possible pulmonary toxicity on June 26, 1989. The sodium oxybate dose at discontinuation was 4.5g. The event resulted in in-patient hospitalization. The SAE report notes that the event was not related to trial medication, but source documents note that the event was "possibly related to the GHB or even the sodium load associated with GHB use". Follow-up efforts with the patient to determine if the event resolved with trial medication discontinuation were unsuccessful.

4.5.4 DEATHS – SCHARF TRIAL

Eleven patients died in the Scharf trial, including 5 deaths from cardiovascular-related causes, 5 deaths from cancer (3 lung, 1 colon, and 1 bladder), and 1 death related to a boating accident. None of the deaths was considered related to trial medication.

A significant prior history of contributory disease was present in all 5 cardiovascular-related deaths. In 2 of the 5 deaths from cancer, there was significant past history of malignancy. The medical history for 1 of the patients who developed lung cancer included persistent cold symptoms. No significant factors prior to diagnosis were identified for the remaining 2 cancer deaths.

The deaths occurred following 1.2 to 10.4 years of treatment with sodium oxybate. Of the 11 deaths reported to FDA, in only 5 cases did the date of death occur within 30 days of the last reported dose of sodium oxybate. In 4 of these cases, there was significant past medical history of disease; in the fifth case there was a history of persistent respiratory symptoms prior to the diagnosis of lung cancer.

This analysis does not reveal a pattern that could be viewed as causally related to sodium oxybate.

4.6 OMC-SXB-21 Trial

The OMC-SXB-21 clinical trial was a randomized, double blind, placebo-controlled, multicenter trial in 55 patients to assess the long-term efficacy of sodium oxybate compared with placebo. This trial was specifically designed to provide evidence of long-term efficacy of sodium oxybate based on the return of cataplexy symptoms upon cessation of a minimum of 6 months of open-label sodium oxybate treatment. A 2-week lead-in period with single-blind treatment with Xyrem at the patient's established dosage was followed by a 2-week period of double-blind treatment with either Xyrem or placebo.

Patients randomized to placebo experienced abrupt cessation of treatment and a return of cataplexy as the definitive endpoint measure. A total of 17 patients (31%, 17/55) – 7 of 26 (27%) Xyrem patients and 10 of 29 (34%) placebo patients – experienced at least 1 AE during the trial. In the double-blind period, there were no statistically significant differences between the Xyrem and placebo groups in the incidence of patients with an AE (12% for Xyrem, 31% for placebo; p = 0.108), related AEs (4% for Xyrem, 14% for placebo; p = 0.355), or severe AEs (0 for Xyrem, 3% for placebo; p = 1.000). No deaths, discontinuations, or serious AEs occurred during the trial. The incidence and severity of AEs were low. The majority were considered to be unrelated to trial medication. During the double-blind treatment period, patients on placebo did not experience a statistically significant change in vital signs or laboratory values.

Recent literature reports (Friedman 1996, Galloway 1997) indicate that abrupt discontinuation of high-dose, chronic sodium oxybate has resulted in withdrawal symptoms, which consistently include insomnia, anxiety, and tremors. Of these, insomnia, which generally resolved within 3 days, was the most consistently described symptom. Hallucinations (Hernandez 1998) have also been reported. In the OMC-SXB-21 placebo patients, these withdrawal symptoms occurred infrequently (3 [10.3%] of 29) patients, in patients abruptly withdrawn from chronic therapeutic dosages of sodium oxybate (anxiety, 2 [7%] patients, insomnia, 1 [3%] patient). These events were considered by the investigators to be of mild severity and probably (both patients with anxiety) or possibly (the 1 patient with insomnia) related to trial medication.

Overall, the results of this study indicate that Xyrem is well tolerated. Few AEs were related to the study drug. Abrupt discontinuation of long-term Xyrem treatment at therapeutic dosages did not appear to result in an increase in AEs that would indicate the presence of a withdrawal syndrome.

4.7 Safety Summary of the Pharmacokinetic Trials

The 8 clinical pharmacokinetic trials included 6 studies done in 125 normal volunteers and 2 studies (OMC-GHB-4, OMC-SXB-10) conducted in 19 narcoleptic patients. All 8 studies involved acute dosing with either 1 or 2 doses of sodium oxybate.

Table 4.10 summarizes the AEs for the 144 subjects in the 8 integrated pharmacokinetic (PK) trials. Approximately half of the subjects (75 subjects, 52%) experienced at least 1 AE, almost all of which were considered study drug-related AEs. Only 2 subjects (1%) discontinued due to AEs. There were no SAEs and no severe AEs. Most AEs were rated as mild in severity and all AEs resolved spontaneously, with no sequelae.

Table 4.10 Summary of Adverse Events — Integrated Pharmacokinetic Trials

	Sodium Oxybate[a]
Number of Subjects	144 (100%)
All events	
Subjects with ≥ 1 AE	75 (52%)
Subjects with SAEs	0
Subjects with related AEs	72 (50%)
Subjects with severe AEs	0
Subjects discontinuing due to AE	2 (1%)
Subject deaths	0

[a]Subjects are counted only once in each category.

The most common AEs experienced in the PK trials were nausea, dizziness, headache and vomiting. In general the frequency of AEs tended to increase with oxybate dosage but the severity and type of AE did not. In the 3 drug interaction studies, no clinically significant changes occurred in either the pattern or severity of AEs when Xyrem was administered together with protriptyline, modafinil or zolpidem. The highest incidence of AEs occurred in the fasted phase of the food effect study in which the subjects experienced 4 times as many AEs when given a 4.5g dose after an 8 hour fast as compared to the same dose given shortly after a high fat meal. The 2 subjects who discontinued due to the occurrence of AEs are detailed below.

In the dose proportionality study (OMC-SXB-9), Subject #012, a 30 year-old female, failed to return for the second dosing period after experiencing headache and nausea subsequent to the first dosing when she was administered 2 doses of 2.25g four hours apart.

In the food effect study (OMC-SXB-11), Subject #003, a 39 year-old female, was exposed to a single maximum therapeutic dose (4.5g) after a controlled 10-hour fast (overnight), with dosing at 7:00am. Initial adverse event reporting consisted of mild dizziness 30 minutes after dosing. Approximately 1 hour post-dosing, while lying supine, she developed a respiratory obstructive episode, characterized by respiratory stridor and "labored respiration". Initial repositioning did not immediately relieve the obstruction and a brief apneic event supervened. In the subsequent data analysis and report, the respiratory episode was coded with the COSTART preferred term "apnea". No positive pressure respiratory support was required since spontaneous respiratory effort followed the stimulation, and continued unassisted. Supplemental oxygen was provided via a facemask. At the time of the event, blood pressure and pulse were normal. Following the stimulation, she awoke and vomited once, after which she again fell asleep with normal respiratory rate. The duration of this entire sequence of events was approximately 2 minutes.

Again, approximately 1 hour later (that is, 2 hours post-dosing) the subject again developed a respiratory obstructive episode, beginning with respiratory stridor and proceeding to a brief pause in spontaneous respiration that resolved with stimulation and

the placement of a facemask for supplemental oxygen. An episode of fecal incontinence accompanied this event, but the patient was arousable, responded to verbal commands and no tonic/clonic activity was part of the event. Again, blood pressure (110/64) and pulse (57/min) remained normal for the subject. The subject again responded to verbal commands to breathe deeply.

There were no other untoward events relating to medication. Two hours later the subject consumed most of the offered lunch. She remained at the study facility for the full 10 hours post-dosing, along with the other study subjects, and was discharged home with no sequelae. She chose not to return for the second dosing one week later. The plasma oxybate versus time curve for Subject #003 was not significantly different from the other 17 normal subjects dosed identically at the same time.

In addition to adverse events, vital signs (blood pressure, heart rate, respiration rate) were recorded before and at multiple time points after each dosing period in all 8 of the PK studies. No clinically significant changes in vital signs were recorded in any patient or normal volunteer in any of the 8 PK trials. Overall, the safety profile of Xyrem from the 125 healthy subjects in the PK trials was not significantly different from that of the narcoleptic patient population.

4.8 Adverse Events of Special Interest

Subsequent to the submission of the NDA, several questions were raised by the FDA regarding both the Scharf trial and the integrated clinical trials. Responses to these questions were provided to the FDA in a Major Amendment on March 23, 2001, and in an Amendment for the Scharf Trial on April 10, 2001.

The major issues are summarized here, including:

- Further description of patients with
  - AEs coded to confusion
  - AEs coded to convulsion
  - Neuropsychiatric AEs
  - AEs of hyperglycemia or diabetes mellitus
- Analysis of the potential for drug-induced lupus
- Analysis of incontinence AEs and the relationship to seizurogenesis
- Characterization of the 80 patients who did not transfer from the Scharf trial into OMC-SXB-7 as of May 31, 1999.
- Characterization of the 75 occurrences in the Scharf trial with “reaction unevaluable” AEs
- Comparison of the incidence of AEs for sodium oxybate and placebo in the controlled trials

An analysis of AEs for sodium oxybate and placebo in the 4 controlled trials is also included in this section.

No patients in the OMC-SXB-21 trial experienced confusion, convulsions, or any neuropsychiatric event. One patient experienced hyperglycemia during the single-blind lead-in period; this was considered mild and not related to trial medication. No patients in the Lammers trial experienced any of these AEs.

4.8.1 ADVERSE EVENTS CODED AS CONFUSION

4.8.1.1 Updated Integrated Clinical Trial Database

Of the 402 patients in the updated integrated clinical trial database, 30 (7%) patients had 47 AEs with the COSTART preferred term of confusion (Table 4.11). Of these, 1 patient was in the placebo group.

Of the 30 patients who experienced confusion, 2 (<1%) had AEs considered serious by the investigator; 29 (7%) had AEs considered related (including the 1 patient on placebo); and 4 (1%) had AEs considered severe. A total of 3 patients (<1%) discontinued due to the AE of confusion. There were no deaths due to AEs of confusion. Two of the patients (0221 and 0815) had also experienced AEs of confusion prior to any treatment with Xyrem. The incidence of confusion among the 29 patients taking Xyrem does not appear to be dose-related.

Table 4.11 Summary of Patients with AE Preferred Term of Confusion by Dosage at Onset — Updated Integrated Clinical Trials

Confusion: All Events	Total[a]	Placebo	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset[b]				
				3.0	4.5	6.0	7.5	9.0
Number of Patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
At least 1 AE	30 (7%)	1 (2%)	29 (7%)	4 (4%)	6 (2%)	11 (4%)	6 (5%)	10 (8%)
SAEs	2 (<1%)	0	2 (<1%)	0	0	1 (<1%)	0	1 (1%)
Related AEs	29 (7%)	1 (2%)	28 (7%)	3 (3%)	6 (2%)	10 (3%)	6 (5%)	10 (8%)
Severe AEs	4 (1%)	0	4 (1%)	0	2 (1%)	1 (<1%)	0	1 (1%)
Discontinuation due to an AE	3[c] (<1%)	0	3[c] (<1%)	0	0	1 (<1%)	0	2[c] (1%)
Deaths	0	0	0	0	0	0	0	0

[a] Patients are counted only once in the total column.

[b] Some patients were exposed to more than 1 dosage during the trial(s), so the sum of patients exposed to specific dosages exceeds the total number of patients in the updated integrated clinical trial database.

[c] Patient 2632 (9.0 g/d) discontinued due to "patient request" (confirmed by further medical review); therefore, this patient is not included here. However, the AEs of headache/confusion were contributing factors.

Of the 30 patients, 21 (70%) were women, and 20 (67%) were 50 years of age or older (range 25.7 to 73.8 years).

Most of the AEs of confusion were experienced during the first 60 days of trial: 13 patients experienced 15 AEs of confusion during Days 1 to 30; 10 patients

experienced 11 AEs during Days 31 to 60; 5 patients experienced 5 AEs during Days 61 to 120; 7 patients experienced 13 AEs during Days 121 to 365; and 3 patients experienced 3 AEs during Days 366 to 1022. The first occurrence of confusion was during Days 1 to 30 for 13 patients; during Days 31 to 60 for 8 patients; during Days 61 to 120 for 5 patients; during Days 121 to 365 for 2 patients; and during Days 366 to 1022 for 2 patients.

Two events of confusion were not recorded as resolved:

- Patient 2539 (onset Day 74) experienced mild and intermittent "confused awakening," which was listed as ongoing in trial OMC-SXB-6, but is not listed in the patient's follow-up trial OMC-SXB-7. According to the following comment on the CRF for "action taken" for this episode, it appears that a stop date should have been entered in trial OMC-SXB-6: "Patient notes she may awaken after first dose of Xyrem but before second dose . . . she got up a few times initially but realizes she was confused. Now she intentionally goes back to sleep and avoids getting up."

- Patient 2632 experienced a moderate, probably related episode of "disorientation" on Day 267 in OMC-SXB-7 that was categorized as intermittent. On the same day this event of confusion was reported, the patient discontinued due to "patient request" (confirmed by further medical review); therefore, this patient is not listed as discontinuing due to the AE of confusion. However, the AEs of headache/confusion were contributing factors. In OMC-SXB-6, his previous trial, this patient had a similar complaint (Day 10, 9/22/99), which resolved in January 2000. Follow-up with this patient on 3/21/01 by the trial coordinator confirms that this patient's disorientation resolved soon after trial termination and the patient has had no recurrence of these symptoms.

Most of the verbatim descriptions of AEs with the COSTART preferred term of confusion included some form of the words "confusion" or "disoriented." The actual investigator terms were:

- "Confusion," "acute confusional state," or "confusion on awaking" – 15 patients with 25 events
- "Disoriented," "disoriented upon awakening," or "disorientation" – 13 patients with 15 events
- "Confusion/disorientation" – 2 patients with 2 events
- "Feeling 'drunk' after taking drug" – 3 patients with 3 events
- "Dazed feeling" – 1 patient with 1 event
- "Couldn't comprehend" – 1 patient with 1 event
- "Woozy feeling" – 1 patient with 1 event

4.8.1.2 Analysis of Trial OMC-GHB-2

Eleven (8%) of the 136 patients in OMC-GHB-2 (including 1 patient on placebo) experienced an AE of confusion. Since this trial was only 4 weeks in duration, additional analysis was conducted.

The major difference between trial OMC-GHB-2 and the other studies is that patients were assigned dosages in a blinded, randomized manner that excluded any consideration of body weight or size, sex, or disease severity. This non-titrated dosing assignment produced the majority of occurrences of confusion in the 10 patients on active drug:

- Six patients experienced the AE at the 9.0 g/d dosage level
- Six patients experienced the AE in the first week of drug exposure, with 4 of these 6 assigned to the 9.0 g/d dosage

The emergence of these AEs, especially at the 9.0 g/d level, in the short 4 weeks of active treatment gives further support to the proposed dosing strategy, with initial dosing at the 4.5 g/d level and subsequent optimization of clinical response by dosing adjustments of 1.5 g/d every 2 weeks.

Nine of these patients continued into future trials, and only 2 had a recurrence of confusion.

4.8.1.3 Scharf Trial

All patients who had AEs with the COSTART preferred term of confusion during the Scharf trial through the data cutoff of May 31, 1999, were included in this analysis.

Of the 143 patients in the trial, 10 (7%) experienced a total of 15 AEs with the COSTART preferred term of confusion (Table 4.12). One patient experienced an SAE, 5 AEs were possibly or probably related to trial medication, 1 patient had 3 severe AEs, and no patients discontinued due to an AE of confusion.

Table 4.12 Summary of Patients with AE Preferred Term of Confusion by Dosage at Onset – Scharf Trial

Confusion: All Events	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset[b]				
		3.0	4.5	6.0	7.5	9.0
Patients with: At least 1 AE	10[c]	0	3	3	4	0
SAEs	1	0	0	0	1	0
Related AEs	5	0	1	2	2	0
Severe AEs[c]	1	0	1[c]	0	0	0
Discontinuations due to an AE	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

[a] Patients are counted only once in each category.

[b] Dosage at onset. Dosage for patient 248 is listed as "0."

[c] Patient 027 experienced 3 events of "disoriented," all of which were considered severe.

All 15 AEs used verbatim terms including the words "confusion" or "disoriented." Five events were considered possibly or probably related to trial medication, 6 were of unknown relationship, and 4 were not related.

Of the 10 patients, 6 were men and 4 were women. For 8 of these 10 patients, the event of confusion was reported only once. Age at the time of onset ranged from 27.7 to 76.8 years. Of the 15 events, 5 occurred in the first 60 days, 4 occurred from 61 days to 1 year, 3 occurred from 1 year to 2 years, and 3 occurred at > 2 years (Days 3185, 3301, and 3314) on trial medication. The dosage at onset for these events ranged from 4.5 to 7.5 g/d.

Most events (10 of 15, 66.7%) were transient in nature, (single episodes) lasting 1 day or less. One event lasted 15 days; the remaining events (1 in each of 4 patients, 235, 248, 251, and 266) had no stop date listed. Two of these patients (248, "mental confusion", and 251, "confused") discontinued for non-compliance) on Days 89 and 218, respectively); onset of their AEs was Days 5 and 62, respectively. The other 2 patients (235, "disorientation [when awakening from sleep]," and 266 "confused sometimes [not a lot]," with onset of AEs on Days 1 and 273, respectively, transferred into OMC-SXB-7 on Days 4456 and 5623, respectively, with no confusion AEs reported in the OMC-SXB-7 trial.

Only 1 patient (012, "disoriented") experienced an SAE, which resulted in overnight hospitalization. This patient returned to study drug with no further recurrences. No patients discontinued due to AEs of confusion.

4.8.2 ADVERSE EVENTS CODED AS CONVULSION

4.8.2.1 Updated Integrated Clinical Trial Database

Of the 402 patients in the updated integrated clinical trial database, 14 (3%) had AEs with the COSTART preferred term of convulsion(s). Thirteen (93%) of these 14 patients had investigator verbatim terms relating the event to cataplexy (Table 4.13). The single event with the investigator term of "seizures" also appeared to be cataplexy-related (see discussion below).

Table 4.13 List of COSTART and Verbatim Investigator Terms for AEs of Convulsion – Updated Integrated Clinical Trial Database

Patient Number	COSTART Term	Verbatim Term
0221	Convulsions	Increase in major cataplexy attacks
0231	Convulsion	Increased duration of cataplectic events
0243	Convulsion	Increase partial cataplexy
0545	Convulsion	Increase in cataplexy
	Convulsion	Increase in cataplexy
0608	Convulsion	Increased cataplexy
0814	Convulsion	Seizures
0835	Convulsion	Increased cataplexy
	Convulsion	Cataplexy
1130	Convulsion	Cataplexy
1302	Convulsion	Increased cataplexy (significant)
	Convulsion	Increased cataplexy (significant)
1306	Convulsion	Increase in cataplexy
1509	Convulsion	Multiple cataplexy attacks for 10 min. (due to protocol violation of patient: got out of bed to use bathroom 1½ hr. after taking 1st dose of sodium oxybate)
1703	Convulsion	Bit tongue (due to falling faster to ground: cataplexy)
	Convulsion	Hit temple against furniture (due to falling faster to ground: cataplexy)
2936	Convulsion	Cataplexy
3937	Convulsion	Cataplexy

There were 7 patients (2%) with related AEs coded as convulsion and 2 patients (<1%) with severe AEs coded as convulsion (Table 4.14). There were no SAEs, discontinuations, or deaths associated with AEs coded as convulsion. A higher incidence of AEs coded as convulsion was seen in the 9.0 g/d dosage at onset group (5%, compared with 2% for 6.0 g/d, 1% for 4.5 g/d, and 0 for 3.0 and 7.5 g/d). However, patients with the most severe cataplexy are potentially titrated to the highest dosage, which may explain the slightly higher incidence of these cataplexy related AEs, which were coded as convulsion, at 9.0 g/d.

Table 4.14 Summary of Patients with AE Preferred Term of Convulsion, by Dosage at Onset – Updated Integrated Clinical Trials

Convulsion: All Events	Total [a]	Placebo	Xyrem Oral Solution Dosage (g/d) at Onset					
			Total [a]	3.0	4.5	6.0	7.5	9.0
Number of Patients	**402 (100%)**	**54 (100%)**	**399 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
Patients with: ≥ 1 AE of convulsion	14 (3%)	0	14 (4%)	0	3 (1%)	5 (2%)	0	6 (5%)
Convulsion SAEs	0	0	0	0	0	0	0	0
Related convulsion AEs	7 (2%)	0	7 (2%)	0	1 (<1%)	4 (1%)	0	2 (2%)
Severe convulsion AEs	2 (<1%)	0	2 (1%)	0	1 (<1%)	1 (<1%)	0	0
Discontinued due to convulsion AE	0	0	0	0	0	0	0	0
Deaths due to convulsion AE	0	0	0	0	0	0	0	0

[a] Patients are counted only once in each category.

Of the 14 patients, 8 were women and 6 were men. Age ranged from 21.2 to 70.6 years, with 6 patients under the age of 50. Of the 17 events, 5 occurred within the first 30 days after first administration of Xyrem; 1 occurred 31 to 60 days after; 3 occurred 61 to 90 days after; 1 occurred 91 to 120 days after; 1 occurred 236 days after; 1 occurred 333 days after; 3 occurred 1 to 2 years after; and 2 occurred between 2 and 3 years after. The event termed "seizures" in patient 0814 occurred 935 days (2.6 years) after first taking Xyrem. Three of the 17 events (patients 0231, 0608, and 1302) were ongoing at last contact; however, the event for patient 1302 ("increased cataplexy, significant") was recorded as resolved on Day 38 (duration 7 days) at trial entry into OMC-GHB-3. Duration for the remaining 14 events was ≤ 1 day for 5 events, 2 to 7 days for 4 events, 8 to 14 days for 2 events, 34 and 38 days for 2 events, and 151 days for 1 event.

Of the 14 patients, 13 had events related to cataplexy; only 1 patient (0814) had a less definitive assignment of "seizures," which were considered mild, with relationship to trial medication unknown.

Patient 0814, a 58 year old male, had a history of narcolepsy for twenty years prior to the start of cataplexy. He participated in the OMC-GHB-2 trial (beginning treatment on May 28, 1997) and proceeded into OMC-GHB-3 (beginning June 30, 1997). His dose of sodium oxybate was 4.5g/day. He continued into the OMC-SXB-7 trial, beginning May 13, 1999 at the 4.5g/d dose, and remains at this dose. He had a past history of headaches, left breast cancer, and numerous falls with closed head injury due to cataplexy. He sought neurological consultation (April 15, 1999) with a two-year history of memory problems, complicated by getting lost, and a description of "losing gaps of time". Two such adverse events were reported during the study (trial days 220 and 558) with verbatim descriptive terms "fugue state; patient reports being in limbo", and "trance-like state", both of which have been COSTART coded as convulsions. It is important to

note that this neurologic symptomatology preceded study commencement. Neurologic examination on all occasions was normal. His neurologist initiated investigation for these memory lapses, with a possible association of partial complex seizures, or possible early mild dementia or encephalopathy. MRI scan (April 15, 1999) was normal and specifically excluded metastatic disease. His EEG was normal during quiet wakefulness and stage II sleep, and during photic stimulation (hyperventilation was not done). A follow-up ambulatory, twenty-four hour EEG did indicate polyspike and wave activity that could indicate possible generalized seizure activity, but artifact could not be excluded. Overall clinical correlation was advised. A trial of Dilantin 300 mg/day was conducted over a three-month period, with no change in symptomatology. Psychiatric assessment did not contribute explanation for the confusional episodes. These events continue intermittently, and have been suggested by the principal investigator to be possibly related to the narcolepsy syndrome.

4.8.2.2 Scharf Trial

Nine patients experienced 20 AEs that coded to COSTART preferred terms of convulsion or convulsion grand mal (Table 4.15).

Table 4.15 Summary of Patients with AEs of Convulsion, by Dosage at Onset – Scharf Trial

		Sodium Oxybate Oral Solution Dosage (g/d) at Onset				
Convulsion: All Events	**Total [a]**	**3.0**	**4.5**	**6.0**	**7.5**	**9.0**
Number of convulsion AEs	20					
Patients with at least 1 AE	9	0	0	5	2	2
Convulsion SAEs	1	0	0	0	0	1
Related convulsion AEs	1	0	0	0	0	1
Severe convulsion AEs	1	0	0	0	0	1
Discontinuations due to a convulsion AE	2	0	0	1	1	0
Convulsion Deaths	0	0	0	0	0	0

[a] Patients are counted only once in each category, at the highest dosage at onset.

Table 4.16 summarizes the COSTART and verbatim terms for the 20 events in these 9 patients. Ten AEs in 4 patients included the verbatim term “seizure,” including the 1 SAE and 1 related AE (same event) and 2 discontinuations. The remaining five patients reported cataplexy that was reported as convulsion.

Table 4.16 List of COSTART and Verbatim Investigator Terms for Convulsion AEs – Scharf Trial

Patient Number	COSTART Term	Verbatim Term	Dosage at Onset (g/d)
043	Convulsion	Excessive cataplexy	6.0
048	Convulsion	Convulsive-like seizure[a]	8.3
049	Convulsion	Fall, sudden cataplexy	6.0
051	Convulsion	Fell twice, with cataplexy	6.0
064[b]	Convulsion	Seizure	7.5
	Convulsion	Seizure	6.0
	Convulsion	Seizure	6.0
	Convulsion	Seizure during the morning	6.0
	Convulsion	Seizure in the morning	6.0
	Convulsion	Another seizure in afternoon	6.0
	Convulsion	Seizure in the morning	6.0
219	Convulsion	Cataplexy	7.5
	Convulsion	Cataplexy	7.5
247[c]	Convulsion	Seizure, continuous jerking	6.0
255[d]	Convulsion Grand Mal	Brief grand mal seizure	5.3
257	Convulsion	Violent shaking and vibrations[e]	5.3
	Convulsion	Jerking during cataplexy	9.0
	Convulsion	Bad cataplexy[f]	9.0
	Convulsion	Cataplexy[f]	12.0
	Convulsion	Fall from cataplexy caused him to hit his head on furniture, increase in cataplexy resulted[f]	11.3

[a] This event was serious and determined to be possibly related to study medication.

[b] Patient 064, who had a pre-existing left frontal lobe lesion that may have contributed to the seizure activity, discontinued due to series of 7 seizures over 14-month period.

[c] Patient 247 discontinued due to the AE.

[d] Patient 255 had a history of seizures of unknown etiology at enrollment.

[e] This AE was most likely associated with fever and chills due to a severe tonsillar infection.

[f] AE was considered by the investigator to be severe.

Of the 9 patients, 6 were women and 3 were men. Age at onset ranged from 14.5 to 47.7 years, with 2 of the patients (both women) under the age of 20. Of the 20 events, 1 occurred in the first 60 days, 8 occurred from 6 months to 1 year, 5 occurred from 1 to 2 years, and 6 occurred at > 2 years (Days 1878 to 4537) following the start of trial medication. The 10 seizure-related events occurred on Days 275 to 681 (064, 7 events), day 276 (patient 247), day 310 (patient 255), and day 1931 (patient 048) of sodium oxybate treatment.

Four (043, 049, 051, and 219) of the 9 patients with AEs coding to “convulsion” had events related to cataplexy. One patient (257) had 5 events coded to convulsion,

4 events were related to cataplexy and 1 event, verbatim term, violent shaking and vibrations, was considered to be most likely due to a concurrent infection.

Of the 4 remaining patients that had events coded to COSTART term convulsion, 2 patients (064 and 255) had events of verbatim terms seizure (064 experienced 7 separate events of unknown relationship to trial medication) and brief grand mal seizure (255), which was considered unrelated to trial medication. Patient 255 had a previous history of seizure disorders, and patient 064 had a pre-existing left frontal lobe lesion that may have contributed to the seizure activity as suggested by focal EEG changes and continuation of seizures since discontinuation of sodium oxybate study medication in May, 1989. Two patients (048 and 247) had events of verbatim terms convulsive-like seizure and seizure (continuous jerking all over body) that were possibly complicated by polypharmacy, but are considered to represent potential seizurogenesis.

4.8.3 NEUROPSYCHIATRIC ADVERSE EVENTS

Published studies indicate that symptoms of depression and other symptomatology of psychiatric illnesses are seen in 50% or more of narcolepsy patients, making it difficult to accurately characterize the reports of neuropsychiatric AEs. A review of literature concerning the incidence of psychopathology associated with narcolepsy is provided as follows:

Strong associations between neuropsychiatric pathology and sleep disorders, in particular narcolepsy, are proposed in the literature by both retrospective reviews (Sours 1963, Wilcox 1985) with comparative sex- and age-matched controls. Central mechanistic associations have been proposed to link the pathophysiology of psychosis and abnormal central sleep controls (Howland 1997, Saucerman 1997). Further psychiatric morbidity in narcoleptics on chronic high-dose stimulant therapy is well established (Pawluk 1995).

An example of the associated psychotherapy with narcolepsy was defined by John Sours in 1963 when he reviewed clinical records of patients admitted to a New York Hospital from 1932 – 1964 and coded under the categories of hypersomnia, somnolence and narcolepsy. He identified eight patients with schizoid personality disturbances and another ten patients that developed frank schizophrenic psychoses which required prolonged hospitalization. Such an association was established in the 1985 sex- and age-matched review by James Wilcox at the University of Iowa between narcolepsy and the symptoms of schizophrenia. Such associations have led to discussions as to whether psychiatric findings are epiphenomenal to, or inherent in the expression of narcolepsy.

A review of the emotional and psychosocial correlates of narcolepsy in fifty adults who had a current complaint of sleep attacks and cataplexy by Kales et al in 1982 indicated a “high level of psychopathology compared to controls”. However, these authors considered this to be primarily a reaction to the disorder and its effects.

Robert Howland (1997) established clear association between the sleep-onset REM characteristics of narcolepsy and schizophrenia, psychotic depression, and delirium tremors. He proposed this objective EEG measure as an objective surrogate of neurochemical abnormality representing a common mechanistic link.

An association between the HLA antigens related strongly to narcolepsy-cataplexy (HLA-DR2, DQ1) and its subdivision HLA-DR15, DQ6 has been suggested with schizophrenia. Douglass (1993) found that in 56 schizophrenic patients and 56 controls, the incidence of narcolepsy-associated antigens was 3.89 times higher in the schizophrenic patients. Also, that the patients with the narcolepsy-associated antigens had more hospitalizations and higher Brief Psychiatric Rating Scale scores, suggesting a severity association.

As was suggested by Kales, studies using self-report as well as traditional psychiatric measures have found significant depression among narcoleptics. People newly diagnosed with narcolepsy have reported that depression was the personality change they noted at disease onset (Broughton 1976). Recurrent episodes of depression have been reported by 51% of people with narcolepsy (Broughton 1984).

Seven hundred narcoleptics chosen randomly from the patient rolls of the American Narcolepsy Association were surveyed (response rate = 61.4%) with anonymous responses to the Center for Epidemiologic Studies Depression Scale (CES-D), indicating again that a high proportion of narcoleptics (49%) were experiencing depressive symptoms.

Patient status in narcolepsy is obviously a complicated and dynamic representation of:

- Disease-associated psychosocial morbidity.
- Stimulant-induced personality changes.
- Stress variations in daily life.
- Treatment-related co-morbidities.

It is very difficult to interpret causality of events to any single contributor.

4.8.3.1 Updated Integrated Clinical Trial Database

AE terms suggestive of neuropsychiatric events – overdose, coma, death, depression, hallucinations, intentional overdose, manic depressive reaction, overdose, paranoid reaction, personality disorder, psychosis, stupor, suicide, and suicide attempt – were analyzed for the updated integrated clinical trial database.

Of the 402 patients, 52 patients (13%) reported AEs for the specified neuropsychiatric COSTART terms. Of these, 9 patients (2%) had SAEs, 12 patients (3%) had AEs classified as severe, 27 patients (7%) had AEs considered related to trial medication, 12 patients (3%) discontinued the study due to these AEs, and 2 patients (<1%) died in association with these AEs.

There was no clear relationship between incidence of neuropsychiatric AEs and dosage at onset.

Table 4.17 Summary of Patients with Neuropsychiatric AEs, by Dosage at Onset — Updated Integrated Clinical Trials

Neuropsychiatric AEs: All Events	Total[a]	Placebo[b]	Xyrem Oral Solution Dosage (g/d) at Onset[c]				
			3.0	4.5	6.0	7.5	9.0
Number of Patients with:	**402 (100%)**	**54 (100%)**	**97 (100%)**	**269 (100%)**	**290 (100%)**	**133 (100%)**	**129 (100%)**
≥ 1 AE	52[c] (13%)	1 (2%)	5 (5%)	6 (2%)	25 (9%)	5 (4%)	14 (11%)
SAEs	9 (2%)	0	0	2 (1%)	4 (1%)	0	3 (2%)
Related AEs	27 (7%)	1 (2%)	1 (1%)	3 (1%)	12 (4%)	0	12 (9%)
Severe AEs	12 (3%)	0	0	3 (1%)	6 (2%)	0	3 (2%)
Discontinued due to AEs	12 (3%)	0	0	3 (1%)	3 (1%)	1 (1%)	5 (4%)
Patient deaths	2 (<1%)	0	0	0	2 (1%)	0	0

Note: One patient in the 6.0 g/d dosage group (0936, possible overdose) had an SAE resulting in death on 2/24/01, which was 5 months after the data cutoff (9/30/00), but is included here for completeness.

[a] Patients are counted only once in each total column.

[b] Patients were on placebo for a short time (4 weeks) relative to the long-term exposure of those treated with Xyrem.

[c] Some patients were exposed to more than 1 dosage during the trial(s), so the sum of patients exposed to specific dosages exceeds the total number of patients in any category.

Table 4.18 summarizes the neuropsychiatric AEs by COSTART preferred term.

Table 4.18 Summary of Patients with Neuropsychiatric AEs, by COSTART Preferred Term – Updated Integrated Clinical Trials

COSTART Term	Number of Patients[a]
Total	**52[b]**
Depression	27
Hallucinations	9
Stupor	6
Suicide, Suicide Attempt, and Overdose	4[b]
Paranoid Reaction	4
Coma	2
Psychosis	2
Manic Depressive Reaction	1
Personality Disorder	1

[a] Patients may have had more than 1 neuropsychiatric AE, so the sum of patients in all categories exceeds the total number of patients.

[b] One patient (0936, possible overdose) had an SAE resulting in death on 2/24/01, which was 5 months after the data cutoff (9/30/00), but is included here for completeness.

Of the 52 patients, 31 were women and 21 were men. Age ranged from 17.7 to 68.0 years, with 31 patients (62%) under the age of 50. There was no apparent relationship between the incidence of neuropsychiatric AEs and the length of time on sodium oxybate. Of the 64 events, 10 occurred within the first 30 days after administration of Xyrem; 16 occurred 31 to 60 days after; 13 occurred 61 to 90 days after; 9 occurred 91 to 180 days after; 8 occurred 6 to 12 months after; 5 occurred 1 to 2 years after; and 2 occurred more than 2 years later (patient 1704, 2.8 years later; patient 14043. 11.7 years later). Sixteen of the 64 events were ongoing at last contact. Duration for the remaining 48 events was ≤ 1 day for 20 events, 2 to 7 days for 8 events, 8 to 14 days for 5 events, 2 to 4 weeks for 6 events, 1 to 2 months for 4 events, 2 to 3 months for 2 events, 3 to 6 months for 2 events, and 230 days for 1 event.

4.8.3.2 Scharf Trial

Of the 143 patients in the Scharf trial, 41 patients (28.7%) reported neuropsychiatric AEs (terms included overdose, suicide attempt, depersonalization, depression, emotional lability, hallucinations, hostility, neurosis, paranoid reaction, stupor, and thinking abnormal) (Table 4.19). Twelve patients (8.4%) had events that were considered definitely, probably, or possibly related to study drug, 4 patients (2.8%) had SAEs (2 of these patients experienced 2 neuropsychiatric SAEs each), 7 patients (4.9%) had AEs classified as severe (1 patient experienced 2 severe neuropsychiatric events), and 2 patients (1.4%) discontinued from the study due to these AEs.

There was no apparent dose relationship to either the frequency or severity of the selected neuropsychiatric events.

Table 4.19 Summary of Patients with Neuropsychiatric AEs, by Dosage at Onset – Scharf Trial

Neuropsychiatric AEs : All Events	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Number of Neuropsychiatric AEs	84	3	14	23	25	19
Patients with: at least 1 AE	41	1	9	12	11	8
SAEs	4	0	1	0	1	2
Related AEs	12	0	1	4	3	4
Severe AEs	7	2	2	0	2	1
Discontinuations due to an AE	2	0	0	1	0	1
Deaths	0	0	0	0	0	0

[a] Patients are counted only once in each category; patients are classified by the highest dosage at which a neuropsychiatric AE occurred.

Table 4.20 summarizes the neuropsychiatric events by COSTART preferred term, in order of decreasing frequency.

Table 4.20 Summary of Patients with Neuropsychiatric AEs, by COSTART Preferred Term – Scharf Trial

COSTART Term	Number of Patients[a]	Number of Events
Total	41	84
Depression	22	28
Emotional lability	10	14
Thinking abnormal	9	13
Depersonalization	7	7
Hostility	6	8
Stupor	6	7
Neurosis	2	2
Overdose	2	2
Suicide attempt	1	1
Hallucinations	1	1
Paranoid reaction	1	1

[a] Patients may have had more than 1 AE.

Of the 41 patients, 23 were men and 18 were women. Age at the time of AE onset ranged from 14.2 to 76.8 years. There was no apparent relationship between the incidence of neuropsychiatric AEs and the length of time on sodium oxybate. Of the 84 events, 22 occurred in the first 60 days of sodium oxybate treatment; 6 occurred at 61 to 120 days; 21 occurred at 121 days to 12 months; 9 occurred at 1 year to 2 years; and 15 occurred at > 2 years. Eleven events had an unknown onset date.

4.8.3.3 Depression

The assignment of the COSTART term depression to verbatim terms of “depression,” “depressed mood,” “situational depression,” “patient reports ‘down in the dumps,’” and “dysphoria” (reported in the updated integrated clinical trial database) and to verbatim terms of “depression,” “feels quite depressed,” “very down,” “not happy,” or “possible depression” (reported in the Scharf trial) does not constitute a definitive psychiatric diagnosis of Major Depressive Disorder. The essential features of a Major Depressive Disorder (DSM-IV) include a period of at least 2 weeks during which there is either depressed mood or loss of interest or pleasure in nearly all activities. The individual must also experience 4 additional related symptoms. Thus, it is important to distinguish between a transient symptom of feeling depressed and depression as a major psychiatric disorder.

4.8.3.3.1 Updated Integrated Clinical Trial Database

Of the 402 patients in the updated integrated clinical trial database, 27 patients (6.7%) had 30 AEs that were coded to depression. Seventeen of the 30 events were considered not related, 1 was probably related, 8 were possibly related, and 4 were of unknown relationship to test medication administration. Of the 9 related AEs, 7 lasted longer than 2 weeks. Sixteen of the 30 events were continuous, 12 intermittent, and

2 were unknown as to frequency. None of the events was considered serious. Two patients had a previous history of depression.

The actions taken with trial medication included no change in treatment for 26 events, temporary discontinuation of medication for 2 events, and permanent discontinuation for 2 events. Medication was initiated for management of 5 events (3 with Zoloft, 1 with Nortriptyline, and 1 with Sertraline). Depression was considered related to test medication for only 2 of these 5 events.

4.8.3.3.2 Scharf Trial

Twenty-two (15.4%) of the 143 patients participating in the Scharf open-label clinical trial for up to 16 years reported 28 AEs of depression. This included 14 men, with a mean age of 44 years (range 14.8 to 73.6 years) and 8 women, with a mean age 47.6 years (range 18.4 to 63.5 years). The mean dosage at onset was 5.6 g/d (range 2.3 to 9 g/d).

Two of the 28 depressive events were considered possibly related (218 and 238), 25 not related, and 1 of unknown relationship to trial medication. The intensity was considered severe in 5, moderate in 1, mild in 2, and not indicated in 20 of the AEs.

One patient was hospitalized for depression; the event was reported as an SAE (patient 019). This event (considered unrelated to study drug) started 217 days following the start of treatment and while the patient was receiving 6 g/d of sodium oxybate. The patient had a previous history of depression, suicidal ideation, and possible anxiety neurosis.

Three other patients reported relevant medical histories prior to treatment – patient 202 (psychiatric disorder with visual and auditory hallucinations), patient 255 (paranoia and difficulty controlling his temper), and patient 286 (depression).

Of the 2 patients with AEs coded to depression that were considered possibly related to study drug, 1 (238) lasted 2 days and 1 (218) was of unknown duration.

Six of the 28 AEs lasted 1 day, and 1 lasted 30 days. There was no reported stop date for 17 AEs; the start date for these ranged from 1 month to 14.5 years after initiation of sodium oxybate treatment, with a mean of 3.9 years. Four AEs had neither start nor stop date.

The incidence of depression reported in the Scharf trial appears to approximate that reported in the literature. Given the very long duration (over 16 years) of the trial, and the propensity of the narcoleptic population toward recurrent episodes of depression (Broughton 1984), there does not appear to be a causal relationship between depression and sodium oxybate treatment in this setting.

4.8.3.4 Hallucinations

4.8.3.4.1 Updated Integrated Clinical Trial Database

Nine (2.2%) of the 402 patients reported hallucinations. In 3 of these patients, the hallucinations were hypnagogic in nature and are probably attributable to the narcolepsy disease state. A fourth patient experienced unspecified hallucinations that stopped when her sodium oxybate dosage was increased, indicating that these hallucinations were most likely hypnagogic in nature as well.

One patient reported an isolated event (unspecified hallucinations), which was considered possibly related to trial medication. Another patient had hallucinations (described as "colors and shapes"), which were described as continuous and lasted 1 day; this was considered to be probably related to trial medication.

One patient reported on 2 consecutive clinic visits that she experienced a total of 9 auditory hallucinations ("voices"). These occurred over the course of 55 days; they resolved spontaneously and did not recur during the remainder of the trial.

After 20 days on trial medication, another patient experienced confusion, forgetfulness, and unspecified hallucinations and her trial medication was stopped. Ten days later, she developed nausea and after an additional day, intermittent paranoia. All of her symptoms resolved 2 weeks after stopping medication.

A final patient had a previous history of mental illness, including auditory hallucinations, prior to entry in the trial (this information had been intentionally withheld by the patient). On Day 84, she developed moderately severe auditory hallucinations requiring hospitalization. Given her subsequently disclosed past psychiatric history, these symptoms were deemed unrelated to the study medication. Her symptoms subsided following therapy with antipsychotic medication.

4.8.3.4.2 Scharf Trial

One of the 143 patients reported an AE that coded to the COSTART term hallucinations. This event occurred on Day 1918 at a dosage of 9.0 g/d. The patient experienced a hypnagogic hallucination, a REM-related symptom of narcolepsy, during which he dove out of bed and jammed his head against the wall. The event was not considered serious, but did necessitate a visit to the clinic for a neck radiograph. The patient was placed in a neck collar and prescribed Naprosyn and aspirin. The event was considered to be probably related to study medication by the investigator.

4.8.3.5 Stupor

4.8.3.5.1 Updated Integrated Clinical Trial Database

Six (1.5%) of the 402 patients reported AEs that coded to stupor. The verbatim terms all included the terms "drunk" or "intoxicated." Each of the 6 patients reported this AE only

once, with each occurrence lasting 1 day or less. All 6 patients were in OMC-GHB-3; there were 4 women and 2 men, ranging in age from 25 to 55 years. The events occurred following 34 to 66 days of sodium oxybate treatment. Dosage at onset was 4.5 g/d for 1 patient, 6.0 g/d for 3 patients, and 9.0 g/d for 2 patients. Five of the AEs were considered possibly or probably drug-related, while the relationship for the sixth was unknown.

4.8.3.5.2 Scharf Trial

Six (4.2%) of the 143 patients reported 7 AEs that coded to the COSTART term stupor. The verbatim terms used to describe 4 of these events in 3 patients include the words "drunk," "intoxicated," and "tipsy." One of these 4 events was considered probably related, 2 possibly related, and 1 of unknown relationship to trial medication. Two events had a duration of 1 day, 1 event lasted 15 days, and 1 event did not have a stop date recorded These 4 AEs occurred after 1 to 134 days of Xyrem administration, with the dosage at onset ranging from 6.0 to 7.5 g/d. None of these events was considered serious.

One additional patient (257) experienced an AE of verbatim term "acting 'like he's retarded.'" The time of the event and dosage at onset were unknown. The event was not serious and was of unknown relationship to trial medication. The patient continued in the trial through the May 31, 1999 data cutoff.

Two additional patients experienced 2 AEs that were considered serious. Patient 017 experienced an event of verbatim term "unresponsive" that was part of an overdose (see Table 4.9). The second patient (012) experienced an event with verbatim terms "disoriented," "stupor," and "weak" on Day 725 (7.5 g/d). The patient was hospitalized overnight. The patient continued the trial for an additional 8 years with no recurrence of the event.
These descriptive events do not appear to qualify as psychopathology.

4.8.3.6 Suicide Attempt, Overdose, Intentional Overdose

4.8.3.6.1 Updated Integrated Clinical Trial Database

Two suicides (0531 and 0936), 1 attempted suicide (14043), and 1 intentional overdose (1131) were recorded among the neuropsychiatric AEs in the 402 patients in the updated integrated clinical trial database.

One suicide (0531, coded as death) was due to multiple drug toxicity that included toxic levels of 6 psychotropic drugs other than sodium oxybate. The second suicide (0936) by a patient with a history of depression and a subsequent suggested diagnosis of bipolar disease, was officially ruled as a death due to cardiovascular disease (without autopsy by the Medical Examiner) but later evidence pointed to a possible overdose that included lithium, Paxil, and Percocet as well as sodium oxybate. This event occurred on 2/24/01, which was 5 months after the data cutoff (9/30/00), but is included here for completeness.

The attempted suicide (14043) involved an overdose with buspirone in a patient with pre-existing obsessive-compulsive disorder and depression.

The intentional overdose (1131) involved a patient with pre-existing depression and a previously unknown history of attempted suicide. Following a single ingestion of 150 g of Xyrem overdosing, the patient recovered without sequelae in the ER and was hospitalized for 5 days for psychiatric evaluation.

Thus, this series of 402 patients did not include any fatalities singularly attributable to an overdose with Xyrem, in spite of the huge dose taken by the patient overdosing which was approximately 20 times the maximum proposed total daily dose.

4.8.3.6.2 Scharf Trial

One of the 143 patients reported an AE that coded to the COSTART term suicide attempt, after approximately 2 years on trial medication. This event was reported as verbatim term "attempted suicide by taking an overdose of GHB." The patient had a prior medical history consistent with attempted suicide, including depression with suicide ideation and possible anxiety neurosis. The event was considered serious and definitely related to trial medication, and led to patient discontinuation.

Two of the 143 patients reported AEs that coded to the COSTART term overdose. Both cases were serious and involved overdose with trial medication. One patient (017) overdosed on approximately 18.0 g of trial medication on day 541 reported associated with a sleepwalking episode. This event was considered probably related to trial medication. The patient was unresponsive, was hospitalized, and required intubation. The patient continued on the trial with no further overdose episodes until he died 4.5 years later from cardiopulmonary arrest due to atherosclerotic disease. The second patient (267) was taken to the ER after possibly taking a third dose (of unknown volume) of trial medication on Day 1673. The patient did not recall taking the third dose. The patient awoke after an enuresis episode, and the patient's daughter discovered her walking around in a daze. The patient was taken to the ER; by the time she arrived, she was having no further difficulties. She continued on treatment for 6 months with no further recurrence.

4.8.3.7 Paranoid Reaction

4.8.3.7.1 Updated Integrated Clinical Trial Database

Four (1.0%) of the 402 patients reported AEs that coded to the term paranoid reaction. Patient 0202 admitted to occasionally feeling paranoid at 1 clinic visit and also described two consecutive nights of feeling paranoid at bedtime. These feelings were accompanied by visual and auditory hypnagogic hallucination. Patient 0239 described feeling paranoid on a single occasion, with only 1 day's duration. Patient 0702 described intermittent episodes of feeling fearful.

The paranoid reaction AE in the fourth patient was considered serious (patient 0232). This patient suffered an acute paranoid delusional psychosis that occurred after 15 months on study drug and required overnight hospitalization. The trial medication was discontinued and the patient's mental status improved while being treated on antipsychotic medication. This patient was discontinued from the trial.

4.8.3.7.2 Scharf Trial

One (0.7%) of the 143 patients reported an AE that coded to the COSTART term paranoid reaction. The verbatim description of this event indicated that the patient was "acting very paranoid – carries a bat with him while at home and feels someone is watching him." The event start and stop dates were unknown, but the event was considered not related to study drug. The Investigator reported that the patient had hypnagogic hallucinations. The patient was 16 years of age when he started the trial in June 1986. The patient discontinued the trial in June 1988 due to non-compliance with the diary and clinical lab requirements of the trial. The patient had no previous history of neuropsychiatric events.

4.8.3.8 Coma

4.8.3.8.1 Updated Integrated Clinical Trial Database

Two (0.5%) of the 402 patients were described as having experienced coma while taking trial medication. Patient 0238 was heard to fall and was found unconscious on the floor of the kitchen by his spouse. Paramedics were immediately summoned and found the patient unconscious; he received atropine for bradycardia; naloxone was administered without response. On arrival at the ER, he was intubated to support depressed respiration and was transferred to an ICU, where he soon fully recovered from the event. He later admitted to taking his bedtime dose of sodium oxybate in the kitchen. Intensive neurological and cardiac investigation failed to define a cause for this event and it was proposed to be possibly due to an unidentified cardiac event or to cataplexy with additional head trauma from his head striking the floor. Study drug was discontinued.

Patient 2830 was considered to have experienced coma on 2 occasions while on study drug. In both cases, she fell secondary to cataplexy attack and hit her head, causing loss of consciousness. This patient was known for being non-compliant with the study drug regimen, which probably contributed to her cataplexy.

None of these events qualify as a neuropsychiatric AE

4.8.3.8.2 Scharf Trial

One of the 143 patients experienced an AE with verbatim term "comatose" as part of an overdose (See Table 4.9).

4.8.3.9 Psychosis

Two (0.5%) of the 402 patients in the updated integrated clinical trial database reported AEs that coded to COSTART term psychosis. .

Patient 1101 completed double-blind treatment in the OMC-GHB-2 trial where the dose assignment had been 6.0 g/d sodium oxybate. The patient entered the open-label OMC-GHB-3 trial (1/5/98) at 6.0 g/d. The dose of sodium oxybate was titrated to 7.5 g/d (3/8/98) and then to 9.0 g/d (3/17/98) to achieve optimal clinical benefit. The patient had been taking multiple stimulants to include Dexedrine 15 mg twice daily and Ritalin 10mg three times daily concurrently until this regimen was changed to Adderall 20 mg four times daily approximately two months prior to the adverse event. The patient developed symptoms of acute psychosis beginning 4/27/98 considered of moderate intensity and possibly related to trial medication. Following psychiatric consult both the stimulants and trial medication were discontinued. The adverse event did not resolve. Two weeks following the onset of the adverse event the investigator evaluated all findings and considered the adverse event as not related to study drug by requiring specific other treatment that was contraindicated by the protocol.

Patient 2030 suffered symptoms of psychosis after being on study drug for about 6 months. At that time, he was reported by a family member to be increasingly paranoid and suffering from night terrors and hallucinations. The patient was seen in the ER, where he admitted to increasing his Ritalin dose to facilitate cramming for college examinations. The patient was started on antipsychotic medications and was restarted on study drug after the symptoms of psychosis had resolved. A week later these same symptoms and precipitating circumstance recurred, prompting a hospital admission and discontinuation from the study. This event was considered the result of escalated doses of stimulant medication and sleep deprivation.

No patients in the Scharf trial experienced psychosis.

4.8.3.10 Manic Depressive Reaction

An adverse event of bipolar affective disorder (verbatim term) COSTART coded to manic depressive reaction was reported for 1 patient (0931) in the 402 patient updated integrated clinical trial database. The patient was a 29-year-old female with a previous history of depression. The diagnosis of bipolar affective disorder was made during psychiatric consult following reports of intermittent hallucinations for two weeks and unusual behavior (from delayed response to violent agitation on questioning when found asleep in her automobile). The adverse event was considered severe but unrelated to study drug and the patient was discontinued from the trial. The patient was treated and released from hospital. Present day follow-up showed the patient to be functioning well with continued treatment (Haldol, Cogentin) for underlying disease, which excluded further participation in the trial despite positive response in narcolepsy.

No patients in the Scharf trial experienced manic depressive reaction.

4.8.3.11 Personality Disorder

One patient (1530) in the 402 patients in the updated integrated clinical trial database reported an AE that coded to personality disorder. This 25-year-old woman experienced a personality disorder (investigator term "grief reaction" due to the death of a relative) beginning on Day 139 of the OMC-SXB-6 trial. The event lasted 258 days in trials OMC-SXB-6 and OMC-SXB-7. The event was considered mild in severity, intermittent, and not related to trial medication. No action was taken for the event.

No patients in the Scharf trial experienced personality disorder.

4.8.3.12 Emotional Lability

Ten (7.0%) of the 143 patients in the Scharf trial reported 14 AEs that coded to the COSTART term emotional lability. The majority of the verbatim terms relate to conditions of "laughing" or "crying." The dosages at onset ranged from 3.0 to 9.0 g/d. None of the events was considered serious. One event was considered probably related to trial medication, 2 were possibly related, 9 were not related, and 2 were of unknown relationship. Date of onset ranged from Days 0 to 1078, with the majority of events occurring during the first 100 days on trial medication. Seven events resolved in 3 days or less. One patient who experienced an event of verbatim term "heart aches" had a previous history of depression and recurrent melancholia. One patient (259), who experienced a probably related event of "crying a lot" at the 5.3 g/d dosage, discontinued due to this and other AEs.

4.8.3.13 Thinking Abnormal

Nine (6.3%) of the 143 patients in the Scharf trial reported 13 AEs that coded to the COSTART term thinking abnormal. The verbatim terms included "fogginess," and terms relating to problems with concentration, transposition of numbers, and negative thinking. The dosage at onset for these events ranged from 4.5 to 9.0 g/d; the date of onset ranged from Days 0 to 531. One event ("very talkative after gamma dose") was considered probably related to trial medication, 5 events were possibly related, 3 events were of unknown relationship, and 3 events were considered to be not related. Events where resolution dates were recorded usually represented transient episodes, lasting for a day or less. Four patients had a previous history of traumatic head injury, 1 of whom also had a previously diagnosed frontal lobe lesion.

4.8.3.14 Depersonalization

Seven (4.9%) of the 143 patients in the Scharf trial reported AEs that coded to the COSTART term depersonalization. Verbatim terms generally related to unusual behavior or feeling unusual. The dosage at onset for these events ranged from 5.3 to 6.8 g/d; date of onset ranged from Days 3 to 513 after initiation of sodium oxybate treatment. Three events were considered probably related to trial mediation (verbatim terms "bizarre behavior," "felt crazy," and "zombie like state"), 2 were of unknown

relationship, and 2 were considered not related. None of the events was considered serious. Duration is recorded for only 3 events, with 2 occurring for 1 day or less and 1 having a duration of 17 days. One patient (259) discontinued the trial due to the AEs she was experiencing.

4.8.3.15 Hostility

Six (4.2%) of the 143 patients in the Scharf trial reported 8 AEs that coded to the COSTART term hostility. Of the 8 events, 3 were considered possibly related, 3 were considered not related, and 2 were of unknown relationship to trial medication. None of the AEs was considered serious or led to patient discontinuation.

Six of the 8 events were related to anger (including terms temper and rage). The dosage at onset for these 6 events ranged from 4.5 to 9.0 g/d; the date of onset ranged from Days 34 to 1078. Only 1 AE (patient 215, rage) had a stop date recorded, with a duration of 1 day. One patient (286) had a previous history of irritability caused by Ritalin, although it is not certain if he was taking Ritalin at the time of the event.

Two additional events coded to the COSTART term hostility, with verbatim terms “feisty” and “frustration.” The event termed “feisty” occurred on day 124 at the 9.0 g/d dosage. No resolution date was recorded, but the event was considered possibly related to study drug and was not serious. The event termed “frustration” occurred and resolved on Day 20 at the 4.5 g/d dosage. The patient’s history included difficulty controlling his temper. The event was not serious and was considered not related to study drug.

4.8.3.16 Neurosis

Two of the 143 patients in the Scharf trial reported AEs that coded to the COSTART term neurosis. The first event occurred in a female patient on Day 3328 at a 5.3 g/d dosage. The verbatim term (patient’s diary description of the event) indicated that she was “Having trouble keeping my arms down. I put them on my head they cut off circulation some (Go to sleep) and I wake up and can’t find my hands and they are painful.” The patient woke her husband up to help her with the event(s). The event was not serious, not considered related to trial medication, and of unknown duration.

The second event occurred in a male patient on a 6.0g/d dosage starting on Day 3283 and was described by verbatim term “claustrophobia.” The patient was instructed to decrease his Ambien dosage, with no resolution. The patient was then instructed to decrease his trial medication dosage from 6.0 to 3.0 g/d, and the event subsequently resolved. The event was not serious and was considered possibly related to trial medication. The patient continued in the trial, usually at a dosage of 6.0 to 6.6g/d, until the data cutoff of May 31, 1999, with no further recurrence.

4.8.4 BLOOD GLUCOSE

The updated integrated clinical trial database was analyzed for any patients who had AEs with the COSTART preferred term of hyperglycemia or diabetes mellitus, and/or

who experienced clinically significant increases in glucose laboratory values (≥ 70% increase over baseline [from earliest trial] and an absolute value of > 200 mg/dL).

Measurement of blood glucose levels was not done on a routine basis in these long-term studies. Non-fasting glucose measurements were used for all tests in the treatment IND protocols (OMC-SXB-6, OMC-SXB-7), while fasting blood collections were specified in the OMC-GHB-2 and OMC-SXB-3 protocols (although this requirement was not always met).

Of the 402 patients, 5 patients (1%) had 9 AEs with the COSTART preferred term of hyperglycemia or diabetes mellitus. Four patients had 1 AE each; patient 1505 had 4 AEs of hyperglycemia and 1 AE of diabetes mellitus. The incidence of hyperglycemia/diabetes did not appear to be dose-related, with 1 patient in each of 3 of the dosage at onset treatment groups (4.5 g/d, 7.5 g/d, and 9.0 g/d), and 2 patients in the 6.0 g/d group.

There were no deaths, no SAEs, and no discontinuations due to these AEs. All AEs of hyperglycemia/diabetes mellitus were of mild to moderate severity. Four patients had AEs considered unrelated to trial drug, while 1 patient (1610 in OMC-GHB-3) had unknown relationship.

Two of the 5 patients had a history of diabetes (0410 and 1505); 2 patients (1505 and 2633) were obese. The other 2 patients had no relevant medical history. Of the 5 patients, 4 (80%) were men, and 3 (60%) were 50 years of age or older (range 36.4 to 65.4 years).

There was no relationship between the incidence of hyperglycemia/diabetes and the length of exposure to sodium oxybate: 1 patient experienced hyperglycemia on Day 15; 3 patients experienced hyperglycemia or diabetes mellitus during Days 31 to 394; and 1 patient experienced 5 AEs during Days 511 to 1064. Two patients had unresolved AEs (1708, diabetes; 2633, hyperglycemia), and the outcome of 1 AE (patient 1505, elevated glucose) is unknown. All other AEs resolved.

Actual investigator terms were:

- "Elevated blood glucose" or "elevated glucose" – 3 patients with 4 events
- "Abnormally high glucose" – 1 patient with 2 events
- "Hyperglycemia" – 1 patient with 1 event
- "Diabetes" or "poorly controlled diabetes" – 2 patients with 2 events

Two of the AEs were associated with clinically significant increases in glucose values – patients 0410 (verbatim term elevated blood glucose) and 1505 (verbatim term poorly controlled diabetes, on day 650). An additional 4 patients had clinically significant increases in glucose values that were not associated with an AE of hyperglycemia or diabetes mellitus. An elevated glucose level not associated with an AE was also seen on Day 278 for patient 1505.

Two of the 4 additional patients had a history of diabetes. The 7 instances of elevated glucose values for all 6 patients occurred on Days 201 to 363 for 3 events, Days 424 to 618 for 3 events, and Day 1070 for 1 event. Absolute levels ranged from 217 to 403 mg/dL; increase from baseline ranged from 70.2% to 140.0%.

4.8.5 DETAILED ANALYSIS OF ELEVATED ANTI-NUCLEAR ANTIBODY AND STUDY DRUG-RELATED LUPUS

4.8.5.1 Scharf Trial

In 1991, a 49-year-old female patient in the Scharf trial developed clinical symptoms of arthritis, after treatment with sodium oxybate 6.0 g/d for more than 5 years. An anti-nuclear antibody (ANA) test and 2 repeat tests were all positive, raising concern for the possibility of study drug-related lupus. She was withdrawn from sodium oxybate with a subsequent fall in ANA titers, followed by an increase again 1 year later.

At the request of the FDA, ANA profiles were collected for all ongoing patients in the Scharf trial until 1999. Over the next 2 years, 19 (29.2%) of 65 patients tested were shown to have ANA elevations ranging from 1:40 to 1:2560. Some of these elevations were intermittent and no correlation was found between positive ANA titer and duration of treatment, age, or sex. Antihistone antibodies (determined for 15 of the 19 ANA-positive patients) showed a “borderline” positive result in only 1 patient. All 65 patients tested were requested to complete a symptom questionnaire, which showed a low overall incidence of symptoms possibly related to lupus and no discernible difference in the subgroup of ANA-positive patients.

No association emerged between the occurrence of positive ANA findings and the development of symptoms consistent with systemic lupus erythematosus (SLE), medication-induced lupus, or any rheumatic disease except for the first patient who had acute arthritis symptoms and a positive ANA when last tested. In medication-induced lupus, positive ANA findings are accompanied by positive antihistone antibodies in more than 90% of cases (Schur 1996). This occurred in only 1 of 15 ANA-positive patients who were tested, and this patient did not display symptoms characteristic of lupus.

These data indicate that long-term use of sodium oxybate may result in ANA elevations without the corresponding increase in antihistone antigens characteristic of most reported cases of medication-induced lupus. In addition, narcoleptic patients with positive ANA findings did not present with or subsequently develop symptoms suggestive of lupus-related disease. Finally, no patients in the Scharf long-term trial have developed SLE during treatment with sodium oxybate for up to 16 years.

Dr. Evelyn Hess, an internationally recognized expert on medication-induced lupus and SLE, concurred with these findings and could find no evidence of either SLE or medication-induced lupus. In her opinion, the most that could be concluded was that sodium oxybate, like some 80 other drugs in the scientific literature, may be associated with low-level increased titers of ANA of no known clinical significance.

4.8.5.2 Updated Integrated Clinical Trial Database

In response to an FDA request for a post-hoc evaluation of the potential for symptoms of drug-induced lupus, the updated integrated clinical trial database was examined in 2 ways. First, the AE listings were visually examined for a combination of potential lupus symptoms occurring within a given patient. Second, the AE database was queried electronically to identify all patients who reported 1 or more of the 9 selected possible drug-related lupus symptoms (as COSTART terms) – arthralgia, arthritis, myalgia, joint disorder, pain, alopecia, fever, malaise, and rash. These COSTART terms were selected following examination of the previously submitted drug-induced lupus review article by Dr. Evelyn Hess (Hess 1991) and a telephone discussion with Dr. Hess on 3/12/01. According to Dr. Hess, patients with drug-related lupus present with multiple symptoms, particularly the articular symptoms (arthritis and/or arthralgia in multiple joints), which occur in over 80% of drug-related lupus patients.

Alopecia was reported on 5 occasions but did not occur in any of the 402 patients in conjunction with any of the other 8 possible drug-related lupus symptoms. Thus, alopecia was dropped from further evaluation and consideration in the analysis.

As expected, the COSTART term “pain” (not otherwise specified) was the most common AE, occurring 168 times in 46 of the 402 patients. In 22 of these 46 patients, nonspecific pain was the only lupus-related symptom reported on 2 or more occasions. Nonspecific pain was generally not associated with the more specific lupus symptom terms of arthralgia, arthritis, joint disorder, and myalgia.

The database was re-examined to identify only those patients who reported one of the 7 remaining drug-related lupus symptoms on more than 1 occasion or more than 1 of the 7 symptoms.

A total of 19 patients were identified with 2 or more of these events. Seven of these 19 patients reported only 1 of the 7 selected symptoms on multiple occasions – 2 patients with 6 events for myalgia, 2 patients with 5 events for fever, 1 patient with 2 events for joint disorder, 1 patient with 3 events for malaise, and 1 patient with 2 events for rash. Since no other symptoms suggestive of possible drug-related lupus were recorded for these 7 patients, no further analysis was indicated.

The remaining 12 patient case records were reviewed in detail to determine if any patient developed AEs suggestive of possible drug-related lupus. For 11 of the patients, there was no convincing evidence of symptoms consistent with a possible diagnosis of drug-related lupus. For the twelfth patient (1633), symptoms of joint pain developed while on treatment, persisted for several months, and disappeared within 2 months after stopping the drug. Follow-up 1 year later indicated no recurrence of joint pain. Thus, drug-related lupus cannot be totally ruled out. However, in the absence of any supportive laboratory measures (such as positive ANA and antihistone antibodies) and any other symptoms of lupus, the diagnosis of drug-induced lupus cannot be established.

In conclusion, none of the 402 patients in the updated integrated clinical trial database developed SLE or were diagnosed with drug-induced lupus during participation in any of the 5 trials. A systematic review of the AE data collected on these 402 patients definitively excluded symptoms suggestive of drug-induced lupus in all but 1 patient.

4.8.6 DETAILED ANALYSIS OF INCONTINENCE AES AND RELATIONSHIP TO SEIZUROGENESIS

Animal studies have shown that high dosages of sodium oxybate may be associated with EEG changes and symptomatology representing absence-seizure-like states. This has been developed as a model for absence seizures in primates (Snead 1978), using high dosages of IV sodium oxybate. Myoclonus has also been described as a frequent accompaniment of anesthesia induction with IV sodium oxybate.

4.8.6.1 Updated Integrated Clinical Trial Database

In their review of the OMC-GHB-2 clinical trial report (submitted October 10, 1998), the FDA requested an analysis of a potential relationship between incontinence and seizurogenesis. Our investigation included:

- A questionnaire to all affected investigators to review any observed abnormal nocturnal observations suggestive of seizures, urological history preceding oxybate therapy, and any new neurological symptoms
- Correlation between CNS AEs that could be related to seizures and incontinence (either urinary or fecal)
- Overnight full-montage EEG recording in 6 patients with a prior history of incontinence during sodium oxybate treatment (at a Xyrem dosage of 9 g/d)
- Review of the data by an independent expert (Dr. Nathan Crone, Johns Hopkins University Medical Center)

In review of the data, there was no evidence to support seizurogenesis in our clinical trials. An analysis of all AEs reported in OMC-GHB-2 and OMC-GHB-3 suggestive of incontinence (66 events), as well as CNS anomalies, showed no relationship between the two. The analysis noted that “episodes of neurological dysfunction, including tremor, incoordination, focal sensory loss and/or confusion (83 events), were simultaneous with enuresis on only 4 occasions.”

Over the clinical experience of approximately 750 patient-years with sodium oxybate, the analysis noted, most of the patients had bed partners, none of whom reported behavior suggestive of seizures. Since the seizures that most commonly cause urinary incontinence are generalized tonic-clonic seizures, these would be expected on at least some occasions to awaken a bed partner.

The analysis described 15 events of enuresis or urinary incontinence in 8 of the 136 patients in OMC-GHB-2, and 51 events in 13 of the 118 patients in OMC-GHB-3. A single patient (0819) in OMC-GHB-3 accounted for 15 events. One additional patient in each trial experienced fecal incontinence. Two patients in each trial experienced urinary incontinence and a CNS anomaly simultaneously. No events suggestive of seizure occurred in either of the patients (0124 and 0702) in OMC-GHB-2, or in either of the patients (0219 and 0819) in OMC-GHB-3.

In the full-montage EEG studies, 1 patient had urinary incontinence during the recording. There was no EEG evidence of seizure activity in any of the 6 patients.

Overall, in the updated integrated clinical trial database, 36 of the 402 patients (9.0%) experienced incontinence urine or urinary incontinence; 2 patients (0.2%) experienced fecal incontinence.

One subject (003) from the 8 pharmacokinetic trials experienced an adverse event of "labored respiration" coded to the COSTART term "apnea". Two hours post-dosing (with a single 4.5 g dose) the subject experienced a second event of respiratory stridor which was accompanied by fecal incontinence. The subject was arousable, and responded to verbal commands. The event resolved and two hours later the subject consumed a lunch.

4.8.6.2 Scharf Trial

We conducted a similar analysis on the 143 patients enrolled in the long-term clinical (Scharf) trial, in which 33 of the 143 patients (23.1%) experienced urinary incontinence, and 1 patient (0.7%) experienced fecal incontinence.

The analysis included 2 independent examinations of all AE terms suggestive of incontinence. AE terms suggestive of CNS anomalies were also carefully examined. There was 1 observation of fecal incontinence in 1 patient, 140 observations of urinary incontinence or enuresis in 33 patients, and 704 observations of any nervous system anomaly in 104 patients (42 specific terms).
An analysis to identify those patients in whom fecal or urinary incontinence or enuresis occurred in temporal association with any nervous system anomaly (which could suggest seizurogenesis) revealed 10 incontinence events and 12 CNS events in 7 patients (Table 4.21).

Table 4.21 Patients Exhibiting Enuresis, Urinary Incontinence, or Fecal Incontinence and CNS Anomalies – Scharf Trial

Patient Number	Enuresis, Urinary Incontinence, or Fecal Incontinence AEs			CNS Anomalies		
	Verbatim Term	Onset Date	Resolution Date	Verbatim Term	Onset Date	Resolution Date
017	Enuresis episode	09/20/92	09/20/92	Sleepwalking episode	09/20/92	09/20/92
	Enuresis episode	08/12/93	08/12/93	Sleepwalking episode	08/12/93	08/12/93
048	Enuresis	09/11/84	09/11/84	Confusion	09/11/84	09/11/84
				Numb all over	09/11/84	09/11/84
	Urinary incontinence with seizure	02/07/89	02/08/89	Convulsive-like seizure	02/07/89	02/08/89
207	Wet the bed	03/22/85	03/22/85	Sleepwalking	03/22/85	03/22/85
247	Enuresis	04/27/90	04/27/90	Seizure (continuous jerking all over)	04/27/90	04/27/90
255	Urinary incontinence	02/21/91	02/21/91	Brief grand mal seizure (while at Dr.'s office)	02/21/91	02/21/91
257	Loss of bowel control	01/26/91	01/26/91	Intense body shaking	01/26/91	01/26/91
	Loss of bladder control	01/26/91	01/26/91	Jerking during cataplexy	01/26/91	01/26/91
262	Bedwetting (3 episodes)	01/24/96	01/31/96	Dizzy	01/24/96	01/25/96
				Felt like head rolling around	01/24/96	01/25/96

Analysis of these 7 cases revealed 6 occurrences of enuresis that were deemed probably related to study drug and were associated with sleepwalking, confusion, and dizziness, also believed to be related to study medication. None of these CNS events supported seizure activity relating to the incontinence event. Four additional observations were possibly associated with seizure activity:

- One patient (255) experienced a witnessed major motor seizure; however, he also had a history of seizures prior to taking study drug. It was determined to be unlikely that the study drug was responsible for this event.

- In 3 other instances, fecal (1) or urinary incontinence or enuresis (2) occurred with coincident CNS anomalies that were suggestive of seizures:

- Patient 048 reported urinary incontinence that occurred in conjunction with a "convulsive-like seizure." Although the patient's EEG was normal, these events were felt to be possibly related to the study drug.

- Patient 247 had 1 case of enuresis (probably related to study drug) associated with "continuous jerking all over"; this patient had 10 other episodes of enuresis that were not associated with any CNS anomaly. While the relationship between the continuous jerking and the study drug is unknown, seizure activity cannot be excluded.

- The fecal and urinary incontinence associated with "body shaking" and "jerking during cataplexy" experienced by patient 257 were considered unrelated to study drug. The inclusion of this patient may reflect a coding error, since this patient experienced events where the COSTART term "convulsions" was used for verbatim terms of "cataplexy," "bad cataplexy," "fall from cataplexy," and "violent shaking and vibrations." In addition, fecal incontinence is known to occur secondary to narcolepsy and cataplexy (Vgontzas 1996).

In all other instances of urinary incontinence or enuresis, there was no correlation between any CNS observations; it is likely that the incontinence was due to the narcolepsy disease state (Sher 1996).

Thus, despite the appearance of absence-seizure-like states in primates at IV dosages far exceeding the human therapeutic dosage, there is no support, in the updated integrated clinical trial database, the long-term (Scharf) clinical trial, or in the literature reporting human experience in therapeutic dosages, for a relationship between incontinence and seizures.

4.8.7 SUMMARY OF DISCONTINUED PATIENTS - SCHARF TRIAL

From the time of study initiation in 1983 to the time of study closure in 2000, a total of 143 patients participated in the Scharf trial. As of the data cutoff of May 31, 1999, 63 (44%) of these patients had transferred into the Orphan Medical Treatment IND protocol OMC-SXB-7. Of the remaining 80 patients, 8 continued to participate in the Scharf trial under the Investigator IND, 71 patients had discontinued from the Scharf trial prior to the cutoff date, and 1 was a screen failure.

Comparison of age and gender at trial entry for the 80 patients that did not enroll in OMC-SXB-7 as of May 31, 1999, and the 63 patients who entered Orphan Medical trial OMC-SXB-7 showed no differences between the 2 groups. The mean age at trial entry for 79 of the 80 patients (1 patient who was a screen failure [211] was not included in the calculations) who did not enroll in OMC-SXB-7 was 47.0 years, compared with 44.3 years for the 63 patients who transferred into OMC-SXB-7. Male patients accounted for 57% of the patients in both population subsets.

Table 4.22 summarizes the reasons for discontinuation for the 71 patients who discontinued prior to the data cutoff. The majority of the discontinued patients were terminated from the trial due to non-compliance or cost (37 of 71, 52.1%). Only 6 of the discontinuations were due to possibly or probably related AEs. Of the remaining AE discontinuations, the 10 deaths were due to cardiovascular and neoplastic diseases, none of which was considered related to trial medication. Four patients discontinued because of lack of efficacy, and 1 patient who cited the cost of the drug as a reason for discontinuation also noted a lack of efficacy.

Table 4.22 Patient Disposition – Scharf Clinical Trial

Patient Disposition	Number of Patients
Patients screened	143
Patients treated	142
Continued treatment	71
Ongoing treatment (OMC-SXB-7)	63
Ongoing treatment (Scharf)	8
Discontinued treatment	71
Non-compliance	24
Failure to provide diaries	22
Failure to follow dosing instructions	2
AEs	23
Death (coded as an SAE)	10
Other AE	13
Cost of medication	13
Patient request/withdrawal of consent	5
Lack of efficacy	4
Protocol deviation	1
Other (transfer to fibromyalgia study)	1

[a] In the initial Scharf Report, 11 deaths were reported, however, one patient (202) died in a boating accident seven months following discontinuation of study medication. The case report form lists patient request as the reason for discontinuation.

Patient non-compliance was the most common reason for patient discontinuation. The majority (22 of 24) of patient non-compliance discontinuations were the result of patients' failure to complete and return the patient daily diary sleep logs and/or questionnaires as required by the protocol. The other 2 non-compliance discontinuations were due to patients not conforming to the study drug dosing regimen.

Of the 23 discontinuations due to AEs, 10 patients died. An additional patient (202) died in a boating accident approximately 7 months after discontinuing study drug. Although the CRF listed the death as an SAE, the reason for discontinuation should properly be listed as patient request. None of the deaths was considered possibly or probably related to study medication. It should be noted that the Scharf clinical trial report indicated that 19 patients, not 23, were discontinued due to an AE. On review of source documents, case report forms, and data listings for the 80 patients that did not enroll into OMC-SXB-7 as of May 31, 1999, 4 additional patients were found to have discontinued

due to an adverse event. Of these patients, 2 died (017 – cardiopulmonary arrest due to atherosclerotic disease; 241 – small cell carcinoma of the lung), 1 (006) experienced an event of stimulant-induced rage, and 1 (270) became pregnant. None of these events was considered to be related to trial medication.

Of the remaining 13 AE discontinuations, 6 were considered possibly or probably related to study drug, including: attempted suicide by sodium oxybate overdose (patient 019, who had a previous history of depression and suicide ideation); high ANA titer/possible drug-induced lupus (patients 066 and 244, neither of whom ever manifested the symptoms of lupus); possible pulmonary toxicity (patient 254); depersonalization, emotional lability, hypertonia, and pain chest (patient 259); and swelling of ankles and feet (patient 271). Three of the 6 probably or possibly related AE discontinuations were reported in the Scharf clinical trial report. The remaining 3 were the result of a review of the 80 aforementioned patients in response to the FDA request and data was derived from primary source clinical records and possible patient contact to expand and clarify the data. These patients were, 066, 244, and 254.

The cost of medication, which was communicated to patients prior to study entry in the informed consent document of the Scharf trial, was the reason for discontinuation for 13 patients. Unlike most investigational drug studies, patients treated in the Scharf trial were required to pay a fee of $1,000 per year ($250 paid quarterly) to partially defray the costs incurred by the investigator in providing the study drug. This requirement was clearly specified in the written informed consent statement signed by each patient prior to beginning the trial. It is noteworthy that except for the initial limited funding provided by the FDA Orphan Drug grant, Dr. Scharf conducted this large clinical study independently for over 10 years, without any additional grant support or external funding beyond the stated patient contributions.

Table 4.23 summarizes the 80 patients who did not enroll in OMC-SXB-7 by the data cutoff (sorted by reason for discontinuation).

Table 4.23 Summary of 80 Scharf Patients Who Were Not Enrolled in OMC-SXB-7 as of Data Cutoff (May 31, 1999)

Patient No.	Sex/Age at Trial Entry (yr)	Date Started Sodium Oxybate Treatment	Date of Last Dose	Comments
Reason for Discontinuation: AE – Patient Death				
001	M/46	11/17/1983	7/31/1989	Metastatic colon carcinoma
009	M/58	11/28/1984	11/30/1994	Arteriosclerotic cardiovascular disease
014	M/41	4/13/1987	10/31/1995	Cardiac arrhythmia and severe coronary atherosclerosis
017	M/62	2/7/1989	2/28/1995	Cardiopulmonary arrest due to atherosclerotic disease
032	F/64	7/25/1984	10/19/1994	Lung cancer
053	M/47	3/29/1984	7/31/1994	Myocardial infarction
200	M/66	5/22/1985	9/30/1990	Lung cancer
232	M/64	6/16/1987	3/13/1992	Myocardial infarction secondary to bladder carcinoma
241	M/55	2/27/1985	5/26/1989	Small cell carcinoma of the lung
243	M/58	6/20/1984	2/28/1989	Myocardial infarction
Reason for Discontinuation: AE				
005	F/49	11/16/1987	7/12/1992	Increased difficulty sleeping
006	M/14	7/24/1985	12/31/1992	Stimulant-induced rage
019	M/41	7/12/1987	7/30/1989	Attempted suicide by GHB overdose
064	F/13	6/16/1987	5/00/89	Increased seizure activity
066	F/44	3/25/1985	4/20/1991	High ANA titer/possible drug-induced lupus
238	M/45	11/30/1983	10/20/1985	Decrease in short-term memory (COSTART term "amnesia")
244	F/55	6/21/1988	5/3/1989	High ANA titer/possible drug-induced lupus
247	F/33	7/25/1989	4/30/1990	Seizure
254	F/61	5/2/1988	6/26/1989	Possible pulmonary toxicity
259	F/41	6/3/1987	7/15/1987	Depersonalization, emotional lability, hypertonia, and pain chest
270	F/24	1/16/1994	4/22/1999	Patient became pregnant
271	M/46	10/24/1994	4/30/1995	Swelling of ankles and feet
273	F/59	11/6/1994	9/30/1995	Weight loss
Continued in the Scharf IND Protocol				
004	M/61	1/21/1988	NA	
027	F/55	3/28/1984	NA	
054	M/63	2/10/1987	NA	

(continued)

Table 4.23 Summary of 80 Scharf Patients Who Were Not Enrolled in OMC-SXB-7 as of Data Cutoff (May 31, 1999)

Patient No.	Sex/Age at Trial Entry (yr)	Date Started Sodium Oxybate Treatment	Date of Last Dose	Comments
065	F/39	11/16/1983	NA	
228	M/16	2/17/1986	NA	
262	F/63	3/27/1991	NA	
269	M/50	7/8/1993	NA	
283	M/56	12/3/1997	NA	
Reason for Discontinuation: Cost				
013	M/47	1/18/1988	3/26/1988	
016	M/29	2/19/1986	1/31/1989	
023	F/34	4/18/1984	12/31/1992	
029	F/40	1/11/1984	2/28/1989	
204	M/49	6/27/1984	11/27/1984	
205	F/54	4/1/1985	9/25/1986	
214	M/53	7/25/1985	11/1/1985	
224	F/45	2/20/1987	4/20/1988	
239	F/59	11/30/1984	11/11/1985	
242	M/40	2/1/1984	8/12/1985	
245	M/49	4/18/1984	8/18/1985	
252	M/61	6/27/1984	11/27/1984	
285	M/43	8/14/1991	11/30/1994	Also noted lack of efficacy
Reason for Discontinuation: Lack of Efficacy				
007	M/54	8/13/1985	3/16/1991	Started on Anafranil to control cataplexy
208	M/51	10/17/1984	11/13/1984	Patient's chief complaint was excessive daytime sleepiness
221	F/43	5/23/1984	6/17/1984	
253	F/75	9/30/1987	12/26/1987	
Reason for Discontinuation: Non-Compliance				
048	F/27	10/26/1983	2/28/1989	
063	F/26	5/6/1988	5/31/1997	
201	F/47	10/26/1983	12/31/1983	
203	F/39	4/18/1984	5/14/1984	
207	F/32	2/1/1984	3/31/1985	
209	F/30	6/27/1984	10/2/1984	
210	M/30	10/5/1984	5/3/1985	
212	M/58	7/29/1985	11/16/1985	
213	F/45	6/3/1985	12/23/1985	

(continued)

Table 4.23 Summary of 80 Scharf Patients Who Were Not Enrolled in OMC-SXB-7 as of Data Cutoff (May 31, 1999)

Patient No.	Sex/Age at Trial Entry (yr)	Date Started Sodium Oxybate Treatment	Date of Last Dose	Comments
215	F/46	10/26/1983	10/30/1988	
216	M/49	11/26/1984	2/22/1987	
217	M/52	1/27/1986	7/19/1986	
222	F/72	3/5/1987	4/21/1988	
223	M/45	7/15/1986	1/24/1987	
240	M/42	1/5/1988	7/5/1988	
246	M/59	7/15/1986	4/22/1987	
248	M/73	7/17/1986	10/13/1986	
251	M/65	4/18/1984	11/21/1986	
256	M/16	6/10/1986	6/10/1988	
258	M/54	11/14/1990	Unknown	
263	M/61	1/30/1991	5/31/1991	
267	F/61	4/29/1992	7/31/1997	
268	M/22	7/11/1993	3/00/97	
288	F/27	7/10/1998	10/31/1998	
Reason for Discontinuation: Other				
279	F/35	9/13/1996	6/20/1998	Patient transferred to fibromyalgia study
Reason for Discontinuation: Patient Request				
012	M/74	8/20/1984	8/31/1994	
036	M/31	2/6/1989	10/00/98	
202	M/55	12/20/1984	3/8/1986	Patient died in boating accident approximately 7 months after discontinuing study drug
206	F/53	1/13/1984	8/26/1984	Patient concerned about smoking while sleepwalking
218	F/40	5/26/1984	6/00/84	
Reason for Discontinuation: Protocol Deviation				
276	M/31	12/12/1995	2/26/1996	Failed to meet inclusion criteria (not a narcoleptic)
Screen Failure				
211	F/NA	NA	NA	Patient did not receive study drug

4.8.8 EVALUATION OF "REACTION UNEVALUABLE" PATIENTS (SCHARF TRIAL)

At FDA request, Orphan Medical sought to provide explanation for a total of 75 Adverse Events in the Scharf trial which were initially coded as "reaction unevaluable." Table 4.24 summarizes these 75 events. The description of the AE is based on a review of the documentation (eg, source records, CRFs). The events were categorized as follows:

- Treatment – The event was a treatment procedure or medication for one of the following:
  - A previously described AE
  - Conditions described in the patient's medical history
  - A treatment that was entered in the CRF in place of the AE(s) that precipitated the need for treatment
- Diagnostic Procedure – The patient underwent diagnostic testing because of an AE (eg, angiography performed for an AE of chest pain)
- Elective Surgery – Patient underwent elective surgery
- Not an AE – The event was captured in the CRF, but was not an AE (eg, the prophylactic use of aspirin for prevention of cardiovascular disease)
- Unknown Medication – Patient diary or CRF noted that patient took a drug, but there was no indication listed for the drug

Table 4.24 Summary of "Reaction Unevaluable" AEs – Scharf Trial

Event Type	Number of Events
Total	75 (100%)
Treatment	44 (58.7%)
Diagnostic Procedure	16 (21.3%)
Not an AE	7 (9.3%)
Elective Surgery	6 (8.0%)
Unknown Medication	2 (2.7%)

Of the 75 "reaction unevaluable" events analyzed, the review process clarified 73 events; 2 events (2.7%) were for medications taken for unknown conditions, and could not be resolved.

Fifteen (20%) of the 75 events were considered serious. Only 2 of the "reaction unevaluable" events were considered "probably related" to study drug. These 2 events, both coding to COSTART term "overdose," were among the 15 SAEs.

4.8.9 ADVERSE EVENTS: COMPARISON OF SODIUM OXYBATE AND PLACEBO IN CONTROLLED TRIALS

Table 4.25 summarizes AEs occurring in ≥ 5% of any group for sodium oxybate (all dosages combined) and placebo in the 3 double-blind, randomized, 4-week, placebo-controlled trials with washout periods (no treatment for cataplexy) of 1 to 7 weeks (OMC-GHB-2, Scrima, and Lammers) and for the double-blind, randomized, 2-week, placebo-controlled trial with a 2-week lead-in of single-blind Xyrem (OMC-SXB-21).

In the 3 trials with washout periods, 69% of the sodium oxybate-treated patients experienced 1 or more AEs, compared with 49% of the placebo-treated patients. The most frequently reported AEs for sodium oxybate-treated patients were dizziness (23%), headache (20%), and nausea (16%). For placebo-treated patients, headache was the most frequently reported AE (15%); all other AEs occurred in less than 10% of placebo patients.

In OMC-SXB-21, 12% of the sodium oxybate-treated patients experienced 1 or more AEs, compared with 31% of the placebo-treated patients. No AE was reported by more than 1 patient (4%) in the sodium oxybate group. For placebo-treated patients, headache and anxiety were the most frequently reported AEs (2 patients, 7% each); all other AEs occurred in only 1 patient (3%).

Table 4.25 AEs Occurring in ≥ 5% of Any Group, by Body System, COSTART Preferred Term, and Treatment Group (Active or Placebo) — Controlled Trials

Body System	OMC-GHB-2, Scrima, and Lammers			OMC-SXB-21		
COSTART Preferred Term	Total[a]	Placebo	Sodium Oxybate	Total	Placebo	Sodium Oxybate
Number of Patients	**226 (100%)**	**79 (100%)**	**147 (100%)**	**55 (100%)**	**29 (100%)**	**26 (100%)**
Patients with ≥ 1 AE	130 (58%)	39 (49%)	101 (69%)	12 (22%)	**9 (31%)**	3 (12%)
Body as a Whole	79 (35%)	24 (30%)	60 (41%)	4 (7%)	3 (10%)	1 (4%)
Headache	39 (17%)	12 (15%)	29 (20%)	2 (4%)	2 (7%)	0
Infection	11 (5%)	1 (1%)	10 (7%)	0	0	0
Pain	19 (8%)	3 (4%)	17 (12%)	0	0	0
Cardiovascular System	11 (5%)	2 (3%)	9 (6%)	1 (2%)	1 (3%)	0
Digestive System	46 (20%)	9 (11%)	37 (25%)	0	0	0
Dyspepsia	14 (6%)	5 (6%)	9 (6%)	0	0	0
Nausea	28 (12%)	4 (5%)	24 (16%)	0	0	0
Vomiting	10 (4%)	1 (1%)	9 (6%)	0	0	0
Musculoskeletal System	9 (4%)	1 (1%)	8 (5%)	0	0	0
Nervous System	80 (35%)	17 (22%)	66 (45%)	5 (9%)	5 (17%)	0
Anxiety	5 (2%)	1 (1%)	4 (3%)	2 (4%)	2 (7%)	0
Confusion	12 (5%)	1 (1%)	11 (7%)	0	0	0
Dizziness	36 (16%)	2 (3%)	34 (23%)	1 (2%)	1 (3%)	0
Nervousness	12 (5%)	6 (8%)	7 (5%)	0	0	0
Sleep disorder	15 (7%)	2 (3%)	13 (9%)	1 (2%)	1 (3%)	0
Somnolence	24 (11%)	7 (9%)	17 (12%)	1 (2%)	1 (3%)	0
Respiratory System	20 (9%)	6 (8%)	14 (10%)	2 (4%)	1 (3%)	1 (4%)
Skin	15 (7%)	4 (5%)	11 (7%)	2 (4%)	1 (3%)	1 (4%)
Special Senses	10 (4%)	3 (4%)	7 (5%)			
Urogenital System	24 (11%)	7 (9%)	18 (12%)	1 (2%)	0	1 (4%)
Incontinence, urine	8 (4%)	0	8 (5%)	0	0	0

[a] Two of the trials (Scrima and Lammers) were crossover trials, with patients in both the placebo and sodium oxybate groups.

4.9 Other Safety Information

4.9.1 ANALYSIS OF ADVERSE EVENT DOSE-RESPONSE INFORMATION

4.9.1.1 Dosage Justification

4.9.1.1.1 Historical Clinical Experience

At the time the first controlled clinical trial contained in this application was initiated (Scrima trial report, Scrima 1989, 1990), information was available on suitable dosage ranges for sodium oxybate from published reports of open-label clinical trials (Broughton 1979, 1980; Scharf 1985; Mamelak, 1986) that suggested that nightly dosages of 3.0 to 9.0 g/d, usually taken in divided nightly doses, were effective in reducing cataplexy and other symptoms of narcolepsy and were well tolerated. Mamelak (1981) reported a single case study in which sodium oxybate at a dosage of approximately 5 g/d was effective and well tolerated in the treatment of narcolepsy. Since that time, an additional paper by Bédard (1989), using EEG measures, demonstrated the efficacy of sodium oxybate in improving the disrupted sleep architecture (decreasing REM latency, time awake after sleep onset, and duration of stage 1 sleep; and increasing the number of sleep-onset REM periods, amount of REM, and REM efficiency) of patients with narcolepsy at a dosage of 2.25 g/d (single nightly dose).

4.9.1.1.2 Dosage Justification

In the long-term, open-label clinical trial (Scharf, begun in 1983), 6.0 g/d as a divided dose was the most frequent dosage.

The Scrima trial (begun in 1986) employed a dosage based on body weight (50 mg/kg), approximately equivalent to a dosage of 3.5 g/d for a 70-kg person. Based on the actual body weights of patients enrolled in the study, the mean dosage actually administered was 4.2 g/d (ranging from 3.0 g/d to 5.7 g/d for individual patients).

The Lammers trial (begun in 1987) employed a slightly higher dosage, also on a per-kilogram basis (60 mg/kg; 4.2 g/d for a 70-kg person). Based on the actual body weight of the patients enrolled in the study, the mean dosage actually administered was 4.7 g/d (ranging from 3.7 g/d to 5.5 g/d for individual patients).

For the OMC-GHB-2 trial (begun in 1997), the above-cited studies were used as a basis for selecting the dosage, as was expert opinion solicited by Orphan Medical. At the request of FDA (August 1995), higher and lower dosages (3 g/d and 9 g/d) were also included in the study design to look for evidence of dose-responsiveness: the 3 g/d dosage was selected as being marginally below what was thought to be the minimum effective dosage, and 9 g/d was selected to approximate a maximum tolerated dosage.

Final dosages in open-label studies OMC-GHB-3 (begun in 1997), OMC-SXB-6 (begun in 1999), and OMC-SXB-7 (begun in 1999) were arrived at by titration to optimal clinical effect. Patients began at a dosage of either 6.0 g/d (OMC-GHB-3) or 4.5 g/d

(OMC-SXB-6) and investigators titrated patients' dosages up or down to maximize therapeutic benefit while minimizing any potentially drug-related adverse experiences. This dosage-selection procedure was intended to more closely resemble actual clinical practice, in which patients will be recommended to begin treatment at 4.5 g/d and increase or reduce their dosage in 1.5 g/d (0.75 g per individual dose) increments at intervals of 2 weeks to maximize clinical benefit.

The distribution of final dosages in OMC-GHB-3, OMC-SXB-6, and OMC-SXB-7 (through the data cutoff of September 30, 2000) is summarized in Table 4.26.

Table 4.26 Distribution of Final Dosages — Open-Label Studies (OMC-GHB-3, OMC-SXB-6, and OMC-SXB-7)

Trial	Total	Sodium Oxybate Last Dosage (g/d)				
		3.0	4.5	6.0	7.5	9.0
OMC-GHB-3	117[a]	15 (13%)	20 (17%)	37 (32%)	25 (21%)	20 (17%)
OMC-SXB-7	185	4 (2%)	52 (28%)	73 (40%)	27 (15%)	29 (16%)
OMC-SXB-6	236	5 (2%)	39 (17%)	76 (32%)	59 (25%)	57 (24%)

[a] Does not include the 1 patient who did not receive sodium oxybate.

Dosages employed in the clinical trials included in the updated integrated clinical trial database, and in OMC-SXB-21, ranged from 3 to 9 g/d, taken in divided nightly doses.

4.9.1.2 Adverse Event Dose-Response Analysis

In the updated integrated clinical trial database, a higher incidence of AEs was seen with the patients taking 9.0 g/d sodium oxybate. This was true for patients with at least 1 AE (78% for 9.0 g/d, compared with 51% to 62% for the other 4 dosage at onset groups), patients with related AEs (55% for 9.0 g/d, vs. 28% to 40% for the other 4 dosage at onset groups), patients with severe AEs (16% for 9.0 g/d, vs. 3% to 12% for the other 4 dosage groups), and discontinuations due to AEs (12% for 9.0 g/d, vs. 2% to 6% for the other 4 dosage groups). Interestingly, the incidence for the patients in the placebo group with at least 1 AE (70%) and patients with related AEs (57%) was similar to that for the 9.0 g/d group for patients. No similar trend was apparent for patients with SAEs.

For the most frequently reported AEs, there were no apparent differences in incidence of headache and pain among the 6 dosage at onset groups, including placebo and the 5 sodium oxybate groups. There was a higher incidence (23%) of nausea in the 9.0 g/d group, compared with 7% for placebo and 8% to 11% for the other 4 sodium oxybate groups. A higher incidence of dizziness was seen in the 3.0 g/d and 9.0 g/d groups (16% and 17%, respectively), compared with 4% for placebo and 6% to 12% for the other 3 sodium oxybate groups. No inferential statistical analyses were performed for the integrated database.

A slight dose-related effect was seen in the OMC-GHB-3 trial for nausea ($p = 0.021$) and viral infection ($p < 0.001$), with a 16.7% incidence for both AEs in the 9.0 g/d sodium oxybate dosage group, compared with 9.8% and 3.3%, respectively, in the 3.0 g/d

sodium oxybate dosage group. In the OMC-GHB-2 trial where doses were assigned in a blinded, randomized fashion, a dose-related effect was apparent for dizziness ($p = 0.0178$), infection ($p = 0.0338$), nausea ($p = 0.0045$), urinary incontinence ($p = 0.0143$), and vomiting ($p = 0.0475$).

4.9.2 LONG-TERM ADVERSE EVENTS

As discussed in Section 4.2, of the 399 patients in the updated clinical trial database, 296 patients took Xyrem for $\geq$ 6 months, 223 patients took Xyrem for $\geq$ 1 year, and 48 patients took Xyrem for $\geq$ 2 years. Of the 479 patients in the combined experience from the updated integrated clinical trial database and the Scharf trial, 360 patients took Xyrem for $\geq$ 6 months, 286 patients took Xyrem for $\geq$ 1 year, and 150 patients took Xyrem for $\geq$ 2 years.

Analyses comparing AEs in different time periods were carried out in the OMC-GHB-3 trial (first 12 months vs. entire 24 months) and the Scharf trial (first 6 months vs. remainder of trial). In OMC-GHB-3, almost all AEs appeared to initiate within the first 12 months of the trial. Only 15 additional COSTART terms were reported during the second 12 months, only 3 of which occurred in more than 1 patient – GI distress (3 patients), bilirubinemia (2 patients), and increased alkaline phosphatase (2 patients). Only 1 patient experienced urinary incontinence during the second 12 months. In the Scharf trial, 95.1% of the 143 patients experienced 1 or more AE at any time during the trial; 87.4% of the patients experienced an AE during the first 6 months, again supporting the conclusion that few new AEs are seen after the first 6 to 12 months of treatment.

The profile of SAEs in the Scharf trial (with an incidence of 37.8%) was consistent with the serious illnesses that would be expected in a patient population of older adults. The most frequent SAEs were related to cardiovascular disease and narcolepsy. The incidence of serious accidental injury was not unexpected in patients with cataplexy. Several contributing factors could account for the incidence of SAEs, including:

- The increasing age of the patients during the trial (from a mean of 45.3 years of age at entry to a mean of 61 years of age), which would be associated with the development of chronic illness

- Underlying cardiovascular abnormalities, which were present in approximately 20% of patients at baseline, and the expected age-related progression and presentation of cardiovascular morbidities

- Possible maladaptive patterns of behavior for some patients as a result of long-standing disease (average time from diagnosis of narcolepsy to trial entry, 9.5 years)

4.9.3 WITHDRAWAL EFFECTS

To determine if REM rebound effects (ie, rebound cataplexy) occur on abrupt withdrawal of sodium oxybate, the incidence of AEs suggestive of REM rebound (increased cataplexy attacks, sleep disturbance, hallucinations, and abnormal dreams) during the

period of up to 5 days prior to Visit 6 (end of treatment period) was compared with that during the period of 3 to 5 days after Visit 6 during which no oxybate treatment was given in the OMC-GHB-2 trial. There was no evidence of acute rebound cataplexy and no exacerbation of AEs suggestive of REM rebound effects, suggesting that REM rebound effects do not appear when sodium oxybate is withdrawn for 3 to 5 days.

In the OMC-SXB-21 trial, abrupt double-blind discontinuation of long-term Xyrem treatment at therapeutic dose range for 2 weeks led to an increase in cataplexy attacks (median increase 21.0, compared with 0.0 for the Xyrem group), but did not appear to result in an increase in AEs that would indicate physical dependence or withdrawal syndrome.

4.10 Safety Summary

In dosages between 3.0 and 9.0 g/d in nightly divided doses, sodium oxybate was generally well tolerated in the 5 trials included in the updated integrated clinical trial database, the Lammers trial, the Scharf trial, and the OMC-SXB-21 trial, with side effects that were usually mild and most frequently included nausea, dizziness, and headache, with occasional urinary incontinence (enuresis) and somnambulism (sleepwalking).

Of the 399 patients in the updated clinical trial database, 296 patients took Xyrem for $\geq$ 6 months, 223 patients took Xyrem for $\geq$ 1 year, and 48 patients took Xyrem for $\geq$ 2 years. Of the 479 patients in the combined experience from the updated integrated clinical trial database and the Scharf trial, 360 patients took Xyrem for $\geq$ 6 months, 286 patients took Xyrem for $\geq$ 1 year, and 150 patients took Xyrem for $\geq$ 2 years. Total exposure to sodium oxybate was 329.89 patient-years in the updated integrated clinical trial database, 2.08 patient-years in the Lammers trial, and 996.15 patient-years in the Scharf trial, or a total of 1,328.12 patient-years.

Of the 402 narcolepsy patients included in the updated integrated clinical trial database, 331 (82%) experienced at least 1 AE. As expected, a higher incidence (95%) was seen in the long-term (16-year) clinical trial (Scharf); however, the incidence of AEs during the first 6 months of treatment with sodium oxybate was similar in the OMC-SXB-6, OMC-GHB-3, and Scharf trials.

Related AEs were seen for 247 of the 402 patients (61%) in the updated integrated clinical trial database. Severe AEs were seen for 82 of the 402 patients (20%). In the Scharf trial, severe AEs were seen for 21 of the 143 patients (14.7%) during the first 6 months on sodium oxybate.

SAEs were experienced by 27 of the 402 patients (7%) in the updated integrated clinical trial database and 54 of the 143 patients (37.8%) in the long-term (16-year) Scharf trial. Two deaths (0.5%) were reported in the OMC-SXB-7 trial, including patient 0936 who died after the data cutoff, and 11 [7.7%] deaths were reported in the Scharf trial over 16 years. None of these deaths was considered related to trial medication. Fifty-two patients (13%) discontinued due to 1 or more AEs in the updated integrated clinical trial database and 23 patients (16.1%) in the long-term (Scharf) trial. Of these patients,

42 (10%) in the updated integrated clinical trial database and 3 (2%) in the Scharf trial discontinued due to AEs considered to be related to trial medication.

In the updated integrated clinical trial database, the most frequently reported AEs included headache (29%), nausea (23%), dizziness (19%), and pain (18%). In the Scharf trial, the most frequently reported AEs (nearly all of which would be expected in a long-term trial and were associated with common intercurrent illnesses) included viral infection (56.6%), headache (52.4%), pain (48.3%), accidental injury (42.0%), nausea (40.6%), flu syndrome (38.5%), pharyngitis (37.8%), rhinitis (36.4%), increased cough (34.3%), sleep disorder (sleepwalking; 31.5%), diarrhea (28.0%), dizziness (27.3%), fever (26.6%), abdominal pain (26.6%), sinusitis (26.6%), and dyspepsia (25.2%).

Overall, a slight dose-response relationship was seen for the incidence of patients with 1 or more AEs in the updated integrated clinical trial database. Statistical analysis showed a dose-response relationship for specific AEs in 2 trials (dizziness, infection, nausea, urinary incontinence, and vomiting in OMC-GHB-2; nausea and viral infection in OMC-GHB-3). Examination of the data in the long-term (up to 16 years) clinical trial (Scharf) for AEs (during the first 6 months, and during the remainder of the study) showed no strong evidence of a dose-response relationship.

Special analyses showed no evidence of seizurogenesis (based on an analysis of incontinence AEs) or of medication-induced lupus (based on an analysis of increased ANA levels).

An analysis of the 3 placebo-controlled trials with washout periods of 1 to 7 weeks (OMC-GHB-2, Scrima, and Lammers) showed a higher incidence of patients with 1 or more AEs for sodium oxybate (69%) than for placebo (49%). The most frequently reported AEs for sodium oxybate-treated patients were dizziness (23%), headache (20%), and nausea (16%). For placebo-treated patients, headache was the most frequently reported AE (15%); all other AEs occurred in less than 10% of placebo patients.

In the placebo-controlled OMC-SXB-21 trial (with a 2-week lead-in of single-blind Xyrem), the incidence of patients with 1 or more AEs was 12% for sodium oxybate, compared with 31% for placebo. No AE was reported by more than 1 patient (4%) in the sodium oxybate group. For placebo-treated patients, headache and anxiety were the most frequently reported AEs (2 patients, 7% each); all other AEs occurred in only 1 patient (3%).

Laboratory evaluations for the integrated clinical trial database and the Scharf trial included blood chemistry, hematology, and urinalysis. The only potentially significant laboratory abnormality was hypocalcemia. Although this was present in 23 of the 132 patients tested in the 5 integrated clinical trials, it was a variable measure in 15 patients, with a return to normal during treatment. In all cases, the reduction in calcium levels was minor, and not of clinical significance.

4.11 Overall Conclusion

Safety information collected for this orphan indication from clinical trials is intrinsically limited. The safety data collected for Xyrem (sodium oxybate) suggests an acceptable safety profile as summarized herein and represented in greater detail in the NDA application on file with FDA.

SECTION 5
PHARMACOKINETICS, DRUG INTERACTIONS, AND PHARMACODYNAMICS

5.0 PHARMACOKINETICS, DRUG INTERACTIONS, AND PHARMACODYNAMICS

5.1 Human Pharmacokinetics and Drug Interactions Summary

Eight (8) Phase I clinical pharmacokinetic studies of sodium oxybate were sponsored. The first was a pilot study that evaluated the single-dose pharmacokinetics of sodium oxybate in narcoleptic patients who had been taking oxybate for 2 to 13 years (OMC-GHB-4). Thereafter, the pharmacokinetics of sodium oxybate were evaluated after single and repeated (8-week) administration in oxybate-naïve narcoleptic patients (OMC-SXB-10). Dose-proportionality (OMC-SXB-9), sex-related differences (OMC-SXB-8), and effects of food (OMC-SXB-11) on sodium oxybate pharmacokinetics were assessed in 3 studies in healthy volunteers. The potential for interaction between sodium oxybate and 3 classes of drugs (hypnotics, antidepressants, and stimulants) commonly used in the treatment of narcoleptic symptoms were assessed in 3 studies in healthy volunteers using zolpidem (Ambien®) (OMC-SXB-12), protriptyline (Vivactil®) (OMC-SXB-14), and modafinil (Provigil®) (OMC-SXB-17). Potential for drug interactions through inhibition of cytochrome P450 (CYP) isoenzymes was also assessed *in vitro* (Covance Study No. 6627-129).

Since Xyrem (sodium oxybate) is a true solution for oral administration and is not a solid dosage form, absolute bioavailability studies and/or bioequivalence studies are not required for New Drug Application (NDA) submission in the United States. At a meeting between Orphan Medical and FDA in August 1998, the Agency concurred that no bioequivalence studies are required for this application and none were performed.

5.1.1 NARRATIVE SUMMARIES FOR XYREM (SODIUM OXYBATE) ORAL SOLUTION BIOPHARMACEUTIC STUDIES

The 8 clinical pharmacokinetic studies and one *in vitro* study sponsored by Orphan Medical Inc. are summarized below. Several features were common to the 8 clinical pharmacokinetic studies. All were open label single center studies and none used biomarkers or surrogate end-points. With the exception of the pilot study (OMC-GHB-4), all the pharmacokinetic studies used a Xyrem (sodium oxybate) oral solution[1] identical to the one to be released to the market upon NDA approval. The pilot study used a powder formulation[2] that was readily dissolved in a small volume of water before ingestion by study subjects as an oral solution.

Blood for determination of plasma oxybate concentrations was taken at varying times after sodium oxybate administration. A liquid chromatography atmospheric pressure

[1]In addition to sodium oxybate (500 mg/mL), the liquid formulation contains malic acid, FCC NF, sodium hydroxide, NF, and purified water, USP.
[2]Unit doses of the powder formulation were packaged in twin pouches: one containing sodium oxybate and the other the flavor excipient. The contents were dissolved in two ounces of water before ingestion. The powder formulation was also used in clinical trials OMC-GHB-2 and OMC-GHB-3.

ionization tandem mass spectrometry (LC/MS/MS) analytical method with a limit of quantification (LOQ) of 5 µg/mL oxybate for a 0.1 mL aliquot of plasma was used in all studies except the pilot study, which used a gas chromatographic method with mass selective detection (LOQ 7.02 µg/mL for a 1.0 mL aliquot of plasma).

In all studies, plasma oxybate concentration versus time data from each subject following dosing were subjected to non-compartmental analysis using WinNonlin (version 1.1) and SAS (versions 6.11 and 8) and the following pharmacokinetic parameters determined: peak plasma concentration (C_{max}), corresponding peak time (T_{max}), elimination half-life ($T_{1/2}$), area under the curve from time zero to time infinity (AUC_{inf}), plasma clearance divided by absolute bioavailability (CL/F), and volume of distribution divided by absolute bioavailability (V_z/F). The mean and coefficient of variation (CV) for each parameter was calculated from the individual subject data.

5.1.1.1 Pharmacokinetics of Sodium Oxybate in Oxybate-Experienced Narcoleptic Patients (OMC-GHB-4)

This was a pilot Phase I open label pharmacokinetic study of orally administered sodium oxybate in 6 narcoleptic patients who had been receiving nightly doses of oxybate for 2 to 13 years. Patients received 2 consecutive 3-g doses of sodium oxybate, the first just prior to bedtime and the second 4 hours later. Unit doses of sodium oxybate (and flavoring excipient) were dissolved in 2 ounces of water and the resultant solution ingested by study subjects as a liquid formulation.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 6 patients.

First 3-g Dose		Second 3-g Dose		$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg
C_{max} µg/mL	T_{max} hour	C_{max} µg/mL	T_{max} hour				
62.8 ± 43%	0.67 ± 15%	91.2 ± 28%	0.59 ± 19%	0.88 ± 36%	295 ± 27%	4.2 ± 21%	307 ± 18%

Capacity limited elimination kinetics was observed in 3 of 6 patients following two consecutive 3 g oral doses of sodium oxybate. From a pharmacokinetic perspective, dividing the nightly sodium oxybate dose into 2 portions and administering the 2 portions at a 2.5- to 4-hour interval is rational because the elimination half-life of sodium oxybate in narcoleptic patients is short (< 1 hour). The pharmacokinetics of sodium oxybate in narcoleptic patients (who had been ingesting this agent nightly for years) appears to be comparable to that observed in healthy human subjects (Palatini 1993) and in alcohol dependent patients (Ferrara 1992).

5.1.1.2 Pharmacokinetics of Sodium Oxybate After Single and Chronic (8-week) Dosing in Oxybate-naïve Narcoleptic Patients (OMC-SXB-10)

This study was to examine the pharmacokinetics of Xyrem (sodium oxybate) oral solution in narcoleptic patients after a single 4.5 g dose and after 8 weeks of nightly dosing with 4.5 g. Each dose was taken just before bedtime. Subjects were 13 (3 male, 10 female) oxybate naïve narcoleptic patients.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 13 patients.

Time of Determination	C_{max} µg/mL	T_{max} hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg
First dose	90.0 ± 34%	0.75[a]	0.67 ± 25%	226 ± 33%	4.0 ± 28%	226 ± 29%
8-weeks	104 ± 30%	0.50[a]	0.67 ± 31%	254 ± 31%	3.5 ± 31%	197 ± 34%

[a]median

On average, the nightly treatment with Xyrem for 8 weeks resulted in a 13% increase in systemic exposure to oxybate based on AUC_{inf} and a 16% increase in peak plasma concentration. While the changes were statistically significant ($P<0.05$; paired t-test of log transformed values), these modest increases are not considered to be clinically significant. It was also concluded that chronic Xyrem treatment did not result in auto-induction (self-induction of metabolism).

5.1.1.3 Pharmacokinetics of Sodium Oxybate in Healthy Male and Female Volunteers (OMC-SXB-8)

This study examined the pharmacokinetics of Xyrem (sodium oxybate) oral solution in 18 male and 18 female healthy adult volunteers who received a single 4.5 g dose just before bedtime. Urine levels of oxybate, for determination of the extent of renal excretion of unchanged oxybate, were also assessed in this study.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 18 males and 18 females.

Sex	C_{max} µg/mL	T_{max} hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg
Male	88.3 ± 24%	1.25 ± 53%	0.65 ± 35%	241 ± 34%	3.8 ± 34%	202 ± 30%
Female	83.0 ± 23%	1.14 ± 43%	0.61 ± 20%	233 ± 35%	4.2 ± 38%	218 ± 40%

There was no difference in the systemic exposure to oxybate between male and female subjects. Based on unpaired t-test or Wilcoxon rank sum test (T_{max} only), there was no significant difference ($P > 0.05$) between male and female volunteers for log-transformed AUC_{inf}, log transformed C_{max}, T_{max}, CL/F (per kg), $T_{1/2}$, percentage of dose excreted unchanged in urine, or apparent renal clearance. The $T_{1/2}$ of Xyrem was 39 min in men and 37 min in women, resulting in very low plasma concentrations by 6 hours after a 4.5 g dose. Urinary excretion of unchanged oxybate was a minor elimination pathway (1% – 7%) in both sexes.

5.1.1.4 Dose Proportionality of Sodium Oxybate (OMC-SXB-9)

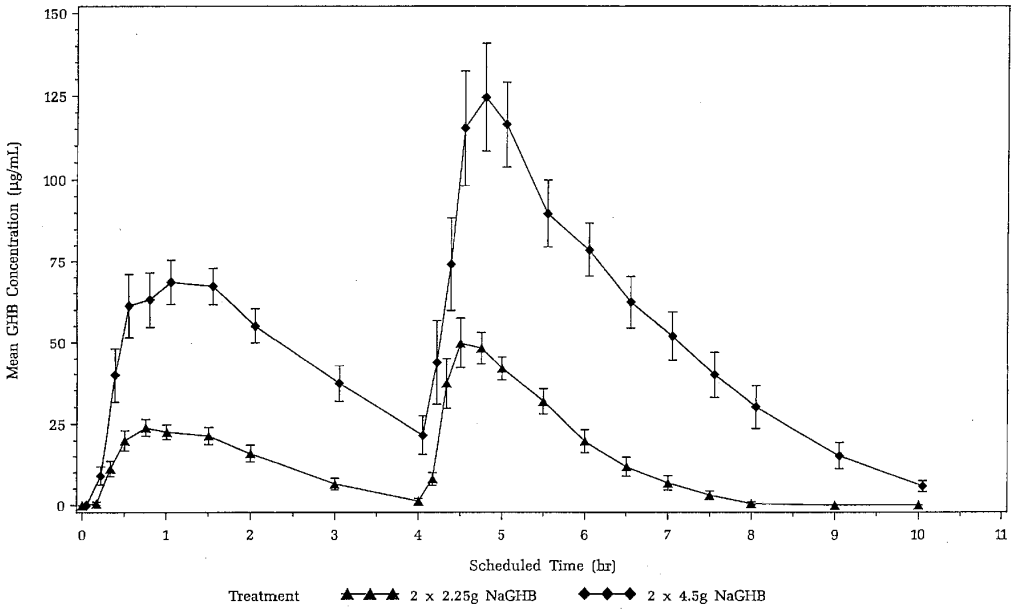
This was a 2-way crossover study that examined the pharmacokinetics of Xyrem (sodium oxybate) oral solution in 10 male and 3 female healthy adult volunteers. Each subject received two treatments with sodium oxybate, one at a dose of 4.5 g and the other at a dose of 9.0 g. For each treatment, doses were divided (2 x 2.25 g or 2 x 4.5 g), with the first half being given just before bedtime and the second 4 hours later. A 7-day washout separated the two treatments. Urine levels of oxybate, for determination of the extent of renal excretion of unchanged oxybate, were also assessed in this study.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in the 12 volunteers who completed the study.

Xyrem Dose g	First Nightly Dose		Second Nightly Dose		$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg
	C_{max} µg/mL	T_{max} hour	C_{max} µg/mL	T_{max} hour				
4.5 (2 x 2.25)	26.6 ± 32%	0.85 ± 42%	60.1 ± 29%	0.64 ± 49%	0.59 ± 22%	138 ± 36%	6.6 ± 32%	325 ± 24%
9.0 (2 x 4.5)	77.6 ± 32%	1.17 ± 46%	142 ± 35%	0.72 ± 63%	0.83 ± 23%	518 ± 38%	3.6 ± 38%	249 ± 36%

The systemic exposure of human subjects to oxybate increased disproportionately with dose. Doubling the nightly dose from 4.5 g (2 x 2.25 g) to 9 g (2 x 4.5 g) resulted in a 3.8-fold increase in AUC_{inf}. C_{max} values were higher after the second half of the nightly dose (administered 4 hours after the first half of the nightly dose) (Figure 5.1).

Figure 5.1 Mean Oxybate Concentration Versus Time After Divided Doses of 4.5 g and 9.0 g in Healthy Volunteers



The apparent $T_{1/2}$ of oxybate was < 1 hour, resulting in very low plasma concentrations by 10 hours after the start of this dosing regimen. Renal excretion of unchanged oxybate was minimal (<10%).

5.1.1.5 Effect of Food on Pharmacokinetics of Sodium Oxybate (OMC-SXB-11)

This was a randomized 2-way crossover study that determined the effect of food on the bioavailability of Xyrem (sodium oxybate) oral solution in 36 adult female healthy volunteers. Each subject received two treatments with 4.5 g sodium oxybate, one given after a high fat meal and the other after an overnight fast. Urine levels of oxybate, for determination of the extent of renal excretion of unchanged oxybate, were also assessed in this study.

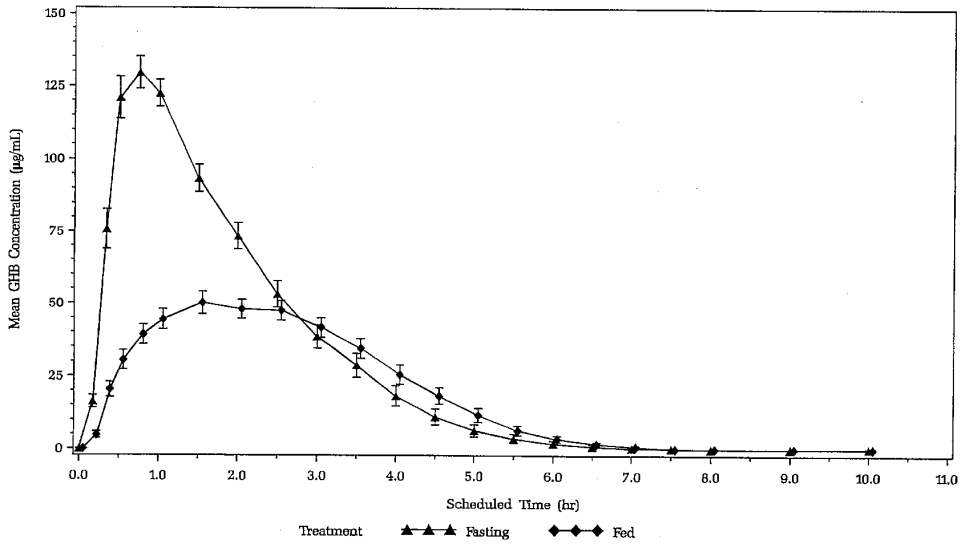
The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 34 subjects who completed the study.

Food State	C_{max} µg/mL	T_{max}^{**} hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg
Fed	60.1* ± 33%	2.00*	0.68 ± 32%	188* ± 43%	6.2 ± 52%	384 ± 84%
Fasted	142 ± 24%	0.75	0.57 ± 53%	288 ± 38%	3.7 ± 38%	190 ± 51%

*Significantly different than fasted state (P<0.05)
**T_{max} value is median

A high fat meal significantly delayed Xyrem absorption following oral dosing (Figure 5.2). The systemic exposure of subjects to oxybate when Xyrem was administered after a high fat meal was not equivalent to the systemic exposure when Xyrem was administered after an overnight fast. On average, C_{max} decreased by 59% and AUC_{inf} decreased by 37% in the fed compared to fasted state. The 90% confidence interval for the fed:fasted ratio of C_{max} was 0.37-0.46 and of AUC_{inf} was 0.57-0.69. Absorption of Xyrem appeared to be slower when Xyrem was administered after a high fat meal than after an overnight fast, resulting in a later T_{max} of 2 hours compared to 0.75 hour. The apparent half-life of oxybate was <1 hour for both dosing conditions. Urinary excretion of unchanged oxybate was a minor elimination pathway (<10% of the dose).

Figure 5.2 Mean Plasma Concentration Versus Time of Oxybate After an Overnight Fast and After a High Fat Meal



5.1.1.6 Hypnotic Drug Interaction: Sodium Oxybate and Zolpidem (OMC-SXB-12)

This randomized 3-way crossover study determined the interaction between sodium oxybate and zolpidem tartrate (Ambien®) in 10 male and 5 female healthy adult volunteers. Each subject received each of the following treatments: a single dose of sodium oxybate (3 g) alone; a single dose of sodium oxybate (3 g) in combination with zolpidem (5 mg); and a single dose of zolpidem (5 mg) alone.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 15 subjects.

Treatment Regimen	Analyte	C_{max} µg/mL	T_{max}* hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg
sodium oxybate alone	oxybate	83.8 ± 29%	0.50	0.74 ± 30%	136 ± 32%	4.3 ± 30%	260 ± 28%
sodium oxybate + zolpidem	oxybate	93.5 ± 30%	0.75	0.73 ± 25%	143 ± 34%	4.4 ± 52%	281 ± 82%
	zolpidem	107 $x10^{-3}$ ± 44%	0.75	3.35 ± 56%	420 $x10^{-3}$ ± 51%	2.6 ± 50%	643 ± 35%
zolpidem alone	zolpidem	96.3 $x10^{-3}$ ± 37%	0.50	3.34 ± 48%	424 $x10^{-3}$ ± 54%	2.8 ± 50%	640 ± 26%

*Median reported for T_{max}

The systemic exposure of healthy adult volunteers to oxybate when Xyrem was administered with zolpidem was equivalent to the systemic exposure when Xyrem was administered alone. On average, C_{max} of oxybate increased by 6% and AUC_{inf} by 3% in the presence of zolpidem. Conversely, the mean zolpidem C_{max} decreased by 8% and AUC_{inf} decreased by 2% in the presence of Xyrem. Overall, however, co-administration of Xyrem and zolpidem presents no pharmacokinetic changes for either drug that are clinically significant.

5.1.1.7 Antidepressant Drug Interaction: Sodium Oxybate and Protriptyline (OMC-SXB-14)

This randomized 3-way crossover study determined the interaction between sodium oxybate and protriptyline hydrochloride (Vivactil®) in 5 male and 7 female healthy adult volunteers. Each subject received each of the following treatments: sodium oxybate in a divided dose of 4.5 g (2 x 2.25 g) alone; sodium oxybate (2 x 2.25 g) in combination with protriptyline (10 mg); and a single dose of protriptyline (10 mg) alone.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 13 patients.

Treatment regimen	Analyte	C_{max}[a,b] µg/mL	T_{max}[a] hour	$T_{1/2}$ hour	AUC_{inf}[b] µg·hr/mL	CL/F[b] mL/min·kg	V_z/F[b] mL/kg
sodium oxybate alone	oxybate	64.6 ± 24%	0.50[c]	0.57 ± 33%	178 ± 41%	5.7 ± 44%	248 ± 18%
sodium oxybate + protriptyline	oxybate	58.3 ± 39%	0.75[c]	0.57 ± 32%	183 ± 43%	5.9 ± 56%	263 ± 37%
	protrip-tyline	4.7 $x10^{-3}$ ± 30%	8.0[c]	72.1 ± 53%	452 $x10^{-3}$ ± 67%	0.41 $x10^{3}$ ± 68%	32.0 $x10^{3}$ ± 36%
protriptyline alone	protrip-tyline	5.0 $x10^{-3}$ ± 26%	8.0[c]	68.2 ± 57%	463 $x10^{-3}$ ± 67%	0.40 $x10^{3}$ ± 75%	30.6 $x10^{3}$ ± 57%

[a]Shown are the C_{max} and T_{max} from the second of the divided doses of sodium oxybate; parameters from the first divided dose were no different when sodium oxybate was given alone or in combination with protriptyline; the mean (CV) C_{max} was 55.1 (26%) vs 55.5 (34%) µg/mL, respectively and median T_{max} was 0.75 vs 0.63 hours, respectively.
[b]Units for protriptyline have been converted from reported units for Cmax (ng/mL), AUC_{inf} (ng·hr/mL), CL/F (L/min·kg), and V_z/F (L/kg).
[c]median

On average, the oxybate C_{max} decreased by 2% and 16% after the first and second portion of the dose, respectively, and the combined AUC_{inf} decreased by 3%, following co-administration with protriptyline. Conversely, mean protriptyline C_{max} increased by 7% and AUC_{inf} increased by 3% following co-administration. Overall, however, co-administration of Xyrem and protriptyline presents no pharmacokinetic changes for either drug that are clinically significant.

5.1.1.8 Stimulant Drug Interaction: Sodium Oxybate and Modafinil (OMC-SXB-17)

This randomized 3-way crossover study determined the interaction between sodium oxybate and modafinil (Provigil®) in 7 male and 6 female healthy adult volunteers. Each subject received each of the following treatments: a single dose of sodium oxybate (4.5 g) alone; a single dose of sodium oxybate (4.5 g) in combination with modafinil (200 mg); and a single dose of modafinil (200 mg) alone.

The pharmacokinetic parameters observed or derived from the study are tabulated below and are expressed as the mean ± CV of observations in 12 subjects.

Treatment regimen	Analyte	C_{max} µg/mL	T_{max} hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg
sodium oxybate alone	oxybate	146 ± 21%	0.50[a]	0.76 ± 24%	302 ± 39%	3.1 ± 29%	190 ± 16%
sodium oxybate + modafinil	oxybate	135 ± 26%	0.50[a]	0.76 ± 28%	294 ± 56%	3.4 ± 38%	205 ± 20%
	modafinil	5.5 ± 31%	2.0[a]	12.3 ± 19%	71.8 ± 26%	0.66 ± 21%	690 ± 20%
modafinil alone	modafinil	5.2 ± 27%	1.0[a]	12.0 ± 15%	74.2 ± 27%	0.64 ± 20%	657 ± 21%

[a]median

On average, the oxybate C_{max} decreased by 8% and AUC_{inf} decreased by 7%. Conversely, mean modafinil C_{max} decreased by 6% and AUC_{inf} increased by 4%. It was concluded that Xyrem and modafinil when administered together presented no pharmacokinetic changes for either drug that are clinically significant.

5.1.1.9 Potential for Drug Interaction Through Inhibition of Cytochrome P450 Isozymes (Covance Study No. 6627-129)

The potential for drug interactions by an inhibitory effect of sodium oxybate on human hepatic microsomal cytochrome P450 (CYP) isozymes was assessed in this study. Characterized, pooled, human liver microsomal fractions from 10 individuals were used in these studies and the activity of the following CYP isozymes were determined:

- ethoresoflurin O-deethylase (CYP1A2)
- tolbutamide methyl hydroxylase (CYP2C9)
- S-mephenytoin 4'-hydroxylase (CYP2C19)
- dextromethophan O demethylase (CYP2D6)
- *p*-nitrophenol hydroxylase (CYP2E1)
- erythromycin N-demethylase (CYP3A).

Each assay was performed with a fixed substrate concentration and in the presence and absence of 3, 10, 30, 100, and 300 µM oxybate, with the aim of calculating the concentration of oxybate that inhibited activity by 50% (IC_{50}). However, no inhibitory activity of oxybate was observed in any of the assays at any of the concentrations tested; the IC_{50} was greater than 300 µM in all of the assays. Oxybate, therefore, does not inhibit activities of human CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A. Metabolic interactions with drugs metabolized through these pathways are, therefore, also not anticipated.

5.1.2 PHARMACOKINETICS OF SODIUM OXYBATE

A description of the pharmacokinetic characteristics of sodium oxybate is presented below. Information from the 8 clinical pharmacokinetic studies sponsored by Orphan Medical as well as information from 6 published studies (not sponsored by Orphan Medical) are included. Three published studies were conducted using oxybate oral solution[3]; two were dose-proportionality studies in healthy volunteers (Palatini 1993) and in alcohol-dependent patients (Ferrara 1992) and the other a single-dose study in patients with liver disease (Ferrara 1996). Three studies were conducted using an intravenous route of administration in patients needing sedation or undergoing surgery (Vree 1975, Vree 1978) and in pregnant women undergoing caesarian section (van den Bogert 1978); this study also reported use in a 2-day old neonate (van den Bogert 1978).

A summary of pharmacokinetic parameters derived from each of the studies sponsored by Orphan Medical as well as from published sources is presented in Table 5.1. This table shows the study population (ie, healthy volunteers or patients); dose, route, and duration of dosing with oxybate; mean pharmacokinetic parameters reported in each study; and study reference. A brief narrative description of the pharmacokinetic characteristics (absorption, distribution, metabolism, elimination) of sodium oxybate in healthy volunteers and narcoleptic and other patient populations follows Table 5.1.

[3]Oxybate dissolved in a black cherry syrup

Table 5.1 Pharmacokinetic Parameters for Oxybate in Healthy Volunteers and Patient Populations After Oral or Intravenous Administration

Study population	N	Oxybate administration			C_{max} µg/mL	T_{max} hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg	Reference
		Route	Dose	Duration							
Healthy volunteers	8	Oral	12.5 mg/kg (0.87 g)[a]	Single	23	0.42[b]	0.45	15.1	14	NR	Palatini 1993
			25 mg/kg (1.75 g)[a]	Single	23[c]	0.5[b]	0.37	21.2[c]	9[c]	NR	
			50 mg/kg (3.5 g)[a]	Single	23[c]	0.75[b]	0.38	26.1[c]	7[c]	NR	
Healthy volunteers	15	Oral	3 g	Single	83.8	0.50[b]	0.74	136	4.3	260	OMC-SXB-12
Healthy volunteers	12	Oral	4.5 g	Single	146	0.50[b]	0.76	302	3.1	190	OMC-SXB-17
Healthy volunteers male	18	Oral	4.5 g	Single	88.3	1.25	0.65	241	3.8	202	OMC-SXB-8
female	18	Oral	4.5 g	Single	83.0	1.14	0.61	233	4.2	218	OMC-SXB-8
Healthy volunteers fed	36	Oral	4.5 g	Single	60.1	2.00[b]	0.68	188	6.2	384	OMC-SXB-11
fasted	36	Oral	4.5 g	Single	142	0.75[b]	0.57	288	3.7	190	OMC-SXB-11
Healthy volunteers	12	Oral	4.5 g (2x2.25 g)	Single	64.6[d]	0.50[b,d]	0.57	178	5.7	248	OMC-SXB-14
Healthy volunteers	12	Oral	4.5 g (2x2.25 g)	Single	60.1[d]	0.64[d]	0.59	138	6.6	325	OMC-SXB-9
			9.0 (2x4.5)	Single	142[d]	0.72[d]	0.83	518	3.6	249	

[a]Dose calculated for a 70-kg subject presented for comparative purposes
[b]median
[c]normalized to 12.5 mg/kg
[d]Values for second half of divided dose presented
NR = not reported

Table 5.1 Pharmacokinetic Parameters for Oxybate in Healthy Volunteers and Patient Populations After Oral or Intravenous Administration, continued

Study population	N	Oxybate administration			C_{max} µg/mL	T_{max} hour	$T_{1/2}$ hour	AUC_{inf} µg·hr/mL	CL/F mL/min·kg	V_z/F mL/kg	Reference
		Route	Dose	Duration							
Narcoleptic patients	13	Oral	4.5 g	Single	90.0	0.75[b]	0.67	226	4.0	226	OMC-SXB-10
			4.5 g	8 weeks	104	0.50[b]	0.67	254	3.5	197	OMC-SXB-10
Narcoleptic patients	6	Oral	6 g (2x3 g)	single	91.2	0.59	0.88	295	4.2	307	OMC-GHB-4
Liver disease: Child's Class A patients	8	Oral	25 mg/kg (1.75 g)[a]	single	68	0.75[b]	0.53	85.4	4.5	198	Ferrara 1996
Child's Class C patients	8	Oral	25 mg/kg (1.75 g)[a]	single	47	0.75[b]	0.93	94.1	4.1	285	Ferrara 1996
Alohol-dependent patients	10	Oral	25 mg/kg (1.75 g)[a]	single	54	0.5[b]	0.45	52	9.6	NR	Ferrara 1992
				13 doses	55	0.5[b]	0.43	52	9.2	NR	
			50 mg/kg (3.5 g)[a]	single	45[c]	0.75[b]	0.58	90.3[c]	5.3[c]	NR	
Surgical patients	3	IV	50 mg/kg (3.5 g)[a]	single	NR	NR	~0.5	ND	ND	ND	Vree 1975
Surgical patients or sedation	6	IV	30-100 mg/kg (2.1-7 g)[a] (bolus)	single bolus and infusion	NR	NR	~0.67	ND	ND	ND	Vree 1978
Caesarian section patients	14	IV	26.7-50 mg/kg (1.9-3.5 g)[a]	single infusion	NR	NR	ND	ND	ND	ND	van den Bogert 1978

[a]dose calculated for a 70-kg subject presented for comparative purposes
[b]median
[c]normalized to 25 mg/kg
[d]values for second half of divided dose presented
NR = not reported
ND = not determined

5.1.2.1 Absorption

Xyrem (sodium oxybate) oral solution is rapidly absorbed following oral administration. The mean time to achieve peak plasma oxybate concentration (T_{max}) ranged from 0.5 to 1.25 hours across the 8 studies and was similar in narcoleptic and other patient populations (Table 5.1). The absorption characteristics of sodium oxybate were similar in males and females (OMC-SXB-8) and were not changed by chronic dosing (OMC-SXB-10).

The absorption characteristics of oxybate were influenced by food, which significantly (P<0.05) delayed the absorption of oxybate (OMC-SXB-11) (Figure 5.2). The average T_{max} in a fed state was 2.0 hours, representing an increase of over 100% when compared to a fasted state. The C_{max} was decreased by almost 60%, and the AUC_{inf} by 37%, following a high fat meal (OMC-SXB-11).

The absorption characteristics of oxybate were also dose-dependent. In Study OMC-SXB-9, peak plasma concentrations of oxybate were observed somewhat later at the higher dose, with T_{max} being approximately 0.9 hours after 2.25 g sodium oxybate and 1.2 hours after 4.5 g (Figure 5.1). Others have also reported the absorption of oxybate from the gastrointestinal tract to be dose-dependent. Palatini (1993) showed T_{max} increased as the GHB dose was increased from 12.5 mg/kg to 50 mg/kg (0.875 g to 3.5 g for a 70 kg subject) (Table 5.1). These observations were indicative of capacity limited absorption, which has also been reported in animal studies.

5.1.2.2 Distribution

The average apparent volume of distribution of oxybate divided by absolute bioavailability (V_z/F) ranged between 190 and 384 mL/kg across the studies sponsored by Orphan Medical (Table 5.1). In the only other study reporting this parameter, similar values were found in cirrhotic patients without and with ascites (198 and 285 mL/kg, respectively) (Palatini 1996). Vree (1978) reported the absolute bioavailability (F) of oral oxybate was approximately 27% and using this value, the volume of distribution ranges from 51 mL/kg to 104 mL/kg.[4]

The inter-subject variability of the apparent volume of distribution term for oxybate is indicated by the coefficient of variation, which ranged between 16% and 84% across the different studies. This wide range of inter-subject variation could be due to 2 factors. First, oxybate follows dose (or concentration) dependent pharmacokinetics. Second, the dose (and hence plasma concentration) at which non-linear pharmacokinetics of oxybate is observed varies among subjects, which, in comparison to a drug that follows linear kinetics, results in a wider range of AUC values for the same dose. The apparent volume of distribution term V_z/F is inversely related to AUC_{inf}, which increases more than proportionately once the oxybate dose is increased above 3 g. As a consequence, the inter-subject variation in the volume of distribution term is expected to increase exponentially once the threshold of non-linear pharmacokinetics is reached.

[4]Calculated by multiplying values for V_z/F (190 and 384 mL/kg) by F (0.27)

Oxybate readily crosses the placenta and is distributed to the fetus after intravenous injection in pregnant women undergoing cesarian section (van den Bogert 1978). Although fetal plasma oxybate concentration reached equilibrium with maternal concentration after approximately 30 minutes, it was rapidly eliminated from the neonate and doses of 35-45 mg/kg maternal weight were considered safe for this procedure (van den Bogert 1978). Rapid clearance of oxybate was also observed in a 2-day old male given 30 mg/kg oxybate (IV bolus) and the pharmacokinetic profile in this individual was similar to that observed in a 15-year old male given the same dose (van den Bogert 1978).

Plasma protein binding was not evaluated in the studies sponsored by Orphan Medical. Palatini (1993) reported that the free fraction of oxybate in plasma was consistent at 0.99 over a range of plasma concentrations between 3 and 300 μg/mL (pre-dialysis) and concluded that oxybate essentially does not bind to any plasma component.

5.1.2.3 Metabolism

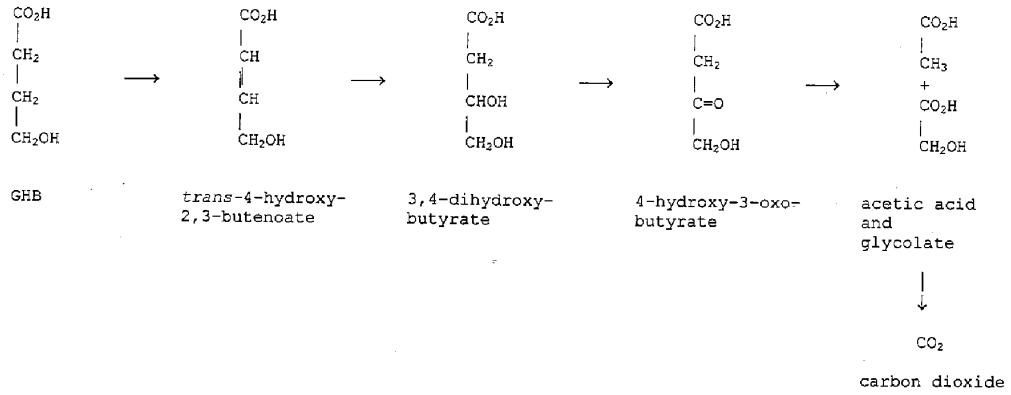
On average, less than 5% of an oral oxybate dose is eliminated unchanged in human urine (OMC-SXB-8, OMC-SXB-9, and OMC-SXB-11). Hence, metabolism is the major elimination pathway for oxybate.

Orphan Medical Inc. did not sponsor a mass balance and metabolic fate study in humans. The metabolism of exogenous and endogenous oxybate is well understood based on published investigations and the end product of the metabolism of oxybate, a simple 4-carbon molecule, is carbon dioxide regardless of biotransformation pathway. In addition, a ^{14}C-labeled mass balance and metabolic fate study in human volunteers is unethical because of the very real possibility of the radiolabel (*ie*, ^{14}C derived from ^{14}C-oxybate) being incorporated in structural protein via the amino acid pool.

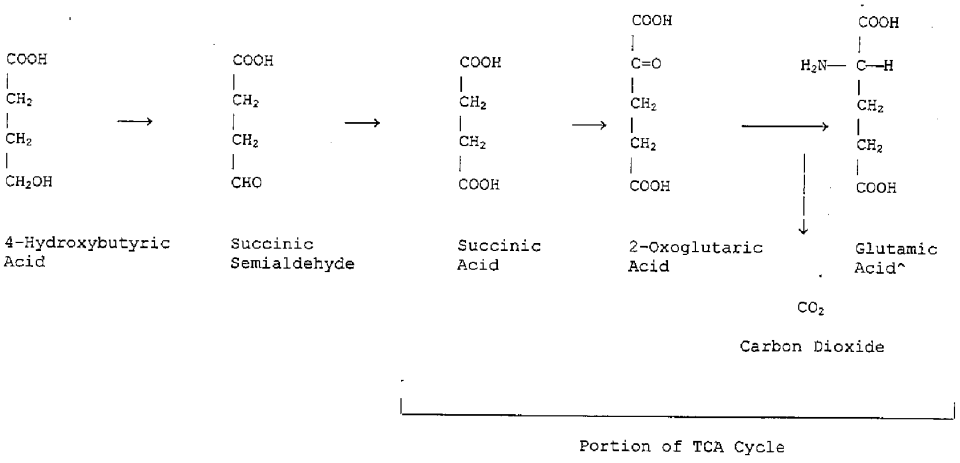
A review of the scientific literature shows that GHB may be metabolized via two distinct biotransformation pathways (Figure 5.3), one involving a β-oxidation pathway (Figure 5.3, upper panel) and the other involving the entry of an intermediate metabolite, succinic acid, into the tricarboxylic acid cycle (Figure 5.3, lower panel). The end product of both pathways is carbon dioxide.

The ß-oxidation pathway was proposed by Walkenstein and colleagues (Walkenstein 1964) based on the results of a ^{14}C mass balance and metabolism study in rats administered [1-^{14}C]GHB and [4-^{14}C]GHB (40 mg IP; specific activity 0.4 Ci/mg). Radiorespirometry indicated a rapid conversion of both ^{14}C-labeled molecules to ^{14}C-carbon dioxide, with approximately two-thirds of the dose excreted as carbon dioxide within 6 hours and an additional 10-20% over the next 18 hours. An intermediate metabolite, 3,4-dihydroxybutyrate, was identified. The proposed pathway involves biotransformation via β-oxidation to *trans*-4-hydroxy-2,3-butenoate, which became 3,4-dihyroxybutyrate, before proceeding to carbon dioxide (Figure 5.3, upper panel) (Walkenstein 1964).

Figure 5.3 Biotransformation Pathways for Oxybate (GHB)



Pathway 1: β-Oxidation of GHB as the Preliminary Step and Final Degradation to CO_2 from acetic acid and glycolaldehyde. Adapted from Walkenstein (1964) and Lee (1977).



Pathway 2: Formation of Semialdehyde Followed by Subsequent Degradation to CO_2 via the Tricarboxylic Acid Cycle. Adapted from Mohler (1976).

Oxybate and several metabolites of the ß-oxidation pathway (3,4-dihydroxybutyrate, 4-hydroxy-3-oxobutyrate, and glycolate) were identified in the urine of 2 male and 2 female volunteers who received a 1-g dose of oxybate in an aqueous solution (Lee 1977), validating the biotransformation pathway proposed by Walkenstein (1964). Further evidence in support of the ß-oxidation pathway came from a case report of a new inborn error of metabolism, γ-hydroxybutyric aciduria (Jakobs 1984, Jakobs 1990) with clinically manifestations including hypotonia, ataxia, and mental retardation.

Patients who were deficient in the enzyme that catalyzes the oxidation of oxybate to succinic semialdehyde (Figure 5.3, lower panel) developed abnormal accumulation of oxybate. It is of interest to note that Jacobs found the intermediate metabolites of the β-oxidation pathway, 3,4-dihyroxybutyrate and 3-keto-4-hydroxybutyrate (4-hydroxy-3-oxobutyrate), in the urine of such patients.

The second and principal biotransformation pathway (Figure 5.3, lower panel) involves the entry of an intermediate metabolite, succinic acid, into the tricarboxylic acid cycle. Studies in support of this pathway were reported by several researchers (Doherty 1975, Mohler 1976, Kaufman 1979, Kaufman 1983, Kaufman 1987, Kaufman 1988, Gibson 1989) who investigated the biosynthesis and catabolism of oxybate, which is a normal constituent in the brain, heart, kidney, liver, spleen, brown fat, and systemic circulation. Because of the striking effects of oxybate on behavior, most investigators initially limited their research efforts to studies on the central nervous system where oxybate is formed from GABA. The degradation of oxybate in the same tissue should be viewed as a mechanism to regulate its level, because its biosynthesis and catabolism pathways are closely linked.

Indirect evidence for the second biotransformation pathway was first provided by Doherty (1975) who injected [1-^{14}C]oxybate into the brain of rats and found that ^{14}C was incorporated into various amino acids in brain homogenates. Based on these results, it was postulated that brain tissue was capable of metabolizing oxybate to succinic acid via the formation of succinic semialdehyde as a first step. Similar results were observed in mice after intravenous injection of [^{14}C]oxybate (Mohler 1976). As well as demonstrating that oxybate readily crossed the blood-brain barrier, Mohler (1976) also demonstrated that radiolabeled oxybate disappeared from brain tissue quickly with a half-life of approximately 5 minutes and proposed the metabolic pathway for oxybate in brain tissue depicted in Figure 5.3 (lower panel).

Kaufman (1979, 1983, 1987, 1988a) subsequently isolated and characterized the 2 enzymes responsible for the interconversion between oxybate and succinic semialdehyde and subsequent conversion of succinic semialdehyde to succinic acid. An $NADP^+$-linked enzyme, termed GHB dehydrogenase, isolated from the cytosol of hamster liver and brain and purified 300-fold, catalyzes the interconversion between oxybate and succinic semialdehyde (Kaufman 1979, Kaufman 1987). GHB dehydrogenase is distinctly different from lactic dehydrogenase or alcohol dehydrogenase (Kaufman 1979). A second enzyme, hydroxyacid-oxoacid transhydrogenase is located in the mitochondria and is not dependent upon NAD^+ or $NADP^+$ (Kaufman 1988a, 1988b). This enzyme also catalyzes the conversion of oxybate to succinic semialdehyde in the presence of α-ketoglutarate. Succinic semialdehyde dehydrogenase is the enzyme system that catalyzes the biotransformation of succinic semialdehyde to succinic acid (Kaufman 1987). Finally, Gibson (1989) investigated the metabolism of oxybate in other isolated tissues, including the heart and kidney from rats. While the brain, liver, and kidney had the capability to metabolize oxybate, isolated heart tissue was lacking in this respect.

In summary, there is strong evidence for the metabolism of oxybate via 2 separate and distinct biotransformation pathways as depicted in Figure 5.3. The end product of both pathways is carbon dioxide. The succinic semialdehyde pathway plays an important role in the regulation of the endogenous GHB levels in the brain, liver, and kidney, while the β-oxidation pathway is invoked in patients with γ-hydroxybutyric aciduria. The β-oxidation pathway probably is also responsible for the first pass-metabolism of exogenous oral oxybate that results in an absolute bioavailability of <30% (Vree 1978).

5.1.2.4 Elimination

Clinically, plasma clearance (CL/F) is the most important pharmacokinetic parameter because it determines the patient's exposure to oxybate as represented by AUC_{inf}. For the 8 human pharmacokinetic studies sponsored by Orphan Medical, the CL/F term was calculated by taking the ratio between the dose administered and AUC_{inf}.[5]

For agents whose pharmacokinetics are dose independent, plasma clearance generally remains consistent across a wide range of doses. Because the pharmacokinetics of oxybate are dose dependent, plasma clearance decreased as the oral dose of sodium oxybate increased. At the lower end of the therapeutic dose range (4.5 g as 2 x 2.25 g doses given 4 hours apart), the mean oral plasma clearance for oxybate was 6.6 mL/min·kg (OMC-SXB-9). Doubling the dose to the maximum recommended dose (9 g as 2 x 4.5 g doses given 4 hours apart) decreased the mean oral plasma clearance to 3.6 mL/min·kg, representing a nearly 50% decrease compared to the 4.5 g dose. Others have made similar observations. Ferrara (1992) reported an approximate 33% decrease in plasma clearance as oral oxybate dose increased from 25 to 50 mg/kg, while Palatini (1993) showed a 50% decrease (from 14 mL/min·kg to 7 mL/min·kg) as the oral oxybate dose increased from 12.5 mg/kg to 50 mg/kg.

Theoretically, the terminal parts of the elimination curves for different doses of any agent that follows non-linear kinetics are parallel. Practically, the apparent elimination half-life for agents with non-linear pharmacokinetics is dependent on dose. This behavior often is due to limitations imposed by the LOQ of the assay and the wider spacing of the plasma samples, especially around the end of the blood-sampling period. The apparent elimination half-life of oxybate following a 9 g dose (2 x 4.5 g administered 4 hours apart) averaged 0.83 hour and was approximately 40% longer than the mean apparent elimination half-life following a 4.5 g dose (2 x 2.25 g) in the same subjects (OMC-SXB-9). Although a 40% increase might be considered substantial, it is not clinically relevant due to rapid elimination. There were only 2 published studies in which oxybate elimination half-life was evaluated at 2 or more dose levels. Although a similar prolongation in apparent elimination half-life was observed in one study (Ferrara 1992), the second study (Palatini 1993) did not show any difference because its sampling

[5]Note: steady-state area under the curve (AUC_{ss}) is not reported for Xyrem. Because of its short $T_{1/2}$ (<1 hour), steady state plasma oxybate concentration is never achieved based on nocturnal dosing of Xyrem, with the nightly dose divided into 2 equal portions, administered 2.5 to 4 hours apart.

schedule successfully documented the terminal parts of the elimination curves, which were parallel for all 3 doses used in the study.

5.1.2.5 Other Pharmacokinetic Considerations

5.1.2.5.1 Non-linear Pharmacokinetics

Oxybate shows non-linear pharmacokinetics. This was observed in Study OMC-SXB-9, which showed that the highest recommended therapeutic dose of Xyrem (9 g given as 2 x 4.5 g) resulted in an AUC_{inf} that was 3.75 times of the AUC_{inf} elicited by the recommended starting therapeutic dose (4.5 g given as 2 x 2.25 g). Non-linear kinetics were also reported by Ferrara (1992) who determined the mean dose-normalized AUC_{inf} was 46% higher in alcohol dependent patients after a single oral oxybate dose of 50 mg/kg than after 25 mg/kg.

5.1.2.5.2 Chronic Pharmacokinetics

Chronic dosing at therapeutic levels did not alter the pharmacokinetics of Xyrem in a clinically significant manner (OMC-SXB-10). Although treatment with Xyrem for 8 weeks resulted in statistically significant 13% increase in systemic exposure to oxybate based on AUC_{inf} and a 16% increase in peak concentration, these modest increases are not considered to be clinically significant. It was also concluded that chronic Xyrem treatment did not result in auto-induction (self-induction of metabolism).

5.1.2.5.3 Drug Interactions

In clinical studies, there was no evidence for clinically significant interactions between Xyrem and Ambien®, Vivactil®, and Provigil®, which represent three classes of drugs (hypnotics, antidepressants, and stimulants, respectively) commonly used in the treatment of narcoleptic symptoms (OMC-SXB-12, OMC-SXB-14, OMC-SXB-17). There was no indication that oxybate inhibits CYP isoenzymes (Covance Study No. 6627-129).

5.1.2.6 Pharmacokinetics in Special Populations

5.1.2.6.1 Sex-related Differences

There are no significant differences in the single dose pharmacokinetics of Xyrem between male and female healthy volunteers (OMC-SXB-8). Values for log-transformed AUC_{inf}, log transformed C_{max}, CL/F (per kg), $T_{1/2}$, percentage of dose excreted unchanged in urine, apparent renal clearance ($P>0.05$; unpaired t-test), and T_{max} ($P>0.05$; Wilcoxon rank sum test) were no different in male and female healthy volunteers.

5.1.2.6.2 Hepatic Dysfunction

The single dose pharmacokinetics of oxybate were investigated in 16 patients with biopsy-proven liver cirrhosis, 8 without ascites (Child's class A) and 8 with ascites

(Child's class C) (Ferrara 1996) (Table 5.1). Compared to healthy adult volunteers given the same dose in a previous study, the mean apparent oral clearance was markedly reduced in cirrhotic patients without and with ascites (by 51% and 55%, respectively). The apparent elimination half-life was also significantly longer in cirrhotic patients without ascites when compared to healthy subjects (32 vs 22 minutes). These results indicate that from a systemic exposure perspective, it is prudent to start Xyrem therapy in patients with liver dysfunction at the lower end of the therapeutic dosage range and dose escalate in small increments when medically indicated.

5.1.2.6.3 Alcohol-Dependent Patients

Ferrara (1992) investigated the pharmacokinetics of oxybate in 10 alcohol-dependent subjects after single and repeated oral doses (25 mg/kg every 12 hours for 7 days). Oxybate was rapidly absorbed and eliminated with T_{max} of 20-45 minutes and mean $T_{1/2}$ of 27 minutes. The multiple-dose regimen resulted in neither accumulation nor in time-dependent changes of its pharmacokinetics. Administration of a 50 mg/kg dose to 5 of the 10 subjects resulted in significant increases in dose-normalized AUC, $T_{1/2}$ and mean residence time. Oxybate administered at 12-hour intervals did not cause any serious side effects.

5.1.2.6.4 Pediatric Patients

Orphan Medical has not sponsored any pharmacokinetic studies with Xyrem in pediatric patients and is not requesting an approval for use in pediatric patients in this application.

5.1.2.6.5 Patients with Renal Dysfunction

On average, less than 5% of a Xyrem dose was excreted by kidney as unchanged oxybate (OMC-SXB-8, OMC-SXB-9 and OMC-SXB-11). Since the kidney does not play a significant role in the excretion of oxybate, to date no pharmacokinetic study in patients with renal dysfunction has been deemed medically necessary.

5.1.3 OVERALL CONCLUSIONS

Oxybate is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations generally occurring within 1 hour from dosing. Food can delay the absorption of oxybate and Xyrem should be ingested on an empty stomach to obtain maximum systemic exposure. It has low oral bioavailability (<30%), most likely due to first-pass metabolism. It does not bind to plasma proteins and readily crosses the placenta and the blood-brain barrier. Its apparent volume of distribution divided by fraction absorbed into the systemic circulation is 202-384 mL/kg.

Oxybate shows non-linear pharmacokinetics. The elimination of oxybate from the human body is dose-dependent and systemic exposure to oxybate increases disproportionately with the dose of Xyrem administered. The elimination half-life also increases as the dose is increased but does not result in any risk of excessive drug accumulation when given on a divided nocturnal administration schedule. Plasma

oxybate should be non-detectable or at negligible levels 8 hours after the ingestion of the highest recommended daily Xyrem (9.0 g). Oxybate is almost exclusively cleared by biotransformation, eventually being degraded to carbon dioxide via 2 distinct biotransformation pathways. Renal excretion plays an insignificant role in the elimination of oxybate and only 1 to 7% of a dose is recovered as unchanged drug in urine following oral administration.

In vitro studies with pooled human liver microsomes show that oxybate does not significantly inhibit or enhance the activities of human CYP isozymes nor are significant pharmacokinetic interactions observed between Xyrem and zolpidem (Ambien), protriptyline (Vivactil), or modafinil (Provigil) in healthy volunteers.

The kinetics of Xyrem are similar in males and females and are comparable between narcoleptic patients and healthy human subjects as well as alcohol dependent patients. Accumulation of oxybate has not been observed with chronic therapeutic dosing, presumably because of its short half-life. However, severe cirrhosis can cause significant modifications of oxybate disposition kinetics. As a safety precaution, the initial Xyrem dose in narcoleptic patients with significant liver dysfunction should not be higher than 4.5 g per day and the dosage regimen for Xyrem may need to be reduced in such patients.

SECTION 6
ABUSE LIABILITY AND OVERDOSAGE

6.0 ABUSE LIABILITY AND OVERDOSAGE

6.1 Abuse Liability

6.1.1 INTRODUCTION

GHB is abused by those who take substances for perceived non-medical benefits (Dyer 1991, Chin 1998, Friedman 1996) and by those who intentionally adulterate foods and beverages with the intent of committing criminal acts (Galloway 2000). Illicit GHB is abused primarily to produce purported euphoric and/or hallucinogenic states and as an alleged growth hormone releasing/muscle building agent.

6.1.2 GHB MISUSE AND ABUSE

Enactment of Federal Law 106-172 in February 2000 classified GHB as a Schedule I drug when used for purposes other than specified in FDA approved clinical trials. The consequent crack down on Internet and other illegal sources of GHB combined with mandatory harsher penalties that Schedule I mandates have caused a decrease in illicit GHB availability. Despite this, new incidents of GHB misuse and abuse are still being reported in the United States, Europe and Australia (World Health Organization 2000, Substance Abuse and Mental Health Services Administration (SAMSHA) 2000c). For one, while GHB availability has diminished, it may still be obtained through some illicit sources or by home manufacture using recipes available on the Internet using precursor compounds (GBL and sodium hydroxide). However, anecdotal case reports and epidemiological data indicate that, although there has been a decrease in the abuse of GHB itself, illicit use of the GHB precursor compounds, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) has dramatically increased (Ingels 2000, Winickoff 2000, Zvosec 2001, SAMHSA 2000b).

GHB continues to be misused as a “steroid replacement” and a sleep aid. In addition, there has been increased attention to the use of GHB as a “club drug” and as a drug used at “rave” parties (SAMHSA 2000b, Graeme 2000, Weir 2000). Government and public attention remains focused on GHB’s association with “date rape”. Reports of surreptitious GHB administration for purposes of sexual assault continue (LeBeau 2000, Schwartz 2000). The true incidence of GHB intoxication in cases of assault are difficult to determine due to lack of reliable and readily accessible testing but GHB has frequently been arbitrarily associated with any assault in which the victim was highly intoxicated and/or experienced amnesia. A study performed to determine the presence of various drugs in urine following sexual assault found ethanol to be the most prevalent "date-rape" associated drug, being present in almost 40% of the assault cases tested (ElSohly 1999). GHB was present in 4.1% of the cases, as compared to 8.2% for benzodiazepines, 8.2% for cocaine and 18.5% for marijuana, and was frequently present concurrent with one or more additional drugs. While the rapid metabolism of GHB may have underestimated the presence of GHB in these cases, this report suggests that GHB's involvement in drug-facilitated assault may be less common than is generally assumed. In addition, the cited study tested only for the presence of GHB without any

consideration to the role of the drug(s) in the assault or if they were administered unknowingly.

Few controlled studies in humans concerning aspects of GHB abuse potential have been published. In one controlled study of eight patients and in two anecdotal reports, the subjective effects of GHB have been compared to those of benzodiazepines, opiates, and alcohol (Friedman 1996, Galloway 1997, Rosen 1997). However, three of the eight subjects in the controlled study also reported GHB (30 mg/kg) to most closely resemble placebo, as it was unlike the other drugs (Rosen 1997).

Anecdotal reports continue to recount GHB administration resulting in positive subjective ratings (i.e., "feel good") with several accounts of GHB having a calming effect (Chin 1992, Galloway 2000).

Unlike some other drugs of abuse, GHB does not appear to produce strong physical or psychological dependence when administered under a therapeutic regimen (Moncini 2000, Beghe 2000). There continue to be instances of "GHB withdrawal" phenomena in case reports. An abstinence syndrome suggestive of physical dependence has been reported in patients following cessation of chronic high doses GHB (Galloway 2000, Hutto 2000, Miglani 2000, Price 2000, Dyer 2001). In all these cases, the patients had been consuming very frequently administered (i.e., every 3 hours or less), high-dose GHB for weeks to years. Withdrawal signs included insomnia, anxiety, mild diaphoresis and tremors. Some of the patients have also reported hallucinations (Craig 2000, Miglani 2000, Hutto 2000). The general health of these patients was normal with only one exhibiting hypertension and tachycardia (Craig 2000) and a second exhibiting moderate tachycardia (Hutto 2000). Signs associated with abstinence were alleviated by sedative drug administration (i.e., lorazepam, diazepam or chloral hydrate) with concurrent haloperidol administration in occasional cases. All patients' conditions resolved in 15 days or less. Review of the clinical trials underway in Europe for the treatment of opiate and alcohol addiction point to the therapeutic safety of GHB in a population at high risk for substance abuse. In a review of the various clinical trials, Beghé (2000) found that 3 to 10% of patients involved in various outpatient studies (N=732) assessing GHB treatment for ethanol dependence showed a tendency towards craving and dose escalation with only 1 account of a withdrawal syndrome requiring medical intervention following extreme dose escalation (Addolorato 1999a). When evaluated in a non-abusing patient population under therapeutic dosing conditions, there have been no reports of dose escalation, craving or withdrawal subsequent to cessation of treatment. This has been demonstrated in published reports (Broughton 1979, 1980, Scharf 1985, Mamelak 1986) as well as Orphan Medical clinical trials (OMC-GHB-3, OMC-SXB-6, OMC-SXB-7, OMC-SXB-21, Scharf trial). No evidence of dependence has been documented in any of the Orphan Medical narcolepsy clinical trials (OMC-GHB-2, OMC-GHB-3, OMC-SXB-6, OMC-SXB-7, OMC-SXB-21, Scharf Trial).

6.1.3 EXTENT OF THE PROBLEM OF GHB ABUSE

There are relatively few mentions of GHB in the Drug Abuse Warning Network (DAWN) reports (1992 to 2000) as compared to other sedative/hypnotics that are abused

(diazepam > 10,000 each year)(SAMHSA 2000b), but were significant enough to warrant Congressional scheduling of GHB in 2000. Although trending upwards, GHB abuse is still not listed separately in any U.S. database. The latest figures indicate no mentions of GHB in the 1999 Emergency Department Data from DAWN (SAMHSA 2000a) as drugs associated with fewer than 10 deaths per year are typically excluded. Data regarding GHB use was only made available in a special review because of the current focus by NIDA and other government agencies on the abuse of "club drugs". In March of 2000 the Drug Enforcement Administration reported documentation of over 5700 overdoses and law enforcement encounters with GHB-related substances (Federal Register, March 13, 2000, 13235-13238). However, the true incidence of GHB mentions are clouded by the co-mingling of GHB cases with those due to abuse of the two precursor compounds, gamma butyrolactone (GBL) and 1,4-butanediol (1,4-BD). Unfortunately, all mentions of GHB are grouped with those for its precursor chemicals, GBL and 1,4-BD under the heading of "GHB-like drugs". There are extensive data that these three compounds are not identical in quantitative and qualitative pharmacological characteristics.

GHB, GBL and 1,4-BD are all endogenous compounds. It is well documented that both GBL and 1,4-BD can be rapidly metabolized to GHB (oxybate) in the body following ingestion. GBL and 1,4-BD are significantly more lipid soluble than GHB. Thus, following oral ingestion both GBL and 1,4-BD are absorbed more rapidly than GHB and produce higher peak blood levels. As a result GBL and 1,4-BD are significantly more toxic compounds than GHB. Direct evidence of this important difference is shown by comparison of lethal doses in laboratory animals (LD50s). For example, the LD50 (mg/kg) in mice following the intraperitoneal administration of the three drugs is: GHB =3550, GBL =880, 1,4-BD =2180. Likewise, in rats orally, the LD50s are: GHB =9990, GBL =1800, 1,4-BD =1780. These data clearly indicate that GBL and 1,4-BD are 2 to 5 times more toxic than GHB in these species.

The true extent of abuse is also impaired by limited availability of analytical methods to verify the actual illicit substance consumed, the dose ingested or the levels of drug or metabolites in body fluids. For example, since illicit GHB has made been a Schedule I drug (March 13, 2000) and GBL became a listed chemical, much of what is being used illicitly as GHB is actually 1,4-BD. However, emergency room physicians must currently treat presumed GHB overdose or withdrawal patients symptomatically because drug identity, dose and drug plasma levels are unavailable. Furthermore, since GHB is an endogenous substance found in many tissues and body fluids and which actually increases postmortem, bioanalytical methods must be able to clearly differentiate between endogenous GHB and exogenous GHB or GHB analogues.

While mentions of these compounds increased significantly from 1994 to 1999, the actual increase in numbers is relatively small when compared to mentions for sedative hypnotics with known abuse potential. GHB accounted for less than 0.3% of all drug related emergency department (ED) visits. It must also be stated that drug "mentions" in the DAWN system do not imply that the substance was responsible for the ED admission nor whether the drug alone was involved in a case. Of the ED mentions of GHB in 1999, 71% were in combination with one or more drugs, with ethanol being present in over 50% of all GHB mentions. In addition to drugs of abuse which are

identified in the DAWN system, other commonly used drugs which always receive mentions include aspirin, ibuprofen, and fluoxetine (SAMHSA 1999, 2000a).

Additional information concerning GHB and precursor chemical abuse comes from reports by the NIDA Community Epidemiology Work Group (CEWG), a nationwide network of epidemiologists and drug abuse researchers that meet regularly to discuss emerging substance abuse problems. Evidence of localized GHB abuse began to be reported as early as 1995, identifying it as a new "club drug" (CEWG 1996). In each subsequent annual report of the CEWG, increasing attention has been paid to the problem of GHB abuse and more recently the abuse of its precursor chemicals, GBL and 1,4-BD (CEWG 2000b). The June 1999 full report (CEWG 1999), December 1999 advance report (CEWG 2000a) and June 2000 advance report (CEWG 2000b) all describe increasing nationwide abuse of GHB or its precursors in dance clubs and at raves as well as reporting some mortalities associated with this practice. However mention of GHB and its precursors was absent from the December 2000 advance report (CEWG 2001). Whether this reflects an improvement or stabilization in the levels of GHB-like drug abuse is unclear.

Other sources of information on the level of abuse of various drugs as yet provide little data on GHB. As of 2000, questions about GHB have been included in the nationwide "Monitoring the Future" survey of high school students conducted annually. However, the information will not be available until April 2001. Nor is there information available about rates of GHB abuse in reports of the National Household Survey on Drug Abuse as of the most recently reported results which contain the 1998 survey results (SAMHSA, 1999). Although survey respondents may have included GHB under one of the "other" drug categories, since the use of GHB is not queried specifically, it is impossible to know if the prevalence of abuse is below the threshold of about 0.1% of the population which can be detected in the Household Survey.

Deaths attributable to the abuse of GHB have been reported. There is considerable variability, however, in the numbers reported that appears to be dependent on the source. The annual Toxic Exposure Surveillance System review performed by the American Association of Poison Control Centers listed 10 deaths (< 20 total for 1995 through 1999) attributable to GHB or GHB-precursors in 1999 (Litovitz 2000). In two of these cases, GHB was not the primary drug involved. Of the eight cases which were attributed to GHB or GHB-precursor toxicity, only three were accompanied by GHB blood level determinations. The special report from DAWN (2000c) on "club drugs" lists medical examiner reports of GHB or GHB-precursor involvement in a total of 12 deaths from 1994 to 1998. No specific information was provided regarding method of diagnosis of GHB involvement. In contrast to the low level of mortality in these reports, the U.S. Drug Enforcement Administration (DEA 2000) reported that their staff have identified 65 GHB-related deaths since 1990 through aggressive case-finding when deaths have been brought to the attention of agency officials. As yet, no information about GHB tissue levels or method of drug analysis has been provided for these cases.

6.1.4 PRECLINICAL STUDIES RELEVANT TO ASSESSMENT OF ABUSE POTENTIAL OF GHB

Table 6.1 summarizes preclinical studies relevant to the assessment of the abuse potential of GHB.

6.1.4.1 Drug Discrimination

Drug discrimination studies in animals are considered to be predictive of subjective drug effects in humans (Schuster 1988). In addition, when the discriminative stimulus effects of drugs are compared to each other, classifications of drugs based on the results can be predictive of commonalities in cellular sites of action. In rats trained to discriminate IP GHB (200 mg/kg) from saline, none of the variety of different classes of drugs tested fully substituted for GHB (Winter 1981). Notably, GBL produced only partial substitution for GHB, indicating differences in the discriminative stimulus effects of the two compounds. Morphine, lysergic acid diethylamine (LSD), chlodiazepoxide, muscimol, baclofen, and 3-aminopropane sulfonic acid also produced, at best, partial substitution; *d*-amphetamine, apomorphine, and ethanol produced a very low partial substitution; barbital, phencyclidine and the phencyclidine-like compound N-allylnormetazocine, failed to support GHB-lever responding at any dose tested. The discriminative stimulus effects of GHB were not blocked by naloxone, bicucculine, pizotyline, phentolamine, or butaclamol (Winter 1981).

In rats trained to discriminate oral GHB (700 mg/kg or 300 mg/kg) from water, the GHB antagonist NCS-382 antagonized the discriminative stimulus of GHB at either training dose (Colombo 1995a), indicating a possible involvement in the GHB receptor mediating the discriminative stimulus effects of GHB. The $GABA_B$ antagonist, CGP 35348, on the other hand, had differential effects depending on the training dose of GHB. It completely blocked the discriminative stimulus effects of GHB in rats trained to discriminate 700 mg/kg but only partially blocked the effects in rats trained to discriminate 300 mg/kg (Colombo 1995b). Neither the phencyclidine-like drug dizocilpine nor the cannabinoid WIN 55,212-2 substituted for GHB at either training dose (Colombo 1995b). In rats trained to discriminate 300 mg/kg GHB, only one dose of ethanol (1 g/kg) fully substituted for GHB; higher and lower doses of ethanol produced primarily saline-lever responding (Colombo 1995c). Likewise, GHB substituted for ethanol at only one dose (300 mg/kg) and only in rats trained to discriminate a low dose (1.0 g/kg) of ethanol from water; GHB did not substitute in rats trained to discriminate a higher dose of ethanol (2.0 g/kg) (Colombo 1995c). In rats trained to discriminate intragastric GHB (700 mg/kg or 300 mg/kg) from water, baclofen fully substituted in both groups but was more potent in producing GHB-like effects in the high dose group (Lobina 1999).

Metcalf (1999) sought to continue the investigation of the interrelationship between the subjective effects of GHB and ethanol through the use of drug discrimination procedures. In the Metcalf study, rats were trained to discriminate either intragastric (IG) GHB (300 mg/kg) from saline, IG ethanol (1000 mg/kg) from saline, or IG combination of 150 mg/kg GHB and 500 mg/kg ethanol from saline. Subsequent testing for cross generalization found that GHB, at best, partially substituted for ethanol in the ethanol-

trained rats. Similarly, ethanol only partially substituted for GHB in the GHB-trained group. These results did not replicate Colombo's findings of cross generalization across a narrow dose range and were more similar to those obtained by Winter (1981). The results to date in rats suggest that GHB administration produces unique discriminative stimulus effects with some characteristics most similar to those of ethanol and some GABAmimetic drugs, particularly $GABA_B$ drugs, such as baclofen, which are not abused. In addition there is some evidence that different cross substitution patterns can occur at different doses of GHB.

Testing of GHB in both heroin- and phencyclidine-trained rats also failed to demonstrate any substitution with GHB (Beardsley 1996). The results to date suggest that GHB administration produces unique discriminative stimulus effects with some characteristics similar to those of ethanol, morphine and some GABAmimetic drugs, and that the characteristics of these effects are not equivalent across different doses of GHB. Additional studies of the discriminative stimulus effects of GHB have been done as part of the College on Problems of Drug Dependence abuse liability testing program. These results are discussed in section 6.1.4.4.

6.1.4.2 Tolerance and Dependence

Data are available from two additional preclinical studies which do not speak directly to the abuse potential of GHB but do support its clinical use for treating ethanol and opiate withdrawal in humans. Gessa and colleagues (2000) demonstrated the ability of GHB to alleviate a constellation of withdrawal signs in ethanol-dependent rats, supporting previous studies suggestive of a possible cross tolerance/dependence between GHB and ethanol (Fadda 1989, Colombo 1995d). Typically, true cross-tolerance/dependence is seen in drugs with common neural sites of action. Ethanol and GHB have not been shown to have overlapping sites of cellular action. Ethanol has activity as a $GABA_A$ receptor agonist (Ticku 1989) and as an NMDA antagonist (Gonzales 1990). GHB has no activity at the $GABA_A$ receptor and only very low affinity for the NMDA receptor ion channel (Gessa 1993). These studies suggests that the apparent cross-dependence between GHB and alcohol may be reflective of GHB's ability to selectively attenuate some of the signs and symptoms of alcohol withdrawal (Agabio 1998), much as clonidine does for opioid withdrawal (Rosen 1996). In a similar study in morphine-dependent rhesus monkeys, lower, but not higher, doses of GHB were able to significantly attenuate morphine withdrawal signs (Aceto 2000). Again, there are no indications that GHB has any direct activity at opiate receptors which could explain this effect (Feigenbaum 1996b). It is believed instead that this effect is due to GHB-stimulated modulation of endogenous opioid release (Gobaille 1994).

6.1.4.3 Drug Self-Administration and Related Studies

The behavioral effects of GHB have also been examined in animal models said to be predictive of the reinforcing properties of the drug. Conditioned place preference (CPP) relies on pairing of drug administration with a specific environment, and subsequently testing for preference for that environment over one paired with the nondrug condition. In a study by Martellotta and colleagues (1997), GHB was shown to induce CPP. Under

similar testing conditions, other sedative hypnotics, such as diazepam, have also been shown to induce CPP. Typically, drugs with known strong reinforcing effects, such as cocaine and opiates, will produce CPP after only 2 to 3 drug exposures. In the study with GHB, a minimum of 6 drug exposures were required to produce CPP, suggesting a weaker effect compared to highly abused drugs like cocaine.

The pharmacokinetic profile of GHB in rats shows a very rapid metabolism and elimination of GHB with virtually no GHB remaining three hours after i.v. administration (Lettieri 1979). This should make GHB comparable to the shorter acting barbiturates and benzodiazepines that are the most reliably self-administered. A series of studies has been done in which rats were shown to drink GHB solutions. This occurred more readily in rats selectively bred to self-administer alcohol (Colombo 1995a, Colombo 1998b). In this series of studies, rats were given forced access to GHB for a period of a couple weeks and then given a two-bottle choice between a single concentration of GHB and water. On about one-half the days, animals drank more of the GHB solution than they did water. On the other one-half of the days, they drank more water than GHB. Such results would also be expected if there were no preference for the solutions, or a side preference (the bottles were switched from side to side). Because of uncertainties about the interpretation of these drinking studies, it is difficult to unambiguously conclude that they provide evidence for GHB self-administration. There has been a report of i.v. self-administration of GHB in mice, but only in abstract form (Martellotta 1996).

A study of GHB self-administration has been carried out in rhesus monkeys using a substitution procedure widely used for abuse potential assessment (Beardsley 1996). In this study, monkeys experienced in PCP self-administration were tested with a wide range of doses of GHB. The results were negative. In only 1 of 18 tests was the rate of GHB self-infusion greater than for vehicle, and even in this case the rate of responding was very much lower than were obtained with PCP. It is clear that behaviorally-relevant doses of GHB were tested since some observable sedation was seen in the monkeys. A CPDD study of GHB self-administration in barbiturate experienced monkeys is reviewed in section 6.1.4.4 below.

GHB has also been examined for its ability to attenuate self-administration of other drugs of abuse. Non-hypnotic doses of GHB and/or GBL have been observed to reduce ethanol intake in rats and humans as well as decrease cocaine self-administration in rats (Fadda 1983, Biggio 1992, Gallimberti 1992, Addolorato 1996, Martellotta 1998). In humans, this effect was associated with a decrease in craving (Biggio 1992, Gallimberti 1992). There are various possible explanations for these apparently therapeutic effects of GHB. One reason is that GHB may be mimicking the effect of the abused drug. For example, because of the similarities of the behavioral effects of ethanol and GHB, ethanol consumption may be diminished due to a substitution effect. Alternatively, GHB may truly alter the reinforcing efficacy of some drugs of abuse, either by direct receptor interaction or by indirect CNS effects. This is certainly a possibility for the effects on both alcohol and cocaine self-administration given GHB's ability to diminish dopamine neurotransmission (see section 2.1.1.3). A third possibility is that the decrease in drug self-administration is a nonspecific effect of GHB. In the operant studies (Biggio 1992,

Martellotta 1998), no control tests were conducted to determine if GHB could have decreased responding for any reinforcer (e.g. food) because of its depressant effects.

6.1.4.4 College on Problems of Drug Dependence Testing Program

As a service to industry and the government, the College on Problems of Drug Dependence (CPDD) sponsors an animal testing program for assessing drug abuse potential. GHB has been extensively tested under this program. Most of the tests were performed under the Stimulant/Depressant Program, but one study was done under the Opiate Testing Program. GHB was submitted to the testing facilities as CPDD 0044 or NIH 10947. The CPDD testing program includes a battery of validated animal tests designed to provide information relevant to regulatory decisions regarding drug abuse potential. The general approach used by the CPDD testing program reflects the recommendations of many expert groups who have provided guidelines for abuse liability assessment, including the World Health Organization Expert Committee on Drug Dependence (World Health Organization 1978) and the Committee on Problems of Drug Dependence (CPDD) (Committee on Problems of Drug Dependence 1977, Brady 1984, May 1989). The reports of the results of testing GHB by the CPDD Drug Evaluation Program can be found in their annual reports to the College (Jacobson 1997, Jacobson 1998, Jacobson, In Press). In addition, most of the data were assembled for a scientific journal publication (Woolverton 1999).

Drug Discrimination

The discriminative stimulus effects of GHB were compared to those of *d*-amphetamine and pentobarbital in rhesus monkeys using standard 2-lever operant conditioning procedure utilizing food reinforcement. For these studies, monkeys were trained using gavage via a nasogastric tube. GHB tests were conducted using the same route up to doses as high as 170 mg/kg. In *d*-amphetamine-trained monkeys (N=4), GHB produced a maximum mean of 50% drug lever responding. This partial substitution for *d*-amphetamine was not dose-related nor were any response rate decreasing effects obtained. GHB completely failed to substitute for pentobarbital (N=3). There was no pentobarbital-lever responding in any subject at any dose. There was a small increase in rates of responding, suggesting that a behaviorally-effective dose range was tested.

In a separate laboratory, the discriminative stimulus effects of GHB were compared to those of triazolam and flumazenil. Rhesus monkeys were used for both studies. A 2-lever operant conditioning procedure was used with behavior maintained by mild electric shock avoidance. For the triazolam comparison, monkeys (N=3) were trained to discriminate s.c. injections of triazolam and saline. GHB tests also utilized the s.c. route. Only one of the three monkeys showed any evidence for triazolam-like effects of GHB. In that one monkey, 81% and 40% triazolam-lever responding was obtained at doses of 3.2 and 10 mg/kg respectively. A higher dose of GHB did not substitute for triazolam. Some response rate decreasing effects were obtained, suggesting that a behaviorally-active dose range of GHB was tested. The rationale for the flumazenil discrimination study is as follows. These monkeys (N=2) were given daily oral doses of diazepam resulting in diazepam dependence. Thus, flumazenil injections would precipitate a mild

withdrawal that was discriminated from saline injections. GHB did not substitute for flumazenil. These results can help rule out the possibility that GHB is a GABA antagonist.

Drug Self-Administration

A self-administration study was performed with GBL using a standard substitution procedure in rhesus monkeys. These procedures are very commonly used for abuse potential assessment. The monkeys (N=3) were trained to lever-press under a fixed-ratio 10 schedule to obtain intravenous infusions of methohexital during two daily 2-hour sessions. In addition, sessions were frequently conducted in which only saline deliveries were available. Animals typically obtained about 5-10 times more infusions of methohexital than saline. Various doses of GHB were tested once or twice in single sessions in each subject. The number of infusions of GHB that were self-administered was approximately the same as the number of infusions of saline and considerably less than the number of infusions of methohexital. In all tests except two, the number of GHB infusions was not significantly different from the mean number of saline infusions. In two tests, rates of GHB self-administration exceeded those for saline. This occurred in two different monkeys at two different doses, and even in these cases the infusion rates were quite low and did not approach those seen with methohexital in these monkeys. It is also possible that these 2 out of 14 tests with marginally higher rates than on saline tests simply reflect normal variation in day to day response rates under saline availability and thus would be considered false positives. The authors of the study concluded that GHB was, at most, only a weak positive reinforcer.

Interactions with Morphine

A study was done to investigate whether GHB would alter the analgesic effects of morphine or the expression of morphine tolerance (Jacobson, In Press). These studies were done using a mouse tail flick procedure. In the first study, various doses of GHB were tested in combination with doses of morphine that produced about 25% maximal analgesia when given alone. GHB did not produce appreciable analgesia at any dose, but it dose-dependently enhanced morphine analgesia. In mice made tolerant to morphine analgesia, GHB in combination with morphine restored some of morphine's analgesic effects. These studies are not directly related to abuse potential assessment, but do speak to the safety of GHB in combination with opiates and also could suggest additional therapeutic uses.

The CPDD testing program evaluated the abuse potential of GHB using drug discrimination and drug self-administration procedures in rhesus monkeys. These tests show a lack of pharmacological equivalence between GHB and pentobarbital, triazolam and d-amphetamine, supporting the view that GHB has a unique profile of psychoactive effects. Little evidence was obtained for self-administration of GHB, although there was a suggestion of weak reinforcing effects in some subjects. The scientists associated with the testing program concluded that the profile of effects obtained "suggests that GHB has, at most, low potential for abuse" (Woolverton 1999).

6.1.4.5 Conclusions

Based on preclinical studies alone, there is not compelling evidence that GHB represents a significant drug abuse hazard. In the first place, GHB is a natural constituent of the human body. Although high doses of exogenously administered GHB can reasonably be expected to produce effects that would not occur under normal physiological conditions, the difference from normal is likely to be one of degree not a qualitative difference. The idea that a person could be severely dependent on some aspects of one's own physiology is difficult to conceptualize. Secondly, GHB is not pharmacologically equivalent to any existing controlled substances. Although it shares some effects with abused depressant drugs, clear differences from these drugs can also be shown. GHB appears to have a unique cellular site of action in the brain, its own receptor, that is not a receptor for any other drugs except various GHB analogs, an antagonist and several benzamide neuroleptics. GHB does not interact with known sites of action of any abused drug, including any known modulatory sites on the $GABA_A$ receptor. The preclinical pharmacological profile of GHB also differs from classical depressant drugs. Although it can produce depressant effects, it also has excitatory effects at high doses and can be a convulsant. There is some speculation that the sedation seen in some animals with GHB may actually reflect a type of absence seizure.

Self-administration studies of GHB fail to show evidence for strong reinforcing effects. Two studies were performed in rhesus monkeys using a substitution procedure that has been extensively validated for use in abuse potential prediction. One of these was done as part of the CPDD testing program. GHB had, at most, weak reinforcing effects in these studies. Rodent studies with GHB have been inconclusive. There is one study showing a conditioned place preference with GHB, but this procedure has only rarely been used in abuse potential assessment. Both oral and i.v. self-administration has been shown in rodents, but results were variable and difficult to interpret conclusively as reflecting centrally-mediated reinforcing effects.

Repeated administration of GHB can result in tolerance development, although there is some evidence that it is more difficult to produce tolerance with GHB than with ethanol. Many drugs produce tolerance, so this fact alone has little relationship to abuse potential. There are studies showing cross-tolerance with ethanol. The significance of this for abuse is unclear, although it could support a conclusion that GHB and alcohol share some common mechanisms of action. On the other hand, cross tolerance of GHB with baclofen and muscimol have also been reported. There have been no reports of physical dependence development with repeated GHB administration in animals. It could be predicted that it would be difficult to produce primary physical dependence with GHB because its short duration of action would require many multiple daily administrations to maintain elevated levels in the body. There are a few studies showing that GHB can attenuate withdrawal signs in animals made dependent on ethanol. This may be due to a true cross-dependence with ethanol or to a physiological attenuation of specific withdrawal signs. Taken together, preclinical studies of tolerance and dependence could not be used to support a finding that GHB has a high physical dependence potential.

6.1.5 TABULAR SUMMARIES OF PRECLINICAL STUDIES RELEVANT TO ABUSE POTENTIAL ASSESSMENT

Table 6.1. Studies Pertaining to Abuse Liability Assessment of GHB in Animals

ANIMAL						GHB ADMINISTRATION			RESULTS	REFERENCE
Species	Strain	No.	Sex	Age	Weight (g)	Route	Dose (mg/kg)	Frequency/ Duration		
Mouse	CD-1	NA	M	NA	25-28	IV	0.01-0.05 per inject-ion	Determined by mouse	GHB was self-administered at higher rates than vehicle; antagonized by NCS 382	Martellotta 1998 (reviewed in Fattore 2000)
Rat	Sardinian ethanol preferring (SP)	6	NA	NA	NA	PO	300	Twice a day for 5 days	GHB suppressed ethanol consumption	Fadda 1989 (Biggio 1992)
Rat	Wistar	20	M	4 months	400-500	PO	1% (w/v)	Sole fluid for 14 days, then frequency determined by rat	After a 14-day period in which GHB is sole fluid available, GHB and water are self-administered at about the same frequency	Colombo 1995c
Rat	SP & SnP	9-12/group	M	3-4 months	Mean: 400-500	PO	1% (w/v)	Sole fluid for 14 days, then frequency determined by rat	After a 14-day period in which GHB is sole fluid available, GHB was self-administered with higher frequency in SP (alcohol-preferring) rats.	Colombo 1998c
Rat	Long-Evans	NA	M	NA	300-350	IG	175-350	daily	GHB attenuated cocaine self-administration	Martellotta 1996 (reviewed in Fattore 2000)
Rat	Long Evans	5-6/group	M	12 weeks at start of training	80% of free feeding weights	PO	300	daily	GHB could be trained as a discriminative stimulus. One dose of ethanol (1.0 g/kg) substituted for GHB, higher and lower doses did not. In ethanol trained rats, GHB substituted for ethanol at one dose (300 mg/kg) in rats trained to discriminate 1.0 g/kg ethanol, but not 2.0 g/kg ethanol.	Colombo 1995a
Rat	NA	NA	NA	NA	NA	IG	300 or 700	daily	GHB could be trained as a discriminative stimulus at either dose; dizocilpine and WIN 55 212-2 did not substitute for GHB at either training dose. Baclofen blocked the discriminative stimulus of the high, but not the low training dose.	Lobina 1999 (Colombo 1998a [abstract])

Table 6.1. Studies Pertaining to Abuse Liability Assessment of GHB in Animals (continued)

ANIMAL						GHB ADMINISTRATION			RESULTS	REFERENCE
Species	Strain	No.	Sex	Age	Weight (g)	Route	Dose (mg/kg)	Frequency/ Duration		
Rat	Long Evans	10/group	M	Adult	90% of free feeding weights	IG	300	daily	GHB could be trained as a discriminative stimulus. Ethanol produced partial substitution for GHB. In rats ethanol trained to discriminate 1.0 g/kg ethanol, GHB produced partial substitution.	Metcalf 1999
Rat	Sprague-Dawley	8-10/group	M	Adult	180-200	IG	87.5-350	daily	GHB induced conditioned place preference	Martellotta 1997 (reviewed in Fattore 2000)
Rat	Sprague-Dawley	NA	M	3 months at start	250-300	IG	400-1000	daily	Tolerance developed to the motor-impairing effects of GHB and ethanol.	Colombo 1995d
Rat	Sprague-Dawley	16/group	M	NA	200-220	IP	250-1000	Acute	GHB decreased signs of ethanol withdrawal in ethanol-dependent rats	Fadda 1989
Rat	Wistar	7	NA	NA	NA	IP	1000	Acute	GHB alleviated signs of withdrawal in ethanol-dependent rats.	Gessa 2000
Rat	CFN	14	F	8 weeks at start of training	NA	IP	200	daily	GHB could be trained as a discriminative stimulus; other drugs did not fully substitute for GHB, including morphine, LSD, chlodiazepoxide, competitive GABA agonists, d-amphetamine, ethanol, barbital, PCP, PCP-like compounds.	Winter 1981
Rat	Sprague-Dawley	4	M	Adult	85% of free feeding weights	IP	10-300	1 dose every 2-4 days	GHB did not substitute for PCP in rats trained to discriminate PCP from saline	Beardsley 1996
Rat	Sprague-Dawley	5	M	Adult	85% of free feeding weights	IP	10-300	1 dose every 2-4 days	GHB did not substitute for heroin in rats trained to discriminate heroin from saline	Beardsley 1996
Monkey	Rhesus *Macaca mulatta*	7	NA	adult	6.4-12.2 kg	IG	1-170	Acute	GHB did not engender pentobarbital-lever responding in 3/3 monkeys trained to discriminate pentobarbital from saline. GHB engendered a maximum of 50% amphetamine-lever responding in ¾ monkeys trained to discriminate amphetamine from saline.	Woolverton 1999 (Jacobson 1997)

Table 6.1. Studies Pertaining to Abuse Liability Assessment of GHB in Animals (continued)

ANIMAL						GHB ADMINISTRATION			RESULTS	REFERENCE
Species	Strain	No.	Sex	Age	Weight (g)	Route	Dose (mg/kg)	Frequency/ Duration		
Monkey	Rhesus	4	1F/3M	Adult	6.4-11.4 kg	IV	3-7.5 per infusion	Determined by monkey 4-day test	GHB did not maintain responding in monkeys that self-administer PCP	Beardsley 1996
Monkey	Rhesus *Macaca mulatta*	4	NA	NA	8-12 kg	IV	1-10/ infusion	Acute	GHB maintained responding only marginally above that for saline in monkeys that self-administer methohexital	Woolverton 1999 (Jacobson 1997)
Monkey	Rhesus *Macaca mulatta*	5	NA	3 adult 2 juv-enile	3-9 kg	SC	1-178	Acute	GHB does not have flumazenil or triazolam-like discriminative stimulus effects and does not antagonize the discriminative stimulus effects of these benzodiazepines	Woolverton 1999 (Jacobson 1998)
Monkey	Rhesus *Macaca mulatta*	3+	M/F	adult	2.5-7.5	SC	7.5-240	Acute	Lower doses of GHB (7.5, 30) alleviated signs of withdrawal in morphine-dependent monkeys.	Aceto 2000

6.2 Overdosage

The purported rationales for abuse of GHB include its use by body builders as a steroid replacement, as a diet aid, to treat insomnia, and as a euphoria-inducing agent and aphrodisiac (Galloway 2000). More recently, some individuals have turned to GHB in order to combat depression. The latter most likely reflects the influence of the Internet where GHB has been promulgated to be a "natural" antidepressant (http://heelspurs.com/cure.html, http://www.dog.net.uk/claude/ghb-1.html).

In evaluating the anecdotal reports of GHB overdose, identification of the ingested GHB dose and its relationship to the users clinical condition continues to be complicated by three important factors: (1) The drug is usually obtained via clandestine manufacture, including being homemade, making the actual dose ingested unknown; (2) Toxicity due to precursor chemicals is often erroneously included in the case reports as due to GHB based on clinical interpretation; (3) Reports frequently involve coadministration of other drugs of abuse, especially alcohol.

As GHB use has decreased, the incidence of illicit use of its precursor chemicals appears to be increasing. This illicit use of GHB interchangeably with its precursor chemicals, GBL and 1,4-BD, may contribute to variable dosing and consequently to acute toxicity (Ingels 2000, Winickoff 2000, Zvosec 2001). Although these precursor chemicals are metabolically converted in the body to GHB, there are major differences in their kinetic time courses and distribution that can alter pharmacodynamic effects. For one thing, neither GBL nor 1,4-BD show appreciable binding at the GHB-receptor, which has been shown to be primarily responsible for many of GHB's clinical and behavioral effects (Feigenbaum 1996a, Snead 2000). GBL is more rapidly absorbed and is lipid soluble in comparison to oxybate, which is water soluble (Lettieri 1978, Arena 1980). This difference alone will produce significant kinetic and distributional differences. In addition, GBL failed to fully substitute for GHB in preclinical discrimination studies (Winter 1981) and has been noted to have stronger GABAergic characteristics than GHB (Feigenbaum 1996a) suggesting qualitative as well as quantitative differences may exist between the two compounds. As well as having a low level of direct activity as an alcohol (Poldrugo 1984), 1,4-BD is converted to GHB *in vivo* by sequential alcohol dehydrogenase and aldehyde dehydrogenase metabolism (Maitre 1997). Competitive inhibition of alcohol dehydrogenase conversion of 1,4-butanediol to GHB by ethanol has been demonstrated (Poldrugo 1984, 1986). Concurrent ethanol and GHB administration has also been shown to alter the time course of ethanol and 1,4-BD metabolism through competition for the same enzyme in rats (Poldrugo 1985). The clinical impact of these interactions in acute users of 1,4-butanediol/ethanol combinations has yet to be fully investigated but initial studies suggest a prolonged intoxication and/or enhanced toxicity (Shannon 2000).

These pharmacological differences between GHB and its precursor chemicals almost certainly contribute to inexact dosing and subsequent risk of acute toxicity. Sporadic accounts of GHB-related acute toxicity requiring medical attention continue to be reported (O'Connell 2000, Ingels 2000, Yates 2000). Over half of the toxicity cases have been associated with co-ingestion of another drug (Centers for Disease Control 1997,

Chin 1998, Galloway 2000). In the majority of the cases reported, GHB was the presumed cause of the adverse reactions based on the description of the incident, time of onset, etc. (Galloway 1997, Chin 1998, Ingels 2000). Because laboratory tests for GHB are not generally available to clinicians, only rarely have actual blood/urine levels of GHB measured (Dyer 1994, Li 1998b). In some cases, the presence of GHB was noted but actual levels were not provided (O'Connell 2000). This continues to make evaluation of the true risk associated with GHB use difficult, especially when considering that the majority of GHB toxicity cases resulting in hospitalization involved the co-ingestion of alcohol or another drug. More and more frequently, acute toxicities are associated with the consumption of one of the precursor chemicals and not GHB itself (Ingels 2000, Winickoff 2000, Zvosec 2001).

The recommended course of treatment continues to be general symptomatic and supportive care with primary attention to airway protection (Galloway 2000, Graeme 2000) particularly in consideration of the risk of gastric aspiration. As yet, no reversing agent for GHB is available. There is some evidence that physostigmine may be efficacious in rapidly reversing the sedation induced by GHB (Henderson 1976, Yates 2000). This recommendation remains controversial as many concerns have been raised regarding potential toxicity issues with physostigmine use (Mullins 2000), including bradycardia or asystole (Pentel 1980) and seizure induction (Newton 1975). At present, the principles of management remain supportive care with particular attention to maintenance of the airway and blood oxygen levels. Additional attention should be directed toward the institution of laboratory analysis of GHB levels in hospitals in order to more rationally interpret dose response, clinical presentation and patient outcome. Overall, based on the current and previous accounts of overdose cases, prognosis is good for patients receiving medical attention (Li 1998b, Chin 1998, Galloway 2000, O'Connell 2000, Ingels 2000). Mortality was usually associated with unattended individuals who were found already deceased rather than associated with death in the emergency department (Winickoff 2000, Graeme 2000).

SECTION 7
SCHEDULING

7.0 SCHEDULING

7.1 Introduction

The Controlled Substances Act (CSA), Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, is the legal foundation of the government's fight against the abuse of drugs and other substances. The CSA primarily impacts the DEA but the FDA has been charged with the scientific component of this act. The FDA has developed an approach evaluating specific criteria relating to abuse/dependence that forms the basis for recommendations to the DEA on behalf of the Secretary of Health and Human Services (HHS).

The CSA places all substances that are regulated under existing federal law into one of five schedules. This placement is based upon the substance's medicinal use, potential for causing physical harm, and potential for abuse or addiction.

- **Schedule I** is reserved for drugs which have any potential for abuse, that have no recognized medical use or there is a lack of accepted safety under medical supervision. Until FDA approval, any drug scheduled must be placed in Schedule I regardless of whether following FDA approval it is a Schedule II or V entity.
- **Schedule II** is reserved for drugs which have a high potential for abuse, has a currently accepted medical use in treatment in the US or a currently accepted medical use with severe restrictions and potential abuse of the drug may lead to severe psychological or physical dependence.
- **Schedule III** is for drugs, which have a potential for abuse less than the drugs in schedules I and II, have a currently accepted medical use in treatment in the US and abuse of the drug may lead to moderate or low physical dependence or high psychological dependence.
- **Schedule IV** is for drugs, which have a low potential for abuse relative to the drugs in schedule III, have a currently accepted medical use in treatment in the US, and abuse of the drug may lead to limited physical dependence or psychological dependence relative to the drugs in schedule III.
- **Schedule V** is for a drug which has a low potential for abuse relative to the drugs in schedule IV, has a currently accepted medical use in treatment in the US and the abuse of the drug may lead to limited physical dependence or psychological dependence relative to the drugs in schedule IV. This is the classification used for medications with the least potential for physical harm.

When a petition to change the scheduling of a drug is received by DEA, the agency begins its assessment of the drug. DEA may also begin an assessment of a drug at any time based upon information received from law enforcement laboratories, state and local law enforcement and regulatory agencies, or other sources of information.

Once necessary data has been collected, the DEA Administrator requests from HHS a scientific and medical evaluation and a recommendation as to whether the drug should be controlled or removed from control. This request is sent to the Assistant Secretary of the HHS. The HHS solicits information from the Commissioner of the FDA, evaluations

and recommendations from the National Institute on Drug Abuse (NIDA), and on occasion, from the scientific and medical community at large. The Assistant Secretary compiles the information and transmits back to the DEA a medical and scientific evaluation regarding the drug, a recommendation as to whether the drug should be controlled, and in what schedule it should be placed.

This formal evaluation and rule-making process may take a year or more to complete. However, should the Attorney General deem a drug an imminent hazard to public health, that office's emergency powers may be used to add the drug to the Schedule I list of banned substances.

While the scheduling of a drug through the formal rule-making process is most common, the US Congress has legislatively scheduled several drugs when it felt necessary. Some of the drugs legislatively scheduled by Congress are:

Anabolic Steroids	C3 (1990)
Methaqualone	C1 (1984)
Pipradol	C1 (1978)

7.2 The Scheduling of GHB

The scheduling of GHB was first considered in the mid-1990s after data from local law enforcement, Drug Abuse Warning Network (DAWN) and Poison Control Centers showed it to be an increasing drug of abuse. It was also beginning to appear as a drug utilized to facilitate sexual assault. The form used was manufactured GHB or "homemade" GHB. The expansion of the Internet spawned numerous e-commerce sites selling kits, with which to make GHB, for as little as $35.

The Attorney General determined she was unable to use her emergency authority to schedule GHB as a schedule I agent because an active IND for a pharmaceutical formulation of GHB existed which constituted "valid medical use".

Consequently, DEA took steps to begin the administrative scheduling of GHB. In September 1997, DEA forwarded its request to HHS and requested a scientific and medical evaluation and a scheduling recommendation. The FDA's Office of Health Affairs and NIDA undertook that assignment.

In July 1998, the Crime Subcommittee of the House Judiciary Committee, chaired by Rep. Bill McCollum, held a hearing at the request of Rep. Sheila Jackson Lee to consider her proposal to schedule GHB as a Schedule I drug. The Hillory J. Farias Date Rape Prevention Act was initiated by Rep. Jackson Lee following the apparent GHB-related death of Hillory Farias, a LaPorte, Texas high school senior. Most committee members expressed a desire to somehow distinguish the illicit forms of GHB from the pharmaceutical formulation being studied for the treatment of cataplexy.

Rep. Jackson Lee's proposal was re-introduced in January 1999. That month, 15-year-old Samantha Reid died at a Michigan emergency room after drinking a soda spiked with

either clandestinely manufactured GHB or GBL. As a result of that incident, Michigan Congressmen Fred Upton and Bart Stupak sponsored separate bills to schedule GHB. The House Subcommittee on Oversight and Investigation considered those bills at a March 1999 public hearing.

FDA informed members that it was still conducting its scientific and medical evaluation with NIDA, which would result in their scheduling recommendation for GHB.

> "FDA would agree that there is a critical need to protect the public health from the dangers posed by drugs and substances of abuse," the Agency's spokesperson testified. "At the same time, we have to recognize that many drugs that have the potential for abuse may also be medically beneficial, and a large segment of the population might benefit from the optimization of drug development. These interests sometimes create tension in this scheduling process. In FDA's dual role as the evaluator of products that promote public health and the evaluator of substances that present a danger to the public, we will use the best available scientific data to make the speediest and best decisions".

In May 1999, the Attorney General formally asked Congress to use its legislative authority to schedule GHB. Within days of that request, HHS provided DEA with the medical and scientific analysis of GHB and its recommendation regarding the scheduling of GHB. The analysis gave particular notice to the new forms of GHB being abused by rave partygoers as a euphoric when mixed with alcohol, by body builders as a muscle-enhancer and by sexual predators to facilitate sexual assault.

During the approximately 20 months that FDA and NIDA conducted their medical and scientific evaluation, the sources of GHB abuse changed rapidly. Aggressive moves by FDA, DEA and state authorities had shut down numerous GHB Internet sites. But clandestine manufacturers and home-brewers of GHB discovered they didn't have to compound GHB. Instead, they marketed and used certain legal and inexpensive industrial chemicals for their GHB effect. Put simply, they relied on a person's body to naturally convert ingested industrial solutions into GHB.

GBL was apparently the first industrial solvent ingested for its GHB effect. Abuse of GBL as a GHB analogue accelerated in 1998. In January 1999, FDA asked dietary supplement companies to recall all products containing GBL. At that time, GBL products had been associated with reports of at least 55 adverse health effects, including one death. GBL became a list I chemical in 1999 and dietary supplement makers and drug dealers were fast to market a new GHB analogue using another easily available and inexpensive industrial solvent 1,4 BD. Like GBL, 1,4 BD converts to GHB following ingestion. In May 1999, FDA warned consumers to stop using dietary supplement products containing 1,4 BD.

7.3 The HHS - FDA - NIDA Recommendation

In May 1999, the Secretary for Health and Surgeon General at HHS recommended that GHB be scheduled based on its different forms, taking into consideration both the

legitimate medical use and the illicit use. It recommended that illicit forms of GHB be placed in Schedule I. HHS also recommended that authorized formulations of GHB be listed in Schedule III.

The HHS recommendation was made as a result of an eight-factor analysis, which was conducted as stipulated by the Controlled Substances Act. When evaluating the control of any drug, the following factors are considered:

(1) Its actual or relative potential for abuse.
(2) Scientific evidence of its pharmacological effect, if known.
(3) The state of current scientific knowledge regarding the drug or other substance.
(4) Its history or current pattern of abuse.
(5) The scope, duration, and significance of abuse.
(6) What, if any, risk there is to the public health.
(7) Its psychic or physiological dependence liability.
(8) Whether the substance is an immediate precursor of a substance already controlled under this title.

After evaluating the eight factors, the HHS must make a scheduling recommendation based on the substance's relative potential for abuse, its accepted medical use and its capacity for producing physical and psychological dependence.

Under the Controlled Substances Act, substances in Schedule I have a high potential for abuse and no accepted medical use. Substances in Schedule II have a high potential for abuse but do have an accepted medical use. Substances in Schedules III-V have an accepted medical use and a relatively lower potential for abuse.

HHS concluded that illicit forms of GHB - clandestinely manufactured GHB, homebrewed GHB and industrial chemicals used as GHB - have a high potential for abuse. It concluded that illicit forms of GHB have no accepted medical use and, in fact, are unsafe for use under medical supervision. Accordingly, HHS advised that illicit forms of GHB be controlled as Schedule I drugs.

Mindful of the growing list of legal industrial chemicals being ingested for their GHB effect, as well as the ease of home brewing GHB, HHS concluded that authorized investigational formulations of GHB (Xyrem) were unlikely to be sources of abuse. Rather the abuse potential for Xyrem was consistent with substances typically controlled under Schedule IV. Authorized investigational formulations, however did not meet the "accepted medical use" criteria set forth in Schedule IV due to the lack of FDA marketing authorization. Authorized investigational formulations fit more closely with the standard of Schedule II drug having a "currently accepted medical use with severe restrictions".

Under these circumstances, HHS recommended placing FDA authorized formulations of GHB in Schedule III - a level of control higher than Schedule IV in order to take into account the lack of accepted medical use of the investigational product, and a level of

control lower than Schedule II to account for the products low dependence liability and abuse potential.

7.4 Public Law 106-172

HHS's Schedule I/III recommendation for GHB was the foundation for proposals embraced by a broad coalition of Republicans and Democrats in Congress in late 1999 and early 2000. The Senate unanimously adopted its proposal to require the Attorney General to use her emergency powers and immediately list GHB in Schedule I. The measure also listed FDA-approved GHB in Schedule III, if or when FDA approved such products. The House adopted the same bill by a vote of 339 to 2.

The Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 was signed into law on Feb. 18, 2000. Called Public Law 106-172, the measure also penalized the illicit use of any form of GHB (including the FDA-approved formulation) with severe Schedule I penalties; controlled the legitimate sale of GBL the industrial solvent and potential GHB analogue; and criminalized the use of a controlled substance analogue to facilitate a sexual assault.

7.5 WHO Recommendation

In September of 2000 a panel of experts was convened by the World Health Organization (WHO) to review the abuse potential of GHB and to make a recommendation for what schedule GHB should be placed. The recommendation of this expert working group was for placement into schedule IV. This recommendation was published in the US Federal Register in the spring of 2001. Following verbal communication from the Controlled Substances Staff at FDA, there were no comments submitted, either in favor or opposed to this recommendation. Therefore the recommendation will most likely stand and be signed into law by the WHO president. Since a WHO schedule IV is not much different than a US schedule III, no changes are anticipated to US laws as a result of this recommendation. A copy of the WHO recommendation is included with this section.

7.6 Conclusion

The recommendation of HHS, along with the weight of scientific and medical evidence continues to support a placement of Xyrem, if approved by FDA, into Schedule III. Moreover, given the ease with which GHB can be compounded, the availability of inexpensive industrial chemicals that are used as GHB analogues and the specialty distribution system designed to prevent diversion (which is presented in Section 8), the abuse potential of Xyrem is low. Orphan Medical continues to sponsor and assist with state legislation which addresses GHB analogs and inappropriate use of GHB, with both clinical and preclinical studies designed to further investigate the abuse potential of GHB, and distribution systems which minimize diversion while making Xyrem available for patients with narcolepsy.

ATTACHMENT 1

David Satcher, MD, PhD (DHHS) Letter (May 19, 1999),

Gamma Hydroxybutyrate: Eight Factor Analysis (September 1997),

and

James Milford (DEA) Letter (September 16, 1997)

BEST AVAILABLE COPY

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Assistant Secretary for Health
Office of Public Health and Science
Washington D.C. 20201

MAY 19 1999

Mr. Donnie R. Marshall
Deputy Administrator
Drug Enforcement Administration
Washington, D.C. 20537

Dear Mr. Marshall:

In response to your request dated September 16, 1997, and pursuant to the Controlled Substances Act (CSA), 21 U.S.C. §811 (b), (c), and (f), the Department of Health and Human Services (HHS) recommends that gamma-hydroxybutyric acid (GHB) should be subject to control under Schedule I of the CSA, except that GHB substances and products that are the subject of investigational new drug (IND) applications authorized by the Food and Drug Administration (FDA) should be subject to control under Schedule III.

GHB is a central nervous system depressant. As discussed in the attached analysis, GHB has a high potential for abuse relative to substances controlled in Schedules III, IV, and V. GHB has no accepted medical use, and when manufactured clandestinely, it is unsafe for use under medical supervision. Accordingly, and except as provided below, HHS recommends that GHB be controlled in Schedule I of the CSA.

Formulations of GHB currently are being studied under FDA-authorized INDs. At least one sponsor's formulation has been granted orphan drug status under Section 526 of the Food, Drug, and Cosmetic Act, and is available under a treatment use protocol under 21 CFR §312.34. None of the reports of actual abuse of GHB that support the Schedule I recommendation have involved GHB that was diverted from an authorized study. Moreover, given the ease with which GHB can be synthesized from readily available materials, it is unlikely that authorized studies will become a source for abuse. Rather, the abuse potential of GHB, when used under an authorized research protocol, is consistent with substances typically controlled under Schedule IV. Information on the dependence-producing effects of GHB is limited, but available data suggest that its potential for physical and psychological dependence is also consistent with control under Schedule IV.

Authorized formulations of GHB, however, do not meet the "accepted medical use" criteria set forth in Schedule IV. An authorized formulation of GHB is far enough along in the development process to meet the standard under Schedule II of a drug or substance having a "currently accepted medical use with severe restrictions." Under these circumstances, HHS recommends placing authorized formulations of GHB in Schedule III.

You will find enclosed a document prepared by FDA's Drug Abuse Evaluation Staff that is the basis for the combined Schedule I/Schedule III recommendation.

Should you have any questions regarding this recommendation, please contact Stuart L. Nightingale, M.D., FDA's Associate Commissioner for Health Affairs, at (301) 443-6143.

Sincerely yours,

David Satcher, M.D., Ph.D.
Assistant Secretary for Health
and Surgeon General

Enclosure

Gamma hydroxybutyrate:

Eight Factor Analysis

On September 16, 1997, the Deputy Administrator of the Drug Enforcement Administration (DEA) requested that the Department of Health and Human Services (DHHS) develop a scientific and medical evaluation and recommendation to schedule gamma-hydroxybutyric acid (GHB) under the Controlled Substances Act (CSA). GHB is under active development as a therapeutic agent in the United States. The Food and Drug Administration (FDA) recently authorized a sponsor's investigational new drug application for the treatment use of a GHB drug product for cataplexy associated with narcolepsy, to provide early availability of the drug product for patients suffering from this condition (see 21 CFR 312.34), and to facilitate the collection of data in support of a new drug application (NDA). This sponsor has also obtained "orphan" designation of its product from FDA in accordance with section 526 of the Federal Food, Drug, and Cosmetic Act. An orphan drug is a drug that is intended to treat a rare disease or condition that affects fewer than 200,000 people in the United States. To obtain an orphan drug designation, a sponsor must present sufficient information about the drug, or the disease or condition for which it is intended, to establish a medically plausible basis for expecting the drug to be effective in the prevention, diagnosis, or treatment of that disease or condition. The purpose of the Orphan Drug Act is to provide incentives for the development of products which, without incentives, are of little interest to the pharmaceutical industry. There have been no reports of diversion from clinical trials or authorized studies.

At the same time, however, GHB compounds are being manufactured in clandestine laboratories for recreational use, the scale of which is undetermined. Because of this clandestine manufacture of GHB, and its associated abuse, numerous States have controlled GHB under State laws in Schedules II, IV, or I. Some deaths and numerous hospital emergency room cases have been documented from the clandestine substance.

In accordance with 21 U.S.C. 811(b), the DEA gathered information relevant to scheduling GHB in the CSA. Pursuant to 21 U.S.C. 811(b), the Secretary is required to consider on a scientific and medical evaluation eight factors determinative of control under the CSA. Following consideration of the eight factors, if it is appropriate, the Secretary must make three findings to recommend scheduling a substance in the CSA. The findings relate to a substance's abuse potential, legitimate medical use, and its safety or dependence liability.

Administrative responsibilities for evaluating a substance for control under the CSA are performed by the FDA, with the concurrence of the National Institute on Drug Abuse (NIDA), as described in the Memorandum of Understanding (MOU) of March 8, 1985 (50 FR 9518-20).

In this document, FDA is recommending the control of GHB and all mixtures, compounds, and preparations thereof in Schedule I of the CSA, except that GHB drug substances and products being studied under FDA authorized INDs are recommended for control in Schedule III.

1. ITS ACTUAL OR RELATIVE POTENTIAL FOR ABUSE.

GHB, as one might expect of a sedative-hypnotic drug, produces dose- and concentration-dependent CNS depressant effects in humans and a variety of laboratory animals including mice,

rats, rabbit, cat, dog and monkey.[1] Its abuse potential was evaluated in preclinica tests, such as drug discrimination and self-administration[2] in which GHB produced sedative-like stimulus effects. The CNS depressant effects might be expected to correlate with use in a p olydrug abuse setting, such as to counteract the effects of stimulants. The dose-response curve f r the sedative and hypnotic effects of GHB is steep.[3] That is, the onset of effect is rapid, making it an effective hypnotic, but also an effective drug of abuse in some settings.

Discriminative Stimulus Properties. Several studies have characterized GHB's discriminative stimulus effects (i.e., the ability of a subject to distinguish the drug from a control).[4] Results from these studies have shown that GHB can function as a discriminative stimu .s in rats and that the GHB stimulus cue is complex, sharing some properties with some CNS d pressants and, to a lesser extent, with some GABA-mimetic substances and morphine.

The ability of GHB to function as a discriminative stimulus was first reported by Winter (1981).[1] Controls included an array of controlled and non-controlled substances.

> Experiment. Using a two-lever operant procedure under a fixed-ratio (FR 1) schedule of reinforcement, rats (n=14) were trained to discriminate 200 mg/kg (intrap ritoneally) of GHB sodium salt from saline. After criterion was established, morphin (1.0 and 3.0 mg/kg), LSD (0.03, 0.1, and 0.3 mg/kg), phencyclidine (PCP) (2 .0 and 4.(mg/kg), SKF 10,047 (6.0 and 10.0 mg/kg), ethanol (630.0, 945.0, 1260.0 mg/kg), barb ital (80.0 and 160.0 mg/kg), chlordiazepoxide (3.0, 10.0, 20.0, and 30.0 mg/kg), d-amp etamine (0.8, 1 5, and 3.0 mg/kg), apomorphine (0.3, and 1.0 mg/kg) and the G BA-mimetics muscimol (0.3, 1.0, 2.0, 3.0 mg/kg), gamma-butyrolactone (GBL) (10.0, 3(.0, 100.0, and 200 0 mg/kg), baclofen (1.0, 3 0, 6.0, and 10.0 mg/kg), and 3-aminopr pane sulfonic acid (100.0, 150.0, and 300.0 mg/kg) were substituted for GHB. GHB f nctioned as a discriminative stimulus in all rats trained to discriminate 200 mg/kg of GH B. The mean number of sessions required to establish criterion were 43 (S = 5; range 1 -67 sessions). Substitution tests revealed that the discriminative stimulus cue of GH B was more depressant-like.

During substitution tests, PCP (CII), ethanol, barbital, d-amphetamine (CII) and apomorphine failed to generalize to GHB Morphine (CII) and 3-aminopropane partially gen ralized to the GHB cue. The GABA-mimetics muscimol (not controlled), and baclofen (n ot controlled) generalized to GHB in a dose-dependent manner Chlordiazepoxide (CI) also dose-dependently generalized to GHB. These findings confirmed that the discriminativ stimulus cue of GHB was largely depressant-like.

Dose Response. The drug discriminative properties of GHB have been sho n to be dose-responsive

> Experiment. By a T-maze, food-reinforced drug discrimination pro cedure, GHB functioned as a discriminative stimulus in rats.[5] The ability of GHB to function as a discriminative stimulus was evaluated in rats trained to discriminate 300 m g/kg (n=4; 30-minutes pretreatment, i.g.) or 700 mg/kg (n=6; 30-minutes pretreatment; i. g.) from water

in a two-arm T-maze procedure under a FR10 schedule of reinforcement. After criterion (a: the first trial was correct; b: at least 9 correct trials out of 10) was established, substitution tests were conducted with GHB at a range of doses (0, 50, 100, 300, 500, 700, and 1000 mg/kg; i.g.). To assess the ability of the GHB antagonist NCS-382, to block the discriminative stimulus of GHB, doses of NCS-382 (0, 12.5, 25.0, and 50.0 mg/kg; 10-minutes pretreatment) were tested in both 300 mg/kg and 700 mg/kg GHB-trained rats. Both 300 and 700 mg/kg GHB functioned as a discriminative stimulus in rats; time to acquired GHB discrimination was 48.0 @ 5.1 (35-58) and 42.8 @ 2.7 (35-54) days for the 300 and 700 mg/kg group, respectively. GHB dose dependently substituted for the stimulus cue of both training doses of GHB. Complete substitution occurred at doses of GHB equal to and greater than the training dose in the 300 mg/kg GHB group. In the 700 mg/kg GHB group, doses equal to or greater than 500 mg/kg of GHB completely generalized to 700 mg/kg of GHB. During the antagonist test, NCS-382 (25 and 50 mg/kg) attenuated the GHB-discriminative stimulus effects. Pretreatment with 25 mg/kg of NCS-382, 91.2% and 16.7% GHB-appropriate responding was observed in the 300 and 700 mg/kg training groups, respectively. NCS-382 (50 mg/kg) resulted in 7.5 and 9.2 mg/kg percent GHB-appropriate responding in 300 and 700 mg/kg GHB groups, respectively.

Alcohol. GHB and alcohol exhibit common discriminative stimulus effects within a narrow dose range.

Experiment The discriminative stimulus properties of GHB were evaluated in rats traied to discriminate ethanol (1.0 or 2.0 g/kg; p.o.) or GHB (300.0 mg/kg; p.o.) from water in the T-maze procedure (Colombo, et al., 1995c). Once criterion (i.e., 5 consecutive training sessions) was established, doses of ethanol (0.0, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 g/kg) and GHB (0.0, 50.0, 100.0, 300.0, 500.0, 700.0, and 1500.0 mg/kg) were substituted for both ethanol- and GHB-trained rats GHB and ethanol demonstrated common discriminative stimulus effects; however, the symmetrical generalization occurred within narrow dose windows Ethanol dose dependently substituted for the training doses of both 1.0 and 2.0 g/kg of ethanol. When GHB was substituted in the ethanol-trained rats, GHB only generalized to the ethanol cue elicited by the 1.0 m/kg training group. An inverted "U-shaped function" was observed following the substitution of GHB doses. GHB (300 mg/kg) elicited 82.0% ethanol-appropriate responding. Doses lower than 300 mg/kg of GHB did not generalize to the ethanol cue. As reported earlier (Colombo et al , 1995a), doses of GHB generalized to GHB in a dose dependent manner. Substitution of doses of ethanol in GHB-trained rats also elicited an inverted "U-shaped" function curve Ethanol (1.0 g/kg) elicited 90.9% GHB-appropriate responding; whereas 1.5 g/kg of ethanol elicited 72 0% of drug-appropriate responding.

GHB and alcohol have synergistic hypnotic effects. In rats, GHB produces a loss in righting reflex (sleep time) which was significantly potentiated by ethanol, specifically a 4- to 5- fold increase in sleep time in rats administered GHB (0.41 nmole) in combination with 6 51 nmole ethanol.[6]

Cocaine, PCP, and heroin. GHB failed to effect the discriminative stimulus control of cocaine, PCP and heroin in rats at any GHB dose tested.

> Experiment. (Beardsley *et al.*, 1996). The discriminative stimulus effects of GHB were also assessed in rats trained to discriminate cocaine (10.0 mg/kg, i.p.), PCP (2.0 mg/kg, i.p.) or heroin (0.3 mg/kg, s.c.) from vehicle (saline for PCP and cocaine; water for heroin), in a two-lever operant procedure under a FR schedule [FR 10 for (cocaine and heroin trained rats; FR 32 for PCP-trained rats] of reinforcement. After criterion, substitution tests were conducted. (Criterion was as follows: PCP-trained rats: at least 80% of the total responses were made on the correct lever during four consecutive training sessions, and the first 32 consecutive responses were completed on the correct lever during each of these sessions; cocaine- and heroin-trained rats: the first completed fixed ratio occurred on the lever designates correct at least eight of the consecutive training sessions, and at least 80% of the total responses were made on the correct lever during those eight sessions). On substitution test sessions, heroin (0.3-2.0 mg/kg), cocaine (1.0-30.0 mg/kg), and PCP (0.5-6.0 mg/kg) were tested in their respective training groups. Doses of GHB (10.0-300.0 mg/kg) were substituted for PCP- and heroin-trained groups. In the cocaine-trained rats, the ability of doses of GHB (10.0-300.0 mg/kg) to antagonize cocaine discriminative stimulus effects was evaluated. When GHB (10.0-300.0 mg/kg) was substituted for PCP or heroin, the subjects responded exclusively on the vehicle lever. In the antagonist test, GHB failed to affect the discriminative stimulus control exerted by 10.0 mg/kg of cocaine; that is, the mean percent cocaine-appropriate responding was never reduced to below 59% cocaine-appropriate responding at any of the GHB doses tested.

Reinforcing Effects. The reinforcing effects of GHB were evaluated in two primate species (rhesus monkey and baboon) and rodents (rats). GHB has not been shown to be reinforcing in primates trained to self-administer PCP (CII), cocaine (CII) and methohexital (CIV). Preference for GHB over placebo (water) was demonstrated in rodents. These findings are described in the following relevant experiments:

> Experiment1: (Beardsley *et al.*, 1996) Reinforcing effects of GHB were evaluated in rhesus monkeys experienced in self-administration of PCP under a FR 10 schedule of reinforcement for two monkeys and for two other monkeys, the FR requirement was gradually increased to FR 200 for one monkey and to FR 50 for the other. Four adult rhesus monkeys (3 males; 1 female) were trained to self-administer PCP (10.0 or 5.6 µg/kg/injection) under a FR 10 schedule of reinforcement. Upon completion of training, the maintenance dose of PCP was established at 10.0 µg/kg/injection for all four monkeys. The monkeys had access to PCP during daily one-hour sessions. After stable responding was obtained (i.e., less than 20% variation in the number of PCP infusions per session for at least 3 consecutive sessions with PCP), vehicle and GHB (300 - 7500 µg/kg/injection) were substituted for PCP injections for four consecutive days. Following each behavioral session, monkeys were observed immediately afterwards for several hours for signs of overt toxicity and/or drug-induced behavioral changes. Substitution of doses of PCP

produced an inverted "U-shaped" dose-response function with at least thr e doses in all monkeys maintaining responding above saline levels where the range did r ot overlap. In comparison to PCP, GHB failed to maintain rates of responding indicative of reinforcing efficacy in all primates. GHB, at a dose of 3000.0 :g/kg/infusion, occasio ally produced ptosis and lethargy suggestive of sedative-like effects.

Experiment 2: (France *et al.*, 1997) GHB was tested in three rhesus mon keys trained to self-administer 0.1 mg/kg/infusion of methohexital. Four doses (amoun not specified) of GHB were substituted for methohexital. Each of the 3 monkeys re ived the two largest GHB doses (0.1 and 1.0 mg/kg/injection). GHB maintained v ry little self-administration behavior in the primates. Furthermore, the researchers : ated that the number of injections did not exceed the number of saline injectic ns and were considerably less than the number of infusions for methohexital.

Experiment 3: (Ator, 1995) The reinforcing effects of intravenous GHB v ere evaluated in baboons trained to self-administer 0.32 mg/kg/infusion cocaine HCl u der a FR 160 schedule of drug delivery. GHB (3.2 - 100.0 mg/kg/injection) was exa nined in two baboons and initiated in a third, though not completed. Throughout the su dy, each dose of GHB and vehicle was substituted for cocaine for 15 consecutive days, f llowed by re-establishment of cocaine baseline for three consecutive days. GHB di l not reliably maintain self-administration at any of the doses tested under the specific co ditions of the study. Higher doses of GHB could not be evaluated due to limitations of d ug solubility. When 100:g/kg/injection GHB was substituted for methohexital, sedation was observed after the behavioral session.

Experiment 4: Oral self-administration of GHB was evaluated. During th : initial phase of the study, the rats experienced a two-week forced-choice period. Duri g this period, GHB sodium salt (1% w/v in water) was the only available drinking fluid. Subsequently, the rats were changed to a free-choice period; the rats had a choice l etwen GHB solution (1% w/v) and tap water. During the no-choice phase, the i take of GHB remained fairly stable (800-1200 mg/kg/day). The preference for G HB was also established during the free-choice period of the study. However, during his period all rats displayed alternate periods of high daily intake of GHB with tem porarily self-imposed cessation of GHB intake. Large variability among the rats was o served in the length of the GHB- and tap water-preference periods; the range was be ween 1 to 12 days. On GHB-preference days, GHB consumption averaged 666.3 @ 1 .2 mg/kg/day; and there appeared to be a pattern in the self-administration of GHB. ats tended to consume GHB solution in distinct binges which occurred over 3 to 5 ho rs during the dark phase of the light cycle, during which the rats consumed pharmacolo ically relevant doses (100 to 300 mg/kg) of GHB. This 3-5 hour interval between GH B binges was constant with the pharmacokinetics of oral GHB in rats[7] suggesting a self-controlled adjustment of GHB dose by the rats over the 24-hour light cycle.

Clinical Studies of Abuse Potential. There have been no reliable clinical st dies of abuse potential of GHB.

GHB's pharmacology as a sedative/hypnotic and its potentiation with alcohol make it a candidate drug for recreational abuse and use to physically and mentally incapacitate individuals without their knowledge. GHB in low doses produces amnesia and hypotonia. Higher doses produce effects ranging from sedation to profound CNS depression. The onset of effects is seen 15 minutes after administration, lasting up to 3 hours.[8] The rapid onset of sedation, coupled with the amnestic features of this agent, particularly when added to alcohol to conceal its presence and potentiate its effects, would be expected to be a very effective agent in the commission of a crime such as sexual assault. Other sedative hypnotics coupled with alcohol, notably chloral hydrate (CIV) and flunitrazepam (CIV) have in the past demonstrated this same pattern of abuse. However, what increases the likelihood of GHB's use in this manner is the extraordinary availability of chemical precursors and ease of clandestine synthesis by non-chemists.

2. SCIENTIFIC EVIDENCE OF ITS PHARMACOLOGICAL EFFECTS, IF KNOWN.

GHB is a naturally occurring compound found in small quantities in many mammalian tissues.[9] Its administration produces a wide range of pharmacological effects, but its physiologic role has not been clearly defined.[10] GHB can induce nonREM and REM sleep, anesthesia, and hypothermia. It has been studied in cats as a model for petit mal epilepsy. It markedly increases brain dopamine levels. It is also found in many peripheral tissues, in concentrations sometimes higher than in the brain. GHB may act through different neurotransmitter systems including the dopamine and opioid systems. GHB raises dynorphin levels and its metabolic and some pharmacological, but not behavioral, effects can be blocked by naloxone.

Neurochemistry of GHB

GHB is a psychoactive drug that produces its effect when administered intravenously or orally and is fundamentally different from established neurotransmitters that do not normally pass through the blood-brain barrier. Nonetheless, GHB is found unevenly distributed in mammalian brain[11] and patterns of regional distribution are species dependent.[12] Although the physiological role of GHB has not yet been fully defined, there are purported brain receptor sites as well as brain mechanisms for synthesis, release and uptake of GHB.[13]

Endogenous brain GHB is synthesized via transamination and reduction of GABA in neurons. An apparently specific enzyme for GHB biosynthesis from GABA via succinic semialdehyde has been described in both rat and human brain, and is released from reloaded brain slices under depolarizing conditions.[14]

Radioligand studies have identified specific binding sites for GHB in both rat and human CNS.[15] Characterization of GHB binding in rat and human brain synaptosomal membranes showed that binding was saturable, pH dependent, and linear with protein concentration.[16] The density of [^{3}H]GHB binding was highest in the hippocampus and lowest in the cerebellum. Competition and saturation experiments demonstrated the existence of high and low affinity binding sites.

The GHB binding sites in both rat and human synaptosomal membranes appear to be coupled to a chloride anion channel.[17] All ions that are active at the chloride ion channel inhibited the binding of [^{3}H]GHB in a dose-dependent manner. Compounds that were impermeable to the chloride ion channel, i.e., sulfate, acetate, and fluoride, did not inhibit [^{3}H]GHB binding. GABA and its structural analogues (agonists and antagonists), opiate antagonists, and anticonvulsants did not inhibit [^{3}H]GHB binding.[18] Recently, GHB receptors from adult rat brain were solubilized, unmasking a significant amount of membrane-bound receptors, and suggesting the presence of endogenous inhibitors or ligands.[19]

Several recent studies have attempted to find the underlying neurotransmitter system responsible for GHB's effects. GHB appears to act through dopamine and opioid systems, but has no affect on NMDA or GABA systems.[20] GHB causes a rapid and significant increase in brain dopamine when administered to animals in doses that produce behavioral depression.[21]

The effects of GHB on the dopaminergic system have been evaluated in both *in vivo* and *in vitro* assays. Results from these studies indicated that GHB effects on dopamine release is biphasic. Using both striatal slices and microdialysis of caudate-putamen, GHB inhibited the release of dopamine for approximately 5 to 10 minutes which resulted in the accumulation of dopamine within these tissues.[22] Subsequently, as a result of a negative feedback mechanism, an increase in dopamine release occurred. GHB, at doses that produce behavioral depression, causes a rapid and significant increase in brain dopamine levels in animals[23] limited to extrapyramidal regions.[24] Alpha-methyl-p-tyrosine and apomorphine (dopamine agonist) block GHB-induced increase in brain dopamine.

GBL, the synthetic precursor and metabolic prodrug of GHB, also appears to modulate extrapyramdial dopaminergic activity.[25]. Within the pars compacta of the substantia nigra, both GBL and GHB suppressed firing of dopaminergic neurons.[26] In a study conducted by Diana *et al.* (1991), it was demonstrated that the effects on dopaminergic neurons are dose- and route-dependent. Following administration of GHB (50 to 400 mg/kg i.v.), a dose-related stimulation (10-56%) of the firing rate of dopaminergic neurons in the pars compacta of the substantia nigra was produced. In contrast, higher doses of GHB (1000 and 1500 mg/kg) almost completely inhibited the firing rate of the pars compacta's dopaminergic neurons. Administration of GHB (750 mg/kg i p) to unanesthetized rats initially produced a brief stimulation (23% of firing rate followed by a modest reduction in the firing rate (29%)

GHB is not a direct or indirect opiate or opioid antagonist It does not bind to mu, delta or kappa opioid receptors[27] However, several investigators have suggested that GHB may act as an indirect agonist, stimulating the release of endogenous opioid peptides.[28] Following administration of an anesthetic dose of GHB to rats, the brain level of dynorphin was augmented. However, there were numerous differences between the behavioral effects of GHB and dynorphin, indicating that GHB's effects are not likely to occur via enhancement of dynorphin. In one study, opioid-like substances in striatal dialysates were detected after intrastriatal microinfusions of GHB (0 25 nM) in preclinical studies.[29]

GHB's effect on brain serotonin is much less pronounced than its dopaminergic effects. GHB can either increase the turnover rate of brain serotonin or elevate its levels in specific brain regions.[30] This effect appears to be age-related—following the administration of a high dose of GHB, GHB increased the rate of synthesis and degradation of serotonin in adolescent rats and not in neonatal rats.[31].

GHB may modulate the activity of the cholinergic neurons. Following administration of GHB to rats, a selective increase in acetylcholine levels was detected in the midbrain and critical regions. GHB effect on acetylcholine is thought to be an indirect effect arising from the interaction between dopaminergic and cholinergic systems.[32]

Pharmacodynamics—CNS Effects.

Animal studies have evaluated GHB as an anxiolytic. An early study on isolated-induced stress found that 50 mg/kg GHB produced a significant decrease in the appearance of defensive behavior in previously isolated mice, a characteristic stress response.[33] Higher doses (200 mg/kg) reduced the manifestations of passive-defensive behavior, but also produced sedative effects. This study suggested that a low dose of GHB inhibited the appearance of alarm and anxiety, but did not produce general sedative actions. These findings were similar to those observed after administration of benzodiazepines.

GHB produced a loss in righting reflex (sleep time) in rats, which was significantly potentiated by ethanol.[34] There was a 4- to 5-fold increase in sleep time in rats administered GHB (0.41 nmole) in combination with 6.51 nmole ethanol. These authors found synergism when GHB and ethanol are combined, suggesting a common mechanism of action.

In humans GHB doses of 10 mg/kg produce amnesia and hypotonia. Oral or intravenous doses of 20-30 mg/kg promote the normal sequences of REM and nonREM sleep when given to normal subjects Oral doses in this range produce high voltage slow wave activity and occasionally spindle sleep.[35] Higher doses produce effects ranging from sedation to profound CNS depression. The onset of effects is seen 15 minutes after administration, lasting up to 3 hours.[36]

GHB produces dose- and concentration-dependent changes in level of consciousness. Oral or intravenous doses of GHB greater than 50 mg/kg produce anesthesia in children and adults.[37] In children, GHB 70 mg/kg, administered intravenously produces rapid onset (within 5 minutes of infusion) of sleep.[38] In adults, drowsiness, unconsciousness, and profound coma, accompanied by hypertonia, and muscle rigidity, were observed within 30 minutes after oral administration of 50 mg/kg GHB.[39] As GHB levels decrease, these patterns recur in reverse order. GHB is rapidly metabolized and the central effects of a 60-70 mg/kg dose last about 2 hours.

Effects of GHB on Cardiovascular and Respiratory Control and Thermal Regulation

In animal studies, respiratory depression has been shown to occur at high doses of GHB.[40] An intraperitoneal dose of 750 mg/kg GHB in adult rats produced a 40% decrease in the minute

ventilation, although the same dose given subcutaneously resulted in apnea and cyanosis in rat pups.[41]

In humans doses in the range of 65-70 mg/kg do not appear to result in respiratory depression. In children, GHB (70 mg/kg) administered intravenously produced changes in respiration, with no apparent clinical consequences, that is, there was no evidence of respiratory depression.[42] When GHB 65 mg/kg, administered intravenously was used as an anesthetic agent of labor and delivery, normal spontaneous ventilation was maintained with little change in rate or volume.[43] Cardiac output falls, however, as evidenced by a slight decrease in stroke volume and heart rate.

There have been reports of GHB used at high doses (in the setting of recreational use and coadministration with other substances) resulting in toxicity and overdose, which indicate effects on heart rate, blood pressure and respiration.

Effects of GHB on Growth Hormone.

GHB has been found to stimulate release of human growth hormone (HGH) from the anterior pituitary gland in humans. GHB 2.5 grams administered intraveniously in six healthy male volunteers caused a rise in plasma levels of HGH at 30, 45, 60 and 90 minutes after injection.[44] In addition, plasma prolactin levels increased at 45 and 60 minutes after GHB.

The effects of GHB on HGH have been confirmed by several recent clinical studies.[45] Intravenous injection of 1.5 grams of GHB to human volunteers caused a significant increase in plasma levels of HGH without significantly altering levels of other hormones such as prolactin, TSH, LH, ACTH or cortisol.[46] The HGH plasma levels were significantly elevated at 45 and 60 minutes following injection. Oral administration of 1.5 grams of GHB produced a significant rise in plasma HGH levels at 15 to 30 minutes which peaked at 46 to 60 minutes and declined precipitously by 90 minutes post-administration.[47]

3. THE STATE OF CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR OTHER SUBSTANCE.

Chemistry

The sodium salt of GHB is also known as sodium oxybate; sodium oxybutyrate; 4-hydroxybutyrate; 4-hydroxybutanoic acid monosodium salt; 4-hydroxybutyric acid sodium salt; gamma hydrate; NSC-84223; and Wy-3478. The chemical abstract number for GHB is [502-85-2]. Trade names include Anetamin, Gamma-OH, Somsanit and Somatomax PM, and Xyrem™. GHB as the sodium salt is a white hygroscopic powder with a melting point of 115-146°.[48] It is soluble in water and forms crystals from alcohol. GHB (sodium salt) has a formula weight of 126.09 and its molecular formula is $C_4H_7NaO_2$.

GHB is prepared by reaction of sodium hydroxide and gamma-butyrolactone (GBL); high yields and purity of product are obtained. These two main ingredients are readily available and may be

obtained from chemical and cleaning supply businesses, and through the INTERNET. GHB is easily synthesized by base catalyzed hydrolysis of GBL. This is a simple chemical procedure that can be accomplished by individuals who lack knowledge of chemistry.

The immediate precursor, GBL, is a hygroscopic oily liquid with a boiling point of 204-205 °C at 760 mm Hg. It is also known by the following chemical names: dihydro-2(3H)-furanone, 1,2-butanolide, 1,4-butanolide, butyric acid lactone, 3-hydroxybutyric acid lactone, 4-hydroxybutanoic acid lactone. GBL has a molecular weight of 86.09 and formula $C_4H_6O_2$. GBL has wide industrial applications, including use as an intermediate in the synthesis of polyvinylpyrrolidone, D, L-methionine, piperidine, phenylbutyric acid, thiobutyric acids; as a solvent for polyacrylonitrile, cellulose acetate, methyl methacrylate polymers, polystyrene, and in paint removers and textile aids.

Preclinical safety, pharmacokinetics and efficacy

The pharmacokinetics of GHB appear to be extremely complex. The absorption and elimination processes appear to be capacity-limited. In preclinical studies, GHB pharmacokinetics were studied as a function of dose and route of administration.[49] Oral absorption of GHB (200-1600 mg/kg) is fairly extensive; bioavailability of GHB increased from 200 to 400 mg/kg, but declined as the dose increased. Blood levels after oral dosing were found to be considerably lower than those after intravenous administration.[50]

GHB has a half-life of about one hour in the rat, but the half-life is longer in the cat due to its slower clearance.[51] The elimination half-life of GHB in rats is biphasic after oral dosing with an $\forall$ half-life of 1.02 hours and a $\exists$ half-life of 2.68 hours.[52] Similarly, a half-life of 1 to 2 hours was reported for dogs, but this was based on a one-compartment model.[53] A non-linear elimination has been demonstrated in the dog, cat and human.[54]

In rats, cats, and dogs, a relative consistency was found between brain/plasma ratios, confirming penetration across the blood-brain barrier.[55] However, peak plasma levels were relatively low and not dose-dependent; sedative effects and hypnosis were seen only at the highest oral doses.[56] In cats, administration of an anesthetic dose of GHB 3.5 mMol/kg resulted in a GHB level of 0.7 mM in the brain and twice that level in the blood.[57] There is wide variability among animals in the plasma and brain concentrations of GHB when animals recovered from the hypnotic effects of GHB 400 mg/kg, intracardiac or 800 mg/kg, intravenous.[58] In dogs, GHB is taken up into the brain, showing an approximately 2 1 ratio between blood:brain levels, followed by a rapid outflow of GHB from the brain to the cerebrospinal fluid.[59] Thus, GHB passes readily from the bloodstream to the brain and rises to levels of over 100-times its normal endogenous levels, but does not appear to be actively taken up or retained by the brain. This non-linear elimination of GHB was interpreted as due to saturation of one or more of its as yet unknown metabolic pathways.[60]

GHB is metabolized to carbon dioxide, which is eliminated in expired air The exact site and pathway is unknown.[61] Radioisotope studies in animals have demonstrated rapid absorption and metabolism following administration Almost immediately, $^{14}CO_2$ appeared in respired air, after

administration of 1-^{14}C-labelled GHB. Highest levels of drug were found in most tissues within 15 minutes of dosing. Ninety percent of the injected 1-^{14}C-labelled GHB was excreted in the respired air, 10-20% in urine, and virtually none in feces.

In animal studies, respiratory depression has been demonstrated at high doses of GHB.[62] An intraperitoneal GHB dose of 750 mg/kg produced a 40% decrease in the minute ventilation in the adult rat, although the same dose given subcutaneously resulted in apnea and cyanosis in rat pups.[63]

There is some evidence that GHB may provide tissue protection during conditions of hypoxia by conserving cerebral energy utilization.[64]

Dose-dependent hypothermic effects have been found after administration of GHB in a number of laboratory animal species, including mouse, rat, dog, and monkey.[65] In rats, heat loss was found to be due to a decrease in metabolic heat production and an increase in cutaneous circulation. The decrease in body temperature produced by GHB can be blocked by the opioid antagonist naloxone[66] as well as the dopamine receptor antagonist haloperidol.[67]

In mice and cats, oral administration of GHB increases general CNS depression with increasing dosage. The first effect noticed is cessation of spontaneous motor activity, followed by loss of body tone (muscle relaxation). In mice and cats, doses can be administered that produce depression for long periods (up to 5 hours) after which animals have recovered with no obvious ill effects (e.g., nausea or ataxia). GHB potentiates barbiturate sleeping times in mice. It possesses general anticonvulsant activity as indicated by its efficacy in preventing or reducing convulsions induced by electroshock, metrazol or semicarbazide. Antagonism of depression was induced by GHB

Deaths from GHB in animals result with very high doses. GHB has an LD_{50} of 5100 mg/kg (in mice, p.o.) and 3705 mg/kg (in rats p.o.), 4225 mg/kg (mice, i.p.), 2020 mg/kg (rats, i.p.), and 1855 mg/kg (mice i.v.). It should be noted that the recommended dose in humans that has been shown to be effective in treatment of cataplexy associated with narcolepsy is 9 grams/day (or approximately 0.13 gm/kg p.o.) in divided doses.

Human Pharmacokinetics and pharmacodynamics

In humans the absorption from the gastrointestinal tract is rapid and onset of effects occurs within 15 minutes.[68] Oral doses in man of 75 to 100 mg/kg gave peak blood levels of 0.97 and 1.15 nMol/L (90 and 120 mg/L) at 1.5 and 2.0 hours.[69] Oral doses of 12.5 to 50 mg/kg in eight healthy male volunteers resulted in peak plasma concentrations of 20-23 µg/mL after 25-45.[70] Distribution of GHB into tissues follows a two-compartment model. Initial blood levels declined rapidly following a longer period of metabolic degradation. The plasma $t_{1/2}$ after either 12.5, 25 or 50 mg/kg was 22 minutes (range 20-23 minutes). Ascending doses from 12.5 to 50 mg/kg resulted in an increase in t_{max} and $t_{1/2}$ and a decrease in c_{max}.[71] Another study also found that

GHB rapidly metabolized central effects of a 60-70-mg/kg dose lasting about : hours. These doses produced initial plasma levels of 200-300 :g/ml.[72]

GHB in humans induces somnolence leading to arousable sleep at 40-50 mg/k , and, at 60-70 mg/kg, coma for 1-2 hours. As noted above, this amount of GHB approximates t hat some have considered to be an appropriate therapeutic dose. In addition, the LD_{50} has been estimated at 5-15 times that which induces coma. This distinguishes GHB from prototyp schedule IV substances, like the widely used benzodiazepines for which the difference betwe an acceptable therapeutic dose and a dose which would lead to serious harm (true coma or fata) is significant. GHB and alcohol have synergistic hypnotic effects.[73]

Symptoms of acute toxicity with GHB include GI upset, CNS and respirat ry depression, confusion, inebriation, stupor, uncontrolled movements, myoclonus and seizures. There are also reports of GHB overdose and toxicity documenting GHB's effects on heart rat , blood pressure and respiration. This information was not collected from clinical trial experience but rather from anecdotal reports of overdose following illicit use, which frequently includes poly drug use.

Medical Use

Currently, several investigational new drug applications (INDs) are active at the DA, including a treatment IND for cataplexy associated with narcolepsy, which is an orphan in lication. GHB is available for medical use in a number of foreign countries. It is primarily f mulated as an intravenous solution intended for use as an adjunct to anesthesia. In Europe, it manufactured by the German based companies Cemep and Kohler who supply it for use as a g neral anesthetic under the proprietary names Gamma-OH and Sanansit, respectively. GHB is sold as an intravenous formulation under the name Gamma-OH in the Netherlands, Fr nce, Morocco, Hungary, French West Africa, and Tunisia. In France, the Netherlands, Moroc co, and French West Africa, GHB is available in vials containing 200 mg/ml. In Italy it is sold s a solution of 24.5 grams in 140 ml under the name Alcover

There are also several combination products containing GHB in Taiwan, New Z ealand and the Dominican Republic. In Taiwan, GHB is sold as a combination product in t blet form with caffeine, chlorpheniramine, ethenzamide and thiamine under the name Anig -cold. In the Dominican Republic, GHB is available in a combination product (liquid) c ntaining citrus aurantium, cyanocobalamin, cyara scolymus, nicotinamide, pantothenic ac d, pyridoxine, riboflavin and thiamine. In New Zealand, it is sold under the name Nyal Me icated GHB in solution.

GHB is listed in the **United States Pharmacopoeia Drug Information for th Health Care Professional (USP/DI** 1995) as a treatment for narcolepsy and the auxiliar symptoms of cataplexy, sleep, paralysis, hypnagogic hallucinations, and automatic behavior. General dosing information is provided but needs to be individualized for each patient. Doses r nging from 1.5 to 2.25 grams orally at bedtime have been utilized. One or two additional dos s of 1.0 to 1.5 grams may be given at 3- or 4- hour intervals. As much as 9 grams per night in 3 divided doses has been administered without harmful effect. Elderly and debilitated patients sh ould receive an

initial dose of 1.5 grams to avoid development of sedation, dizziness, and/or stupi . In the event of overdosage, vital signs and body temperature should be carefully monitored Patients are required to stay in bed for approximately 8 hours or until the effects of the drug we ar off.

GHB is currently being commercially developed for the treatment of cataplexy a sociated with narcolepsy. The FDA has granted a sponsor orphan status for its GHB product fo the treatment of narcolepsy. In addition, the FDA has determined that there is sufficient data to grant expanded access under medical supervision through an approved Treatment IND for the use of the sponsor's GHB product in the treatment of cataplexy associated with narcolepsy.

4. ITS HISTORY AND CURRENT PATTERN OF ABUSE.

In the late 1980's, GHB became available through health food stores or by mail or er. GHB was sold in California Bay Area retail stores and distributed by San Francisco-bas d companies. Marketed as a sleep and diet aid, GBH was initially used by bodybuilders for its al eged role as a growth hormone releaser, as a diet aid, to counter the effects of stimulants, and o effect sleep after workouts.

Luby *et al.* (1992) traced the source of GHB that was sold in South Carolina bars to local gymnasiums catering to bodybuilders, all of whom (in this study) were white, a verage age of 30, and primarily male. In their report, 71% described themselves as regular use s; 18% mixed GHB with alcohol.

Bodybuilders have accounted for a significant number of emergency room case and cases of dependence. Two of the confirmed deaths associated with GHB have involved bodybuilders Also, GHB is often encountered in product seizures of anabolic steroids. During he time GHB was legally available, medical, law enforcement and poison control center re orts appeared indicating that those who began using the drug as a sleep or diet aid continued t use it for its euphoric effects [74]

In 1990, FDA issued a health alert and prohibited the sale of GHB.[75] Although so e abuse in the bodybuilding community continues, the pattern of GHB use and distribution ha changed. Dyer *et al.* (1994) concluded that although GHB has a history of abuse by bodybui ders, in recent years it has been used for its euphoric effects predominantly by young people at da ce parties. Since the early 1990's, GHB has been sold at nightclubs, rave parties, and bars. K s for making GHB by the general public are sold through magazines and the Internet GHB has been made in small quantities using the kits on college campuses, and in larger scale clandestine laboratories.

GHB is taken orally as a liquid or as a powder that is mixed in a liquid (water, jui e, or alcohol). GHB abuse at nightclubs and rave parties is intended for the purpose of getting hi h, producing a more profound effect from alcohol, countering the effects of stimulants, "regulati g" the effects of hallucinogens, or alleviating withdrawal effects from alcohol. Users claim th at GHB elicits effects common to alcohol and CNS depressants, marijuana, hallucinogens, and n rcotics. GHB euphorigenic effects at low doses or in the early stages of intoxication have bee n compared to those produced by alcohol, barbiturates, marijuana, or MDMA Thus, abusers rep ort using GHB

to "get high", to get intoxicated, to relax, and as a sexual enhancer.

GHB has been abused alone as a substitute for alcohol, MDMA or other depressants, but in many cases, it is taken with other drugs. Users report that reasons for taking GHB with other psychoactive drugs include (1) production of a more profound sedative effect when taken with CNS depressants, including alcohol (primarily), barbiturates and benzodiazepines, (2) countering the effects of stimulants, (3) regulating effects of more powerful hallucinogens, or (4) alleviating the withdrawal symptoms of drugs. Some drug dealers market GHB as MDMA ("Ecstasy"), although files from federal agencies find that only a minority of abusers use GHB for its hallucinogenic effects (often compared to a mild "acid"). The Internet and underground literature include exchanges promoting GHB's aphrodisiac or sexually enhancing effects.

There appears to be an increase in the use of GHB among young individuals in social settings[1]. Recently, the drug has found its way into the rave and party communities where, typically taken in higher doses, it is sold as a "legal" high or a substitute for MDMA. As further evidence of GHB's penetration into the club scene, an August 1995 DEA investigation in Manhattan revealed that some rave clubs owners hire promoters whose job is to establish a club theme and to sell drugs. Analysis of the drugs sold in these clubs by runners included MDMA, cocaine, methamphetamine, and GHB.[76]

According to Mack (1993), a typical single dose of GHB needed to produce intoxication or euphoria is 1 to 3 grams taken orally. Powdered GHB is usually dissolved in a liquid such as alcoholic beverages or fruit-flavored drink prior to ingestion. In some locales, liquid GHB is distributed and dispensed from medicine droppers; for $5, users purchase several drops of GHB, apply it to the tongue and swallow it. GHB dissolved in liquid has been packaged in small vials or in water/sports bottles, and sold in gymnasiums.

There have been a number of high profile cases of GHB used in facilitating sexual assault (so-called "date rape") the reports of which have originated from the states of Florida, Texas, Maryland, Louisiana, California, Michigan, Wisconsin, and Massachusetts.

5. THE SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE.

The DEA considers the abuse and trafficking of GHB to be underreported. Because the substance is not controlled under the CSA, it is not a target or priority of the DEA. However, at the end of 1998, GHB had been encountered in 36 states on 550 occasions. The forms of GHB seized by the DEA included powder, liquid, capsule, and tablet. Up to 1 kilogram has been seized at a time. GHB has been found in a variety of containers, including water bottles, plastic bags, vials, gallon milk containers, buckets and drums

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1 Additional information regarding the demographics of GHB users can be gleaned from the DAWN, Poison Center, and literature reports (DEA report, 1997). The changing pattern of GHB use and abuse is also discussed in the DEA's San Francisco Field Division report of January 23, 1996

All reports of actual abuse relate to clandestinely synthesized and formulated substances. DEA has determined that none of the abused GHB is from the pharmaceutical drug product being developed for medical use and that there has been no diversion from clinical trials and authorized studies.

Several states have controlled GHB under state laws, including Georgia (CI), Rhode Island (CI), Hawaii (CI), Illinois (CI), Nevada (CI), Wisconsin (CI), Michigan (CI), Delaware (CI), Idaho (CI), Oklahoma (CI), Nebraska (CI), Alabama (CI), Florida (CII), California (CII), Louisiana (CII), Indiana (CII), New Hampshire (CII), Tennessee (CIV), Alaska (CIV), and North Carolina (CIV). GHB possession and sale is penalized in three States (Texas, New Jersey and Massachusetts).

According to the DEA, abuse and trafficking of GHB manufactured in clandestine laboratories have been increasing since 1993. DEA has documented over 3,500 "encounters" of GHB. These encounters include overdose, abuse and trafficking encounters in 36 states, 72 deaths associated with GHB abuse, and 13 sexual assault cases involving 22 victims under the influence of GHB. The source of such data originates from the law enforcement arena, poison control centers and hospitals. According to the DEA, GHB that is involved in these abuse cases has been clandestinely manufactured, using simple methods and readily available commercial chemicals, gamma-butyrolactone (GBL) and sodium hydroxide. The methods for manufacture, including kits and information on the effects of GHB, are widely available on the Internet.

There is considerable information on the use, availability, and synthesis of GHB through the Internet and other sources. While FDA and other regulatory and law enforcement agencies have successfully disrupted some of the distribution through websites that claim to offer GHB or its precursors, illicit distributors may have altered their distribution schemes to avoid enforcement actions. At one time, however, a 500g bottle of the GHB precursor GBL was offered at one website for $99.99 with the second bottle at half price. Other websites have offered GHB manufacturing kits with enough material to produce one quart of a solution containing 202 g of the potassium salt, which is equivalent to 180 g of GHB; for $200.

Local, regional and national trafficking of GHB have been identified. For example, in late 1995, the DEA investigated the activities of an MDMA trafficker, which resulted in the seizure of GHB. The sources of GHB were clandestine laboratories, laboratories functioning under the cover of producing "nutritional supplements," or occasionally, smuggled product from Europe. Product seizures ranged from 0.37 grams to 1 kg and 0.001 ml to 6688 ml in containers such as plastic bags, vials, water bottles, gallon milk containers and buckets. Individuals apprehended were distributing GHB through mail order catalogs, often offering MDMA or anabolic steroids as well as GHB.

GHB that is abused is manufactured in clandestine laboratories by procedures that are available on the Internet and underground chemistry "cookbooks." Simple "kitchen" stove top methods, requiring little knowledge of chemistry, are found on the Internet and in underground drug literature (such as the "Underground Steroid Handbook for Men and Women Update: 1992").

Precursor chemicals that are used are gamma-butyrolactone (GBL) and sodium hydroxide. One simple chemical step is all that is needed and heat is not required.

Most of the clandestine laboratory activity, according to the DEA, was reported from California, Georgia, Arizona, Texas, Florida, North Carolina, Rhode Island, New York, Washington, Michigan, and Illinois. A total of 84 clandestine laboratories have been documented by the DEA. Of these, 58 (69%) such clandestine laboratories have been encountered in the United States in 1997 and 1998 alone. In addition, DEA's STRIDE (System To Retrieve Information from Drug Evidence) database have documented 90 exhibits of GHB from 44 cases between 1994 and 1998. Sixty-one (68%) were obtained in 1997 and 1998.

Recent seizures of clandestine laboratories found both small and large (interstate) distribution patterns. Some individuals manufacture GHB in their homes for personal use and for personal contacts. Larger laboratories operate to supply GHB within a single geographical area or across state lines. Law enforcement investigational files indicate that clandestine laboratories have been found throughout the United States. The price of GHB on the black market varies and can be $50.00 to $80.00 for 100 grams (The Informant, February 1996). Reports of GHB overdose and toxicity in the United States are rising [77]

GHB has been identified as a drug of abuse in a number of countries, including Australia, the United Kingdom, Sweden, Spain and Italy (INTERPOL Reports, 2/19/96; 3/7/97) In these countries, GHB is abused for many of the same reasons as in the US. In Sweden, GHB was introduced as a medical anesthetic, but is used illicitly by bodybuilders and affluent individuals. The INTERPOL reports "GHB parties" occurring in Sweden. A recent report from Sweden documented ten emergency room cases involving bodybuilders taking GHB (Myrenfors, 1996). Australian Police reported nine GHB overdoses in 1996 on the eastern Gold Coast of Australia. This incident prompted changes in the federal and state laws in Queensland, New South Wales and the Australia Capital Territory (ACT). Queensland amended its Poison Regulations to include GHB and changes to the Drug Misuse Act in Queensland and Drugs of Dependence Act in the ACT are also being made. Also, the Australian Federal Therapeutic Goods Administration banned GHB as a prohibited import allowing the New South Wales Government to outlaw GHB and its derivatives. GHB is a new drug of abuse in the UK where it has been reported to be available in powder or granule form, and sometimes dissolved in water. GHB is abused in the UK, reportedly for its euphoric effects, as a substitute for MDMA and amphetamines at rave party, and as an aphrodisiac. Several cases of toxicity from GHB were recently reported in the London area with four patients presented in coma (Stell and Ryan, 1996). Thomas *et al.* (1997) reported a UK case of coma and respiratory depression in a 32-year-old man who had taken a tablet of temazepam and "half a bottle" of GHB.

FDA's Office of Criminal Investigation (OCI) conducts investigations involving large-scale interstate manufacturers and distributors. To date, OCI has investigated 124 cases. Of the 124 cases, 35 resulted in convictions. The number of cases investigated had increased recently from 18 cases in 1996 to 33 and 24 in 1997 and 1998, respectively. Between January and March 1999, 17 cases have been under investigation

6. WHAT, IF ANY, RISK THERE IS TO THE PUBLIC HEALTH

The public health risk of GHB results from the feasibility and simplicity of its chemical synthesis, the availability of its chemical precursors, its widespread illicit promotion, and the adverse consequences of its use outside of medical direction.

GHB abuse has resulted from widespread dissemination of information on the Internet related to its manufacture. GHB's easy synthesis and medically unsupervised intake are public health risks. The chemical synthesis is accomplished with two readily available chemicals both of which are legal to possess and the manufacturing recipe which does not require extensive chemistry background or experience to be successfully accomplished. The clandestinely manufactured substance does not meet the standards of an approved drug product, being variable and unpredictable in content. The clandestinely produced GHB is not used for an authorized medical purpose and, as such, lacks product labeling with directions for use, warnings and possible drug or alcohol interaction information. Currently, abuse of GHB appears to fall into two categories: (1) Self inflicted abuse, including recreational use for its effects as an intoxicant, euphoriant, or aphrodisiac and use by bodybuilders for its alleged effects as a growth hormone releasing agent or diet/sleep aid; and (2) Abuse (or misuse) of third parties for the purpose of committing a crime.

GHB is taken in combination with other drugs, primarily alcohol, but also stimulants, hallucinogens, marijuana and sedatives. Of the total GHB-related episodes reported in DAWN, most originated from San Francisco, Dallas, Los Angeles, San Diego and Atlanta. Data reported to DAWN by participating medical examiners show that there were seven deaths associated with GHB reported between 1992-1997, of which five occurred in 1997.

According to the DEA, the GHB that is abused is taken in a dose of one to five grams. GHB onset of effects and duration of action are described above under the **Pharmacokinetics** section. GHB potentiates the CNS depressant effects of alcohol and other CNS depressants. Adverse effects of GHB that are produced include the following: drowsiness, dizziness, confusion, inebriation, stupor, reduced muscle tone, reduced blood pressure, reduced heart rate, decreased respiration, seizures, and coma. DEA has documented 32 deaths related to GHB use since 1990.

Twenty-two (69%) were male and 10 (31%) were female. Deaths have been reported in the following states: Florida (9), California (8), Texas (4), Georgia (2), and one each in Illinois, Maryland, Michigan, Nebraska, North Carolina, Ohio, Missouri, and Virginia. Statistics of the deaths are documented in TABLE's 2 and 3, on the next page.

TABLE 2. GHB Deaths Reported in the United States (1990 to 1998)

YEAR	NUMBER OF DEATHS
1990	1
1993	1
1995	3
1996	12
1997	8
1998	7

Source: DEA

The GHB-associated deaths are further reported by age in the table below:

TABLE 3. GHB Deaths by Age

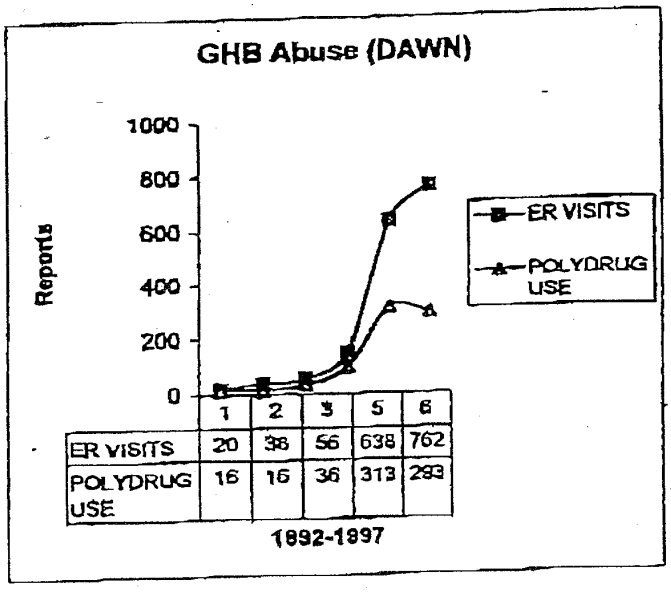
AGES OF DECEASED	NUMBER	PERCENT
10-19 years	3	9%
20-29 years	17	53%
30-39 years	7	22%
40-49 years	3	9%
50-59 years	1	3%
70-79 years	1	3%

Source: DEA

GHB emergency room episodes have been documented in the Drug Abuse Warning Network (DAWN). DAWN reported 1664 GHB-related emergency department episodes from 1991 to 1997. GHB-related emergency department episodes increased from 20 in 1992 to 762 in 1997 (TABLE 4, FIGURE 1) The source of the drug has been clandestinely manufactured GHB of unknown purity. Most of the reports involved Caucasian males, followed by "other" or "unknown" ethnicity. The majority of episodes involved individuals 18 to 25 years of age. The motivation for taking GHB was primarily for recreational use, followed by dependence and suicide. In 60% of the episodes, GHB was taken in combination with alcohol followed by stimulants, hallucinogens, marijuana and sedatives. Consistent with the DEA data, DAWN shows that GHB ED episodes primarily concerned abuse by young people. In addition, Poison Control Center databases show that there were over 600 GHB cases in 1996 and over 900 cases in 1997. None of these cases resulted from abuse of pharmaceutical or research material covered under FDA IND (Source: DEA and DAWN)

These findings suggest that recreational use of GHB has been increasing over the past 5 years, but that the number of deaths relative to that increase is infrequent. The frequency of ER visits related to GHB alone may be approaching that of polydrug use of GHB.

Figure 1



Data from Poison Control Centers (originating from California, Georgia, Florida, South Carolina, Minnesota, Arizona, Ohio, Texas and Virginia) accounted for 57 case reports of GHB intoxication from June through November 1990 (CDC, 1990) Initial symptoms of intoxication were reported to include vomiting, drowsiness, hypnagogic state, hypotonia, and vertigo. Loss of consciousness, irregular and depressed respiration, tremors, or myoclonus sometimes followed. Seizures, bradycardia, hypotension, and/or respiratory arrest have also been reported. Severity and duration of symptoms depended upon the dose of GHB and the presence of other CNS depressants. Although none of the 57 cases resulted in death, most patients required emergency room treatment; at least 11 were hospitalized and 9 required ventilator support or other intensive care As a result of these reports, on November 8, 1990, FDA moved to withdraw GHB from the dietary supplements market (CDC, 1990, 1996).

TABLE 4. Distribution of GHB-related emergency department episodes by selected demographic characteristics: 1992-1997.

	1992	1993	1994	1995	1996	1997
Total	20	38	56	149	638	62
Age						
6-17	-	-	-	-	14	17
18-25	-	13	16	86	427	75
26-34	-	-	16	48	163	01
35 +	-	-	-	-	30	58
Sex						
Male	-	-	29	98	506	30
Female	12	13	12	51	125	28
Unknown	-	-	-	-	-	-
Race/Ethnicity						
White	18	25	47	105	336	70
Black	-	-	-	-	6	8
Hispanic	-	-	-	12	15	6
Other/Unknown	-	-	-	15	281	68
Motive for Taking Drug[1]						
Dependence	-	-	-	15	25	29
Suicide	-	-	-	-	13	8
Recreational Use	14	31	25	85	421	36
Other Psychic Effects	-	-	-	-	17	1
Unknown	-	-	22	41	160	16
Reason for Visit[1]						
Unexpected Reaction	-	-	-	49	172	29
Overdose	11	34	38	94	312	76
Withdrawal	-	-	-	-	-	
Chronic Effects	-	-	-	-	-	
Seeking Detoxification	-	-	-	-	-	17
Other/Unknown	-	-	-	-	138	27
Drug Concomitance						
Single Drug	-	10	-	28	261	90
Multiple Drugs	16	16	36	98	313	93
Unknown	4	12	20	23	64	78

"-" Estimated quantity <10 or = zero.

[1] Motive and Reason refers to entire drug episode, not particular drugs mentioned.

Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network (3-9-99)

Reports of GHB overdose and toxicity in the U.S. appear to be increasing.[78] In 1990, a preliminary study of GHB poisonings, based on data from Poison Control Centers, revealed that at least 57 cases of illness were attributed to GHB exposure in nine states (CDC, 1990). However, GHB-related intoxication is on the rise. In 1996, Poison Control Centers in New York and Texas documented 43 cases of acute poisonings associated with GHB in one year (CDC, 1996). The symptoms of acute GHB toxicity included vomiting, drowsiness, vertigo, and loss of consciousness, respiratory depression, tremors, myoclonus, coma, and seizure activity. Most patients required emergency room care and four fatalities were reported. The demographics of the New York abusers indicated 18 males and 12 females with an average age of 24; there were 8 adverse events reported in teenagers. Eleven of the 30 were admitted to critical care and required intubation or assisted respiration; seizures were reported in two cases.

In Fayette County, Georgia, there were 37 cases of GHB poisoning from 1991 through 1993. Most cases involved white males 17-22 years of age who were body builders. The San Francisco Bay Area Regional Poison Control Center (Dyer *et al.*, 1994) reported 66 encounters with GHB from 1992 though April 1994. In most instances, GHB was reportedly taken alone (79%) but the combined substances featured alcohol (11%), MDMA (1.5%), methamphetamine (4.5%), and opiates (1.5%) and nitrous oxide (1.5%)

In response to fifteen overdose cases that occurred in the last week of December 1995 through the first week of January 1996, the Oklahoma Poison Control Center issued a press release warning about GHB. These cases involved young adults aged 19-27 who had overdosed on GHB and received emergency medical treatment. There were no deaths, but in one incident, a 19-year-old female went into cardiac arrest within 15 minutes of ingesting GHB. All had obtained GHB from a local bar and consumed the GHB with alcohol Individuals have also developed complications from exposure to two of the manufacturing components of GHB, sodium hydroxide and gamma-butyrolactone.

Ross (1995) reported two GHB overdoses occurring in Atlanta. One case involved a 22-year-old male who had been taking 1-2 tablespoons of GHB twice daily for 5 years. The patient confirmed ingesting alcohol with GHB. Since this episode, the patient was treated three additional times for GHB overdose in the emergency department. During all of these episodes the patient required assisted ventilation. A second case involved a 28-year-old female bodybuilder who reported taking 1.5 teaspoons of GHB to help her relax after an intense bodybuilding session. James (1996) described several patients with seizures/decreased levels of consciousness, including one death, a 20-year-old woman who drank GHB in combination with alcohol.

After doses greater than 50 mg/kg orally, somnolence was reported in as little as 15 minutes, unconsciousness and profound coma within 30-40 minutes following ingestion[79] exacerbated when taken with alcohol GHB is relatively short acting After treatment in hospital emergency Symptoms were departments all individuals awoke within 2 to 4 hours of GHB ingestion.[80]

Reports of abuse of illicit GHB use indicate that the drug can be used to endanger the health and safety of others. For example, there have been reports of GHB users driving motor vehicles or caring for young children while impaired.[21] The DEA reported five cases of persons being found behind the wheel of a car while intoxicated with GHB.

Also significant are the reports of how GHB has been used to physically- and mentally-incapacitate women to facilitate sexual assault and "date-rape." The DEA has documented at least seventeen such cases originating from Florida, Texas, Louisiana, and Maryland. These cases have been substantiated by urinalysis and law enforcement investigations.

7. Its Psychic or Physiologic Dependence Liability

Dependence upon GHB has not been formally evaluated in preclinical or clinical studies. Galloway *et al* (1997) published case reports of eight individuals abusing GHB for its sedative, euphorigenic, and anabolic effects. Individuals (6 of 8) abused GHB for its psychoactive effects and obtained drug by illicit purchase. Upon discontinuation of GHB, mild withdrawal symptoms, which included insomnia, muscle cramps, tremor and anxiety, were described. Frederick *et al.* (1995) also described one individual who abused GHB for 1.5 years and described tolerance to GHB's euphoric and sedative effects. In this individual, abrupt cessation resulted in symptoms of insomnia, anxiety, tremor, and sweating. These anecdotal reports originating from the Haight-Ashbury Free Clinic (San Francisco) have all involved clandestinely manufactured GHB.

Although these and other anecdotal reports describe mild withdrawal symptoms following abrupt discontinuation of excessive use of GHB, these reports cannot be relied upon as evidence of significant physical dependence. These symptoms were largely described in the setting of polydrug and alcohol abuse, and therefore in the setting of withdrawal from other substances taken concomitantly. Clinical trial experience has failed to confirm a physical dependence profile

There are no well-developed clinical data from which to conclude that there is psychological dependence on GHB. Psychological dependence may only be intimated by anecdotal reports of escalation of GHB dose, increased frequency of use, and continued use despite adverse consequences.

8. Whether the substance is an immediate precursor of a substance already controlled under this article.

GHB is not an immediate precursor of any controlled substance

RECOMMENDATION

After consideration of the eight factors discussed above, FDA recommends that GHB and all mixtures, compounds and preparations of GHB should be placed in schedule I of the CSA, except that any mixture, compound or preparation of GHB that is the subject of an FDA authorized investigational new drug application pursuant to 21 CFR part 312 should be placed in schedule III.

Part I

Except as discussed in Part II below, GHB meets the criteria for placing a substance in schedule I of the CSA under 21 U.S.C. 812(b)(1).

A. Abuse Potential

GHB can penetrate the blood brain barrier and is active in the central nervous system. It is a sedative-hypnotic agent that produces dose- and concentration-dependent CNS effects in humans. Its onset of sedative action occurs within 15 minutes of oral ingestion and it lasts up to 3 hours. GHB in low doses has been associated with amnesia and hypotonia. Depending on the dose ingested, its effects may range from mild sedation to profound coma and, if respiratory function is not supported, death. It is water soluble and therefore miscible in alcoholic beverages. Its CNS effects are further enhanced by alcohol.

Self-administration and drug discriminative effects studies in animals indicate that GHB's reinforcing and stimulus generalization effects were similar to those of alcohol and substances in schedule IV such as the benzodiazepines rather than schedule I or II opiates and hallucinogens. Its abuse potential is theoretically similar to that of other substances in lower schedules of control.

However, the rapid onset of sedation coupled with the amnestic features of this agent, particularly when added to alcohol to conceal its presence and potentiate its effects, appear to make GHB an effective agent to physically and mentally incapacitate victims in the commission a crime. In addition, pharmacodynamic data indicate that GHB has a narrow therapeutic index, with the difference between the dose of GHB necessary for a desired hypnotic effect and that which produces unconsciousness being relatively small—and even smaller in the presence of alcohol. In comparison, some of the benzodiazepines in Schedule IV have a much wider therapeutic index. Epidemiological data show significant increases in emergency room and medical examiner reports related to GHB, and law enforcement data confirm GHB's use in third party abuse settings.

GHB has one additional characteristic which increases its abuse liability—it can be easily manufactured in a clandestine setting, resulting in a potentially unlimited supply. There is widespread dissemination of information on the INTERNET and other sources regarding its manufacture using a simple, one-step synthesis from readily available and inexpensive chemical

precursors. No specialized training or equipment is needed. In addition, the widesp read availability of illicit preparations of unknown strength and purity raise further pub c health concerns that distinguish GHB's abuse liability from that of other sedative/hypnoti agents.

For these reasons, and except as provided in Part II of this Recommendation, FD believes that GHB has a "high potential for abuse" relative to substances controlled in schedule III, IV and V.

B. Medical Use

FDA has not approved a new drug application (NDA) for a GHB product, nor can HB be marketed lawfully for medical use in the United States without an NDA. For this reason FDA believes that GHB has "no currently accepted medical use in the United States" at his time.

C. Safety

Clandestinely produced GHB is a substance of unknown, unregulated, and highly variable quality, strength, and purity. It has not been studied in any reliable manner and there is no accepted safety profile for this substance. Even if used under medical supervision, the safety of such a substance could not be predicted. Therefore, the FDA believes that there is a "lack of accepted safety for use of the drug or other substance under medical supervision."

Part II

GHB substances and products that are the subject of FDA authorized investigational new drug applications, pursuant to 21 CFR part 312, do not meet the criteria for placement in schedule I. Instead, such products and substances should be subject to control under schedule III of the CSA, 21 U.S.C. 812 (b)(3)

A. Abuse Potential

GHB products are currently being studied under FDA authorized investigational new drug applications. None of the reports of actual abuse of GHB that support the scheduling recommendation in Part I has involved GHB that was diverted from an authorized study. Moreover, given the ease with which GHB can be synthesized from readily available materials, it is considerably less likely that these authorized studies will become a source for unlawful use or abuse of GHB. In essence, the widespread availability of clandestinely produced GHB decreases the abuse liability and potential for abuse of the products being studied in authorized research programs and well-supervised clinics. For this reason, a GHB product or substance that is the subject of an authorized protocol and is being studied under a carefully designed research

protocol has a "low potential for abuse relative to drugs or other substances in sch. dule III" (see 21 U.S.C. 812 (b)(4)(A).

B. Medical Use

As discussed in Part I, GHB does not have a "currently accepted medical use in tr; atment in the United States" as that term has been interpreted in by the FDA and DEA.

A GHB product, however, has recently been granted a protocol under 21 CFR 312.34 to allow for expanded, treatment use of the product in patients who suffer from cataplexy a: sociated with narcolepsy. In this instance, the study and development of a GHB product is sufficiently far along to suggest that authorized formulations of GHB may be considered as havin, a "currently accepted medical use with severe restrictions" under the CSA (see 21 U.S.C. 812 b)(2)(B); see also 47 FR 281241, June 29,1982).

C. Physical or Psychological Dependence

There is no well-developed evidence from clinical studies to suggest that GHB leads to psychological dependence. The few available anecdotal case reports sugge: only mild withdrawal symptoms that may be indicative of low risk of physical dependenc. Similarly, from these few anecdotal reports, instances of escalation of GHB dose, increased frequency of use, and continued use despite adverse consequences are only suggestive of dependence production. There is no evidence, however to suggest that abuse of GHB lead to "severe" dependence (see 21 U.S.C. 812 (b)(2)(C)). When compared to substances in schedules II and III, GHB's physical and psychological dependence producing effects appear to be "lim ited" (see 21 U.S C. 812 (b)(4)(C)).

GHB has a high potential for abuse relative to substances controlled in schedules III IV and V. GHB has no accepted medical use and, when manufactured clandestinely, is unsafe for use under medical supervision. Accordingly, and except as provided below, GHB should be c ntrolled in Schedule I

Formulations of GHB currently are being studied under FDA-authorized INDs. At least one sponsor's formulation has been granted orphan drug status under section 526 of the Food, Drug, and Cosmetic Act, and is available under a treatment use protocol under 21 CFR § 312.34. None of the reports of actual abuse of GHB that support the Schedule I recommend tion has involved GHB that was diverted from an authorized study. Given the ease with wh ch GHB can be synthesized from readily available materials, it is unlikely that authorized studie: will become a source of GHB for abuse. Rather, the abuse potential of GHB, when used under an authorized research protocol, is consistent with substances typically controlled under Schedule IV. Information on the dependence producing effects of GHB is limited, but available d ta suggest that its potential for physical and psychological dependence is also consistent with control under Schedule IV

Authorized formulations of GHB, however, do not meet the "accepted medical use" criteria set forth in Schedule IV. At best, an authorized formulation of GHB is far enough along in the development process to meet the standard under Schedule II of a drug or substance having a "currently accepted medical use with severe restrictions." Under these circumstances, FDA recommends placing authorized formulations of GHB in Schedule III, a level of control higher than Schedule IV to take into account the lack of an accepted medical use and a level of control lower than schedule II to take into account the abuse and dependence liability findings for authorized formulations of GHB.

Endnotes

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[3] Galloway et al., 1997
[4] Winter, 1981; Colombo, et al , 1995b,c, Beardsley, et al., 1996
[5] Colombo et al , 1995b
[6] Fance et al , 1997
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[8] (Jenney et al., 1962; Mamelak et al , 1977, 1986, Mamelak, 1989; Laborit, 1964)
[9] Bessman and Fishbein, 1963; Maitre, 1997
[10] Mamelak, 1989; Cash, 1994; review by Maitre, 1997
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[12] Doherty et al., 1978
[13] Vayer et al., 1987, Tunnicliff, 1992, Maitre, 1997.
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[15] Benavides et al., 1982: Snead and Liu, 1984; Maitre, 1997
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[21] Gessa et al., 1966; Gessa et al., 1968a,b; Roth et al , 1970
[22] Hechler et al , 1991
[23] Gessa et al., 1966, 1968a,b and Roth et al , 1970
[24] Gessa et al , 1966
[25] Gessa et al , 1966, Gessa et al , 1968a,b, Roth et al., 1970; Diana et al , 1991
[26] Roth et al., 1973; Diana et al., 1991
[27] (Feigenbaum and Simantov, 1996

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[33] (Kršiak et al., 1974).
[34] McCabe et al., 1971
[35] Mamelak et al., 1977
[36] (Jenney et al., 1962; Mamelak et al., 1977, 1986; Mamelak, 1989; Laborit, 1964)
[37] Metcalf et al, 1966; Hunter et al., 1971; Mamelack, 1989
[38] Hunter et al., 1971
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[41] Hedner et al., 1985
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[46] . Gerra et al., 1994a.
[47] Gerra et al , 1994c, 1995
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[52] Hoes et al., 1980
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[55] Roth and Giarman, 1966, Shumate and Snead, 1979
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[77] CDC 1990, 1996; Gast and Frenia, 1994; Dyer, 1994; Ross, 1995; James, 1996
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Drug Enforcement Administration

Washington, D.C. 20537

SEP 16 1997

1997

Dr. John M. Eisenberg
Acting Assistant Secretary for Health
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Eisenberg:

In accordance with the provisions of Title 21, U.S.C., Section 811(b), of the Controlled Substances Act (CSA), the Drug Enforcement Administration (DEA) has gathered and reviewed the available data on gamma hydroxybutyrate (GHB). Your scientific and medical evaluation of the enclosed data and your scheduling recommendation for GHB are requested so that the DEA can make a final determination regarding the scheduling of this substance.

GHB is a substance that is currently not controlled under the Controlled Substances Act (CSA). To date, the data available to DEA shows that GHB is abused as a Central Nervous System (CNS) depressant, an intoxicant and euphoriant, a growth hormone releasing agent, and in criminal assaults. It is easily synthesized illicitly in clandestine laboratories with readily obtainable precursors by those inexperienced in chemistry. The drug is easily administered orally, taken in the form of the sodium salt usually dissolved in water or alcoholic drink.

Abuse of GHB is nationwide, increasing and associated with serious public health and safety risks. Since 1990, approximately 500 encounters with GHB have been documented by information gathered from federal, state and local law enforcement agencies, poison control centers, hospitals medical examiners, and the scientific literature. GHB has been encountered in at least 35 states. DEA is aware of 19 deaths associated with GHB use. GHB is sold either in solid or powder form or dissolved in liquid and abused by the oral route. It is trafficked locally, regionally and nationally.

DEA is only aware of limited research into the therapeutic use of GHB in the United States. DEA is not aware of any legitimately marketed products containing GHB in the United States. The Food and Drug Administration (FDA) considered GHB unsafe and banned its manufacture and distribution in dietary supplements. Since GHB is not controlled federally or under most

state laws, it is not the target of law enforcement investigations and its illicit manufacture, abuse and trafficking are severely under reported. Nevertheless, the data contained in the enclosed document show that there is an alarming level of GHB abuse, that it is widespread and increasing, that the GHB is illicitly produced in clandestine laboratories, and that this abuse is associated with many and serious adverse public health and safety risks. These data strongly indicate that GHB has a high potential for abuse and strongly support its placement in a restrictive schedule under the CSA. Final determination of the specific schedule must await the scientific and medical evaluation of the DHHS.

Appropriate members of the DEA staff are available to provide whatever assistance may be needed. In order to facilitate the exchange of information, the DEA staff is authorized to exchange relevant information directly with designated members of your staff. John H. King, Deputy Assistant Administrator, Office of Diversion Control, will act as liaison for this exchange of information. He can be reached at (202) 307-7165.

Sincerely,

James S. Milford

James S. Milford
Acting Deputy Administrator

Enclosure

ATTACHMENT 2

Public Law 106-172 (February 18, 2000)

Public Law 106–172
106th Congress

An Act

To amend the Controlled Substances Act to direct the emergency scheduling of gamma hydroxybutyric acid, to provide for a national awareness campaign, and for other purposes.

Feb. 18, 2000
[H.R. 2130]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000.
Law enforcement and crimes.
21 USC 801 note.
21 USC 812 note.

SECTION 1. SHORT TITLE.

This Act may be cited as the "Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000".

SEC. 2. FINDINGS.

Congress finds as follows:

(1) Gamma hydroxybutyric acid (also called G, Liquid X, Liquid Ecstasy, Grievous Bodily Harm, Georgia Home Boy, Scoop) has become a significant and growing problem in law enforcement. At least 20 States have scheduled such drug in their drug laws and law enforcement officials have been experiencing an increased presence of the drug in driving under the influence, sexual assault, and overdose cases especially at night clubs and parties.

(2) A behavioral depressant and a hypnotic, gamma hydroxybutyric acid ("GHB") is being used in conjunction with alcohol and other drugs with detrimental effects in an increasing number of cases. It is difficult to isolate the impact of such drug's ingestion since it is so typically taken with an ever-changing array of other drugs and especially alcohol which potentiates its impact.

(3) GHB takes the same path as alcohol, processes via alcohol dehydrogenase, and its symptoms at high levels of intake and as impact builds are comparable to alcohol ingestion/intoxication. Thus, aggression and violence can be expected in some individuals who use such drug.

(4) If taken for human consumption, common industrial chemicals such as gamma butyrolactone and 1.4-butanediol are swiftly converted by the body into GHB. Illicit use of these and other GHB analogues and precursor chemicals is a significant and growing law enforcement problem.

(5) A human pharmaceutical formulation of gamma hydroxybutyric acid is being developed as a treatment for cataplexy, a serious and debilitating disease. Cataplexy, which causes sudden and total loss of muscle control, affects about 65 percent of the estimated 180,000 Americans with narcolepsy, a sleep disorder. People with cataplexy often are unable to work, drive a car, hold their children or live a normal life.

(6) Abuse of illicit GHB is an imminent hazard to public safety that requires immediate regulatory action under the Controlled Substances Act (21 U.S.C. 801 et seq.).

SEC. 3. EMERGENCY SCHEDULING OF GAMMA HYDROXYBUTYRIC ACID AND LISTING OF GAMMA BUTYROLACTONE AS LIST I CHEMICAL.

21 USC 812 note.

(a) EMERGENCY SCHEDULING OF GHB.—

(1) IN GENERAL.—The Congress finds that the abuse of illicit gamma hydroxybutyric acid is an imminent hazard to the public safety. Accordingly, the Attorney General, notwithstanding sections 201(a), 201(b), 201(c), and 202 of the Controlled Substances Act, shall issue, not later than 60 days after the date of the enactment of this Act, a final order that schedules such drug (together with its salts, isomers, and salts of isomers) in the same schedule under section 202(c) of the Controlled Substances Act as would apply to a scheduling of a substance by the Attorney General under section 201(h)(1) of such Act (relating to imminent hazards to the public safety), except as follows:

Deadline.

(A) For purposes of any requirements that relate to the physical security of registered manufacturers and registered distributors, the final order shall treat such drug, when the drug is manufactured, distributed, or possessed in accordance with an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (whether the exemption involved is authorized before, on, or after the date of the enactment of this Act), as being in the same schedule as that recommended by the Secretary of Health and Human Services for the drug when the drug is the subject of an authorized investigational new drug application (relating to such section 505(i)). The recommendation referred to in the preceding sentence is contained in the first paragraph of the letter transmitted on May 19, 1999, by such Secretary (acting through the Assistant Secretary for Health) to the Attorney General (acting through the Deputy Administrator of the Drug Enforcement Administration), which letter was in response to the letter transmitted by the Attorney General (acting through such Deputy Administrator) on September 16, 1997. In publishing the final order in the Federal Register, the Attorney General shall publish a copy of the letter that was transmitted by the Secretary of Health and Human Services.

Federal Register, publication.

(B) In the case of gamma hydroxybutyric acid that is contained in a drug product for which an application is approved under section 505 of the Federal Food, Drug, and Cosmetic Act (whether the application involved is approved before, on, or after the date of the enactment of this Act), the final order shall schedule such drug in the same schedule as that recommended by the Secretary of Health and Human Services for authorized formulations of the drug. The recommendation referred to in the preceding sentence is contained in the last sentence of the fourth paragraph of the letter referred to in subparagraph (A) with respect to May 19, 1999.

(2) FAILURE TO ISSUE ORDER.—If the final order is not issued within the period specified in paragraph (1), gamma

hydroxybutyric acid (together with its salts, isomers, and salts of isomers) is deemed to be scheduled under section 202(c) of the Controlled Substances Act in accordance with the policies described in paragraph (1), as if the Attorney General had issued a final order in accordance with such paragraph.

(b) ADDITIONAL PENALTIES RELATING TO GHB.—

(1) CONTROLLED SUBSTANCES ACT.—

(A) IN GENERAL.—Section 401(b)(1)(C) of the Controlled Substances Act (21 U.S.C. 841(b)(1)(C)) is amended in the first sentence by inserting after "schedule I or II," the following: "gamma hydroxybutyric acid (including when scheduled as an approved drug product for purposes of section 3(a)(1)(B) of the Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000),".

(B) CONFORMING AMENDMENT.—Section 401(b)(1)(D) of the Controlled Substances Act (21 U.S.C. 841(b)(1)(D)) is amended by striking ", or 30" and inserting "(other than gamma hydroxybutyric acid), or 30".

(2) CONTROLLED SUBSTANCES IMPORT AND EXPORT ACT.—

(A) IN GENERAL.—Section 1010(b)(3) of the Controlled Substances Import and Export Act (21 U.S.C. 960(b)(3)) is amended in the first sentence by inserting after "I or II," the following: "gamma hydroxybutyric acid (including when scheduled as an approved drug product for purposes of section 3(a)(1)(B) of the Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000),".

(B) CONFORMING AMENDMENT.—Section 1010(b)(4) of the Controlled Substances Import and Export Act (21 U.S.C. 960(b)(4)) is amended by striking "flunitrazepam)" and inserting the following: "flunitrazepam and except a violation involving gamma hydroxybutyric acid)".

(c) GAMMA BUTYROLACTONE AS ADDITIONAL LIST I CHEMICAL.—Section 102(34) of the Controlled Substances Act (21 U.S.C. 802(34)) is amended—

(1) by redesignating subparagraph (X) as subparagraph (Y); and

(2) by inserting after subparagraph (W) the following subparagraph:

"(X) Gamma butyrolactone.".

SEC. 4. AUTHORITY FOR ADDITIONAL REPORTING REQUIREMENTS FOR GAMMA HYDROXYBUTYRIC PRODUCTS IN SCHEDULE III.

Section 307 of the Controlled Substances Act (21 U.S.C. 827) is amended by adding at the end the following:

"(h) In the case of a drug product containing gamma hydroxybutyric acid for which an application has been approved under section 505 of the Federal Food, Drug, and Cosmetic Act, the Attorney General may, in addition to any other requirements that apply under this section with respect to such a drug product, establish any of the following as reporting requirements: Records.

"(1) That every person who is registered as a manufacturer of bulk or dosage form, as a packager, repackager, labeler, relabeler, or distributor shall report acquisition and distribution transactions quarterly, not later than the 15th day of the month succeeding the quarter for which the report is submitted, and annually report end-of-year inventories. Deadline.

Deadline.

"(2) That all annual inventory reports shall be filed no later than January 15 of the year following that for which the report is submitted and include data on the stocks of the drug product, drug substance, bulk drug, and dosage forms on hand as of the close of business December 31, indicating whether materials reported are in storage or in process of manufacturing.

"(3) That every person who is registered as a manufacturer of bulk or dosage form shall report all manufacturing transactions both inventory increases, including purchases, transfers, and returns, and reductions from inventory, including sales, transfers, theft, destruction, and seizure, and shall provide data on material manufactured, manufactured from other material, use in manufacturing other material, and use in manufacturing dosage forms.

"(4) That all reports under this section must include the registered person's registration number as well as the registration numbers, names, and other identifying information of vendors, suppliers, and customers, sufficient to allow the Attorney General to track the receipt and distribution of the drug.

"(5) That each dispensing practitioner shall maintain for each prescription the name of the prescribing practitioner, the prescribing practitioner's Federal and State registration numbers, with the expiration dates of these registrations, verification that the prescribing practitioner possesses the appropriate registration to prescribe this controlled substance, the patient's name and address, the name of the patient's insurance provider and documentation by a medical practitioner licensed and registered to prescribe the drug of the patient's medical need for the drug. Such information shall be available for inspection and copying by the Attorney General.

Applicability.

"(6) That section 310(b)(3) (relating to mail order reporting) applies with respect to gamma hydroxybutyric acid to the same extent and in the same manner as such section applies with respect to the chemicals and drug products specified in subparagraph (A)(i) of such section.".

SEC. 5. CONTROLLED SUBSTANCES ANALOGUES.

(a) RULE OF CONSTRUCTION REGARDING CONTROLLED SUBSTANCE ANALOGUES.—Section 102(32) of the Controlled Substances Act (21 U.S.C. 802(32)) is amended—

(1) in subparagraph (A), by striking "subparagraph (B)" and inserting "subparagraph (C)";

(2) by redesignating subparagraph (B) as subparagraph (C); and

(3) by inserting after subparagraph (A) the following new subparagraph (B):

"(B) The designation of gamma butyrolactone or any other chemical as a listed chemical pursuant to paragraph (34) or (35) does not preclude a finding pursuant to subparagraph (A) of this paragraph that the chemical is a controlled substance analogue.".

(b) DISTRIBUTION WITH INTENT TO COMMIT CRIME OF VIOLENCE.—Section 401(b)(7)(A) of the Controlled Substances Act (21 U.S.C. 841(b)(7)(A)) is amended by inserting "or controlled substance analogue" after "distributing a controlled substance".

SEC. 6. DEVELOPMENT OF MODEL PROTOCOLS, TRAINING MATERIALS, FORENSIC FIELD TESTS, AND COORDINATION MECHANISM FOR INVESTIGATIONS AND PROSECUTIONS RELATING TO GAMMA HYDROXYBUTYRIC ACID, OTHER CONTROLLED SUBSTANCES, AND DESIGNER DRUGS.

21 USC 801 note.

(a) IN GENERAL.—The Attorney General, in consultation with the Administrator of the Drug Enforcement Administration and the Director of the Federal Bureau of Investigation, shall—

(1) develop—

(A) model protocols for the collection of toxicology specimens and the taking of victim statements in connection with investigations into and prosecutions related to possible violations of the Controlled Substances Act or other Federal or State laws that result in or contribute to rape, other crimes of violence, or other crimes involving abuse of gamma hydroxybutyric acid, other controlled substances, or so-called "designer drugs"; and

(B) model training materials for law enforcement personnel involved in such investigations; and

(2) make such protocols and training materials available to Federal, State, and local personnel responsible for such investigations.

(b) GRANT.—

(1) IN GENERAL.—The Attorney General shall make a grant, in such amount and to such public or private person or entity as the Attorney General considers appropriate, for the development of forensic field tests to assist law enforcement officials in detecting the presence of gamma hydroxybutyric acid and related substances.

(2) AUTHORIZATION OF APPROPRIATIONS.—There are authorized to be appropriated such sums as may be necessary to carry out this subsection.

(c) REPORT.—Not later than 180 days after the date of the enactment of this Act, the Attorney General shall submit to the Committees on the Judiciary of the Senate and House of Representatives a report on current mechanisms for coordinating Federal, State, and local investigations into and prosecutions related to possible violations of the Controlled Substances Act or other Federal or State laws that result in or contribute to rape, other crimes of violence, or other crimes involving the abuse of gamma hydroxybutyric acid, other controlled substances, or so-called "designer drugs". The report shall also include recommendations for the improvement of such mechanisms.

Deadline.

SEC. 7. ANNUAL REPORT REGARDING DATE-RAPE DRUGS; NATIONAL AWARENESS CAMPAIGN.

21 USC 801 note.

(a) ANNUAL REPORT.—The Secretary of Health and Human Services (in this section referred to as the "Secretary") shall periodically submit to Congress reports each of which provides an estimate of the number of incidents of the abuse of date-rape drugs (as defined in subsection (c)) that occurred during the most recent 1-year period for which data are available. The first such report shall be submitted not later than January 15, 2000, and subsequent reports shall be submitted annually thereafter.

Deadline.

(b) NATIONAL AWARENESS CAMPAIGN.—

(1) DEVELOPMENT OF PLAN; RECOMMENDATIONS OF ADVISORY COMMITTEE.—

(A) IN GENERAL.—The Secretary, in consultation with the Attorney General, shall develop a plan for carrying out a national campaign to educate individuals described in subparagraph (B) on the following:

(i) The dangers of date-rape drugs.

(ii) The applicability of the Controlled Substances Act to such drugs, including penalties under such Act.

(iii) Recognizing the symptoms that indicate an individual may be a victim of such drugs, including symptoms with respect to sexual assault.

(iv) Appropriately responding when an individual has such symptoms.

(B) INTENDED POPULATION.—The individuals referred to in subparagraph (A) are young adults, youths, law enforcement personnel, educators, school nurses, counselors of rape victims, and emergency room personnel in hospitals.

Deadline. Establishment.

(C) ADVISORY COMMITTEE.—Not later than 180 days after the date of the enactment of this Act, the Secretary shall establish an advisory committee to make recommendations to the Secretary regarding the plan under subparagraph (A). The committee shall be composed of individuals who collectively possess expertise on the effects of date-rape drugs and on detecting and controlling the drugs.

Deadline.

(2) IMPLEMENTATION OF PLAN.—Not later than 180 days after the date on which the advisory committee under paragraph (1) is established, the Secretary, in consultation with the Attorney General, shall commence carrying out the national campaign under such paragraph in accordance with the plan developed under such paragraph. The campaign may be carried out directly by the Secretary and through grants and contracts.

Deadline.

(3) EVALUATION BY GENERAL ACCOUNTING OFFICE.—Not later than 2 years after the date on which the national campaign under paragraph (1) is commenced, the Comptroller General of the United States shall submit to Congress an evaluation of the effects with respect to date-rape drugs of the national campaign.

(c) DEFINITION.—For purposes of this section, the term "date-rape drugs" means gamma hydroxybutyric acid and its salts, isomers, and salts of isomers and such other drugs or substances as the Secretary, after consultation with the Attorney General, determines to be appropriate.

SEC. 8. SPECIAL UNIT IN DRUG ENFORCEMENT ADMINISTRATION FOR ASSESSMENT OF ABUSE AND TRAFFICKING OF GHB AND OTHER CONTROLLED SUBSTANCES AND DRUGS.

Deadline.

(a) ESTABLISHMENT.—Not later than 60 days after the date of the enactment of this Act, the Attorney General shall establish within the Operations Division of the Drug Enforcement Administration a special unit which shall assess the abuse of and trafficking in gamma hydroxybutyric acid, flunitrazepam, ketamine, other controlled substances, and other so-called "designer drugs" whose use has been associated with sexual assault.

(b) PARTICULAR DUTIES.—In carrying out the assessment under subsection (a), the special unit shall—

(1) examine the threat posed by the substances and drugs referred to in that subsection on a national basis and regional basis; and

(2) make recommendations to the Attorney General regarding allocations and reallocations of resources in order to address the threat.

(c) REPORT ON RECOMMENDATIONS.—

(1) REQUIREMENT.—Not later than 180 days after the date of the enactment of this Act, the Attorney General shall submit to the Committees on the Judiciary of the Senate and House of Representatives a report which shall— Deadline.

(A) set forth the recommendations of the special unit under subsection (b)(2); and

(B) specify the allocations and reallocations of resources that the Attorney General proposes to make in response to the recommendations.

(2) TREATMENT OF REPORT.—Nothing in paragraph (1) may be construed to prohibit the Attorney General or the Administrator of the Drug Enforcement Administration from making any reallocation of existing resources that the Attorney General or the Administrator, as the case may be, considers appropriate.

SEC. 9. TECHNICAL AMENDMENT.

Section 401 of the Controlled Substances Act (21 U.S.C. 841) is amended by redesignating subsections (d), (e), (f), and (g) as subsections (c), (d), (e), and (f), respectively.

Approved February 18, 2000.

LEGISLATIVE HISTORY—H.R. 2130 (S. 1561):

HOUSE REPORTS: No. 106–340, Pt. 1 (Comm. on Commerce).
CONGRESSIONAL RECORD:
Vol. 145 (1999): Oct. 12, considered and passed House.
Nov. 19, considered and passed Senate, amended, in lieu of S. 1561.
Vol. 146 (2000): Jan. 31, House concurred in Senate amendments.
WEEKLY COMPILATION OF PRESIDENTIAL DOCUMENTS, Vol. 36 (2000):
Feb. 18, Presidential statement.

○

ATTACHMENT 3

Federal Register Notice (Monday, March 5, 2001; Vol. 66, No. 43)
World Health Organization Scheduling Recommendations

publication of this document in the **Federal Register**. Therefore, a comment is best assured of having its full effect if OMB receives it within 30 days of publication. Written comments and recommendations for the proposed information collection should be sent directly to the following: Office of Management and Budget, Paperwork Reduction Project, 725 17th Street, NW., Washington, DC 20503, Attn: Desk Officer for ACF.

Dated: February 27, 2001.

Bob Sargis,

Reports Clearance Officer.

[FR Doc. 01–5234 Filed 3–2–01; 8:45 am]

BILLING CODE 4184–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00N–1441]

Agency Information Collection Activities; Announcement of OMB Approval; Infant Formula Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a collection of information entitled ''Infant Formula Requirements'' has been approved by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995.

FOR FURTHER INFORMATION CONTACT: Peggy Schlosburg, Office of Information Resources Management (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–1223.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of November 9, 2000 (65 FR 67388), the agency announced that the proposed information collection had been submitted to OMB for review and clearance under 44 U.S.C. 3507. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. OMB has now approved the information collection and has assigned OMB control number 0910–0256. The approval expires on February 29, 2004. A copy of the supporting statement for this information collection is available on the Internet at http://www.fda.gov/ohrms/dockets.

Dated: February 23, 2001.

William K. Hubbard,

Senior Associate Commissioner for Policy, Planning, and Legislation.

[FR Doc. 01–5158 Filed 3–2–01; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00N–1257]

International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization Scheduling Recommendations for 4-Bromo-2,5-dimethoxyphenethylamine (2C–B); Gamma-hydroxybutyric acid (GHB); 4-Methylthioamphetamine (4-MTA); Zolpidem (INN)

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is providing interested persons with the opportunity to submit written comments concerning recommendations by the World Health Organization (WHO) to impose international manufacturing and distribution restrictions, under international treaties, on certain drug substances. The comments received in response to this notice will be considered in preparing the U.S. position on these proposals for a meeting of the United Nations Commission on Narcotic Drugs (CND) in Vienna, Austria, March 20 to 29, 2001. This notice is issued under the Controlled Substances Act.

DATES: Submit written comments by March 15, 2001.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. To ensure expeditious review of written comments, send a copy by facsimile or e-mail to: James R. Hunter (address below).

FOR FURTHER INFORMATION CONTACT: James R. Hunter, Controlled Substances Staff (HFD–9), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2098, Fax: 301–443–9222, e-mail: hunterj@cder.fda.gov.

SUPPLEMENTARY INFORMATION:

I. Background

The United States is a party to the 1971 Convention on Psychotropic Substances (the Convention). Section 201(d)(2)(B) of the Controlled Substances Act (the CSA) (21 U.S.C. 811(d)(2)(B)) provides that when the United States is notified under Article 2 of the Convention that CND proposes to decide whether to add a drug or other substance to one of the schedules of the Convention, transfer a drug or substance from one schedule to another, or delete it from the schedules, the Secretary of State must transmit notice of such information to the Secretary of Health and Human Services (HHS). The Secretary of HHS must then publish a summary of such information in the **Federal Register** and provide opportunity for interested persons to submit comments. The Secretary of HHS must then evaluate the proposal and furnish a recommendation to the Secretary of State that shall be binding on the representative of the United States in discussions and negotiations relating to the proposal.

As detailed below, the Secretary of State has received notification from the Secretary-General of the United Nations (the Secretary-General) regarding substances to be considered for control under the Convention. The notification reflects the recommendations from the 31st WHO Expert Committee for Drug Dependence (ECDD), which met in June 1998. In the **Federal Register** of April 28, 2000 (65 FR 24969), FDA announced the WHO ECDD review, and the agency invited interested persons to submit information for WHO's consideration.

The full text of the notification from the Secretary-General is provided in section II of this document. Section 201(d)(2)(B) of the CSA requires the Secretary of HHS, after receiving a notification proposing scheduling, to publish a notice in the **Federal Register** to provide the opportunity for interested persons to submit information and comments on the proposed scheduling action.

II. United Nations Notification

The formal United Nations notification that identifies the drug substances and explains the basis for the recommendations is reproduced below.

Notification on 2C-B, 4-MTA, GHB and Zolpidem: Reference: NAR/CL.26/2000 CU 2000/240.

C1971/WHO
UNDCP 42nd CND
TLACSB/CNDS–40/00

The Secretary-General of the United Nations presents his compliments to the Secretary of State of the United States of

America and has the honour to inform the Government that, pursuant to article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances, 1971, he has received a notification from the World Health Organization (WHO) concerning proposed recommendations for international control in respect of the following four substances: 2C-B, 4-MTA, GHB and zolpidem.

In accordance with the provisions of article 2, paragraph 2, of the 1971 Convention, the Secretary-General is transmitting the text of that notification as an annex to the present note.

As will be seen from the notification and the attached assessments and recommendations, WHO recommends that 2C-B be included in Schedule II, 4-MTA in Schedule I, and GHB and zolpidem in Schedule IV of that Convention.

Article 2, paragraph 1, of the Convention reads:

> If a Party or the World Health Organization has information relating to a substance not yet under international control which in its opinion may require the addition of that substance to any of the Schedules of this Convention, it shall notify the Secretary-General and furnish him with the information in support of that notification. The foregoing procedure shall also apply when a Party or the World Health Organization has information justifying the transfer of a substance from one Schedule to another among those Schedules, or the deletion of a substance from the Schedules.

Article 2, paragraph 4, reads:

> If the World Health Organization finds: (a) That the substance has the capacity to produce (i)(1) a state of dependence and (2) central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function or thinking or behaviour or perception or mood, or (ii) similar abuse and similar ill effects as a substance in Schedule I, II, III or IV, and (b) That there is sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control, the World Health Organization shall communicate to the Commission an assessment of the substance, including the extent or likelihood of abuse, the degree of seriousness of the public health and social problem and the degree of usefulness of the substance in medical therapy, together with recommendations on control measures, if any, that would be appropriate in the light of its assessment.

Pursuant to article 2, paragraph 2, of the Convention, the notification, together with the assessments and recommendations from WHO as well as any data received from Governments on any of these substances, will be brought to the attention of the Commission on Narcotic Drugs at its forty-fourth session in March 2001. Any action or decision taken by the Commission with respect to that notification, pursuant to article 2, paragraph 5, of the Convention, will be notified to States Parties in due course.

Article 2, paragraph 5, of the Convention reads:

> The Commission, taking into account the communication from the World Health Organization, whose assessments shall be determinative as to medical and scientific matters, and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information from the World Health Organization or from other appropriate sources.

The Secretary-General would appreciate it if the Government would submit data on seizures of any of these substances or on the existence of clandestine laboratories manufacturing them. Such data would assist the Commission in its consideration of possible international control of some or all of the substances under review.

In order to further assist the Commission in reaching a decision, it would be appreciated if any economic, social, legal, administrative or other factors the Government may consider relevant to the question of the possible scheduling of these four substances could be communicated by 12 December 2000 to the Executive Director of the United Nations International Drug Control Programme, c/o Commission on Narcotic Drugs Secretariat Section, P.O. Box 500, A–1400 Vienna, Austria, fax: 43–1–26060–5885.

2 November 2000
NAR/CL.26/2000

Annex—Note Dated 4 October 2000 Addressed to the Secretary-General by the Director-General of the World Health Organization

The Director-General of the World Health Organization presents her compliments to the Secretary-General of the United Nations and has the honour to submit, in accordance with Article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances, 1971, assessments and recommendations of the World Health Organization, as set forth on the annex hereto, concerning the proposed international control in respect of 2C-B, 4-MTA, GHB, and zolpidem.

The Director-General of the World Health Organization avails herself of this opportunity to renew to the Secretary-General of the United Nations the assurances of her highest consideration.

2C-B (4-Bromo-2,5-dimethoxyphenylethylamine) Substance identification

2C-B is chemically 4-bromo-2,5-dimethoxyphenylethylamine; 2-(4-bromo-2,5-dimethoxyphenyl) ethylamine (CAS 66142–81–2). Other names include: α-desmethyl DOB; BDMPEA; MFT; Erox; Nexus; Performax. There are no chiral centres; therefore, no stereoisomers or racemates are possible.

Similarity to Known Substances and Effects on the Central Nervous System

2C-B has structural and pharmacological similarities to brolamfetamine and mescaline. 2C–B is a selective partial agonist for 5-HT_{2A}- and 5-HT_{2C}-serotonin receptors. In humans, 2C–B is more potent than mescaline but less potent than brolamfetamine. In low doses it has sensory enhancing effects: skin sensitivity, heightened responsiveness to smells, tastes and sexual stimulation. In higher doses 2C-B is a strong hallucinogen. 2C-B produces particularly marked visual hallucinations with an intense colour play, intriguing patterns emerging on surfaces and distortions of objects and faces. It was reported to enhance sexual feelings, sexual perception and performance.

Dependence Potential

There are no animal or human studies about the dependence potential of 2C-B.

Actual Abuse and/or Evidence of Likelihood of Abuse

In the 1990s, 2C-B was sold as an aphrodisiac in several countries and some abuse of 2C-B has been reported by a number of countries. These suggest that 2C-B has modest abuse liability like other hallucinogens. Although hallucinogens are rarely associated with compulsive use or dependent use, they are known to have modest abuse potential, particularly in polydrug abusers.

Therapeutic Usefulness

Apart from the controversial experimental use to facilitate psychotherapy, hallucinogens, such as 2C-B, do not have any therapeutic usefulness.

Recommendation

Despite the limited availability of studies, the chemical and pharmacological similarity of 2C-B to the hallucinogen mescaline has been demonstrated. The altered state of mind induced by hallucinogens such as 2C-B may result in harm to the user and to

others. Based on its perceived aphrodisiac effects and known modest abuse potential of hallucinogenic drugs in general, it is estimated that 2C-B may be abused so as to constitute a public health and social problem warranting its placement under international control. However, hallucinogens are rarely associated with compulsive use and abuse of 2C-B has been infrequent, suggesting that abuse of 2C–B is likely to constitute a substantial, rather than an especially serious, risk to public health. On these bases, it is recommended that 2C-B be placed in Schedule II of the 1971 Convention on Psychotropic Substances.

4-MTA (4-methylthioamphetamine) Substance Identification

4-MTA is chemically 4-methylthioamphetamine (CAS 14116–06–4) Other names include: α-methyl 4-methylthiophenetylarnine, *p*-methylthioamphetamine; 4-MTA; *p–MTA;* MTA; MK; S5; S_5; Flatliner; The One and Only Dominator. 4-MTA has one chiral centre and can exist in two enatiomers and a racemate. Only the racemic mixture has been reported to have been synthesised.

Similarity to Known Substances and Effects on the Central Nervous System

4-MTA is a potent serotonin-releasing agent and reversible inhibitor of monoamine oxidase-A, and is structurally similar to 4-methoxyamphetamine. Pharmacologically, it is similar to MDA and MDMA; studies suggest that 4-MTA is six times more potent than MDMA and MDA in inhibiting 5-HT uptake.

Dependence Potential

Drug discrimination studies in rats suggest that 4-MTA produces discriminative stimulus effects similar to MDMA. 4-MTA did not substitute for amphetamine, LSD or phencyclidine. Reports from the United Kingdom indicate that 4-MTA is abused for its stimulant/euphoric effects similar to MDMA.

Actual Abuse and/or Evidence of Likelihood of Abuse

4-MTA is mainly abused in Europe. It appears that 4-MTA is part of the dance music culture although its use is relatively less widespread probably because of perceptions by users that the drug is stronger and more harmful than other ''club drugs'' such as MDMA. 4-MTA has resulted in a number of fatalities and hospital admissions. It appears that toxic effects can be produced directly from the drug and that the presence of other drugs or alcohol may exacerbate such effects.

Therapeutic Usefulness

4-MTA has no recognized therapeutic use.

Recommendation

4-MTA is chemically and pharmacologically similar to MDA and MDMA. 4-MTA is a new synthetic drug which was seized for the first time in 1997. Although evidence of its actual abuse is available only in several countries in Europe, seizures, including those of large quantities reported from a wider range of countries, suggest that the trafficking and abuse of 4-MTA are more widespread than have been reported. Based on this and its similarity to known MDA-type psychotropic substances, as well as data from drug discrimination studies in animals, it is estimated that 4-MTA is likely to be abused so as to constitute a public health and social problem warranting its placement under international control. Taking into consideration that 4-MTA has no recognized therapeutic use and that it has resulted in a number of fatalities, abuse of 4-MTA is estimated to constitute an especially serious risk to public health. It is therefore recommended that 4-MTA be placed in Schedule I of the 1971 Convention on Psychotropic Substance.

GHB (Gamma-hydroxybutyric acid) Substance Identification

GHB is chemically γ-hydroxybutyric acid; 4-hydroxybutyric acid (CAS 591–81–1). GHB usually exists as either the free acid or as the sodium salt. Sodium oxybate (CAS 502–85–2) is a national nonproprietary name for its sodium salt. There are no chiral centres; therefore, no stereoisomers or racemates are possible.

Similarity to Known Substances and Effects on the Central Nervous System

GHB is an endogenous compound and is structurally similar to the neurotransmitter GABA. Pharmacologically, it produces sedative and anaesthetic effects at high doses. Such depressant effects of GHB appear to be associated with its cataleptic effects and are different from those of barbiturates and benzodiazepines. GHB sedation possessed distinct excitatory properties, which may be due to its effect on the dopaminergic system (increase in intracellular neuronal dopamine). GHB has been found to induce anesthesia (but does not provide pain relief), (slow-wave) sleep, bradycardia, vomiting, random clonic movements, hypothermia, reduction in potassium levels, decrease in ventilatory rate and apnoea. However, the respiratory centre remains sensitive to an increase in carbon dioxide.

Dependence Potential

In drug discrimination studies in animals, none of the known abused drugs has the ability to fully substitute for GHB. Morphine, dexamphetamine, LSD and some benzodiazepines produced, at best, partial substitution. There have been few studies regarding the dependence/abuse potential of GHB. However, during the numerous studies involving administration of GHB to patients at varying concentrations, no dependence has been observed at low doses of GHB. At prolonged high doses, however, a withdrawal syndrome including insomnia, muscular cramping, tremor and anxiety has been noted upon discontinuation in some cases.

Actual Abuse and/or Evidence of Likelihood of Abuse

GHB abuse has been reported in Australia, USA and many countries in Europe. Precursors of GHB, such as γ-butyrolaztone and 1,4-butanediol, which are metabolized to GHB in the body, have also been abused. Although initially abused by body-builders for its apparent growth hormone promoting properties, the more recent primary mode of abuse worldwide has been the use of GHB for its subjective hypnotic, euphoric and hallucinogenic effects, especially in the context of the dance music culture (i.e. ''raves''). Some users have also claimed to use GHB as an alternative to alcohol (for relaxation), as a sexual adjunct, appetite suppressant, anti-aging product and has also been implicated in cases of sexual assault.

It appears that toxic effects can be produced directly from the drug and the presence of other depressant or sedative drugs (e.g. opiates, benzodiazepines, alcohol and barbiturates) and possibly other psychoactive compounds (e.g. amphetamine) may exacerbate the effects of GHB. Hospital admissions and deaths have been linked to GHB ingestion and generally involve the onset of coma and respiratory depression.

Therapeutic Usefulness

GHB has been used as an anaesthetic agent and as an aid to alcohol/opiate withdrawal, primarily in France, Germany and Italy, respectively. In USA and Canada it is currently under evaluation for the treatment of narcolepsy-associated cataplexy.

Recommendation

Although GHB is an endogenous compound that exists in the human body, GHB has psychoactive and toxic effects when administered. The pattern and consequences of its abuse in a number of countries in Europe and the USA seem to suggest that its liability to abuse constitutes a significant risk to public health. The current easy availability of GHB and some of its precursors has contributed to its recent abuse. The wide availability is likely to be reduced once GHB is placed under international control. On these bases, it is recommended that GHB be placed in Schedule IV of the 1971 Convention on Psychotropic Substances.

Zolpidem (INN) Substance Identification

Zolpidem is chemically N,N,6-trimethyl-2-p-tolylimidazo [1,2-a]pyridine-3-acetamide; N,N,6-trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide (CAS 82626–48–0). Trade names include: Ambien, Bikalm, Niotal, Stilnoct, Stilnox.

Similarity to Known Substances and Effects on the Central Nervous System

Though chemically different from benzodiazepines, zolpidem produces benzodiazepine-like effects. It acts as an agonist binding with high and low affinity to BZ_1 and BZ_2 receptor subtypes, respectively. It is generally believed to produce relatively greater hypnotic effects than other benzodiazepine-like effects.

Dependence Potential

The results of human laboratory studies suggest that zolpidem and triazolam are generally similar in terms of producing subjective reinforcing effects. As with many of the benzodiazepines, there have been a number of case reports describing withdrawal symptoms after cessation of zolpidem administration. Though withdrawal discomfort does not necessarily lead to compulsory drug taking (drug dependence) in humans, there are reports of clinically diagnosed cases of drug dependence resulting from a prolonged use of zolpidem.

Actual Abuse and/or Evidence of Likelihood of Abuse

Epidemiological studies indicate that zolpidem is associated with relatively low incidence of abuse. Sporadic case reports in the scientific literature have indicated that zolpidem is abused, but these cases usually involved patients with histories of drug abuse or chronic psychiatric disorders. Cases of zolpidem overdose requiring emergency treatment have been reported. Death due to zolpidem overdose is rare. Rates of actual abuse and dependence of zolpidem appear to be similar to other hypnotic benzodiazepines in Schedule IV. In terms of the numbers of cases of abuse, dependence and withdrawal reported as adverse drug reactions to the WHO adverse drug reaction database, less than ten benzodiazepines are ranked higher than zolpidem.

Therapeutic Usefulness

Zolpidem is used for treatment of insomnia in more than 80 countries.

Recommendation

Although zolpidem has a somewhat novel neuropharmacological profile relative to classic benzodiazepines, studies of its abuse potential suggest that it may be comparable to that of many benzodiazepines. Furthermore, rates of actual abuse and dependence of zolpidem in medical use, as well as the risk to public health of its abuse, appear to be similar to hypnotic benzodiazepines presently placed in Schedule IV. On these bases, it is recommended that zolpidem be placed in Schedule IV of the 1971 Convention on Psychotropic Substances.

I. Discussion

Although WHO has made specific scheduling recommendations for each of the drug substances, the CND is not obliged to follow the WHO recommendations. Options available to the CND for substances considered for control under the Psychotropic Convention include: (1) Acceptance of the WHO recommendations; (2) acceptance of the recommendations to control, but control the drug substance in a schedule other than that recommended; or (3) rejection of the recommendations entirely.

4-Bromo-2,5-dimethoxyphenethylamine (2C-B) is a Schedule I controlled substance in the United States. The U.S. Drug Enforcement Administration (DEA) placed 2C-B (including salts, isomers, and salts of isomers: isomers include optical, positional, and geometric) in Schedule I of the Controlled Substance Act (CSA) in June 1995. 4-methylthioamphetamine (4-MTA) is not marketed in the United States and is not currently a controlled substance in the United States. Gamma hydroxybutyric acid (GHB) is a Schedule I controlled substance in the United States. GHB, including its salts, optical isomers, and salts of optical isomers, became a Schedule I controlled substance in March 2000. Registered manufacturers and distributors of GHB when it is manufactured, distributed, or possessed in accordance with an FDA authorized investigational new drug exemption under Section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 USC 355(i)) are subject to Schedule III security requirements. If FDA approves a drug product containing GHB for marketing, the approved product will be placed into Schedule III under Public Law 106–172. Zolpidem, its salts, isomers, and salts of isomers, is a Schedule IV controlled substance in the United States. The DEA placed zolpidem in Schedule IV in February 1993. With the exception of 4-MTA, current controls in the United States on the substances under consideration for international control appear to meet the requirements of the recommended Psychotropic Convention schedules.

IV. Comments

Interested persons may, on or before March 15, 2001, submit to the Dockets Management Branch (address above) written comments regarding this notice. This abbreviated comment period is necessary to allow HHS to furnish a recommendation to the Secretary of State in time for the March 2001 meeting of the United Nations Commission on Narcotic Drugs. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Dated: February 27, 2001.

Ann M. Witt,

Acting Associate Commissioner for Policy.

[FR Doc. 01–5218 Filed 2–28–01; 11:36 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Blood Products Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Blood Products Advisory Committee.

General Function of the Committee: To provide advice and

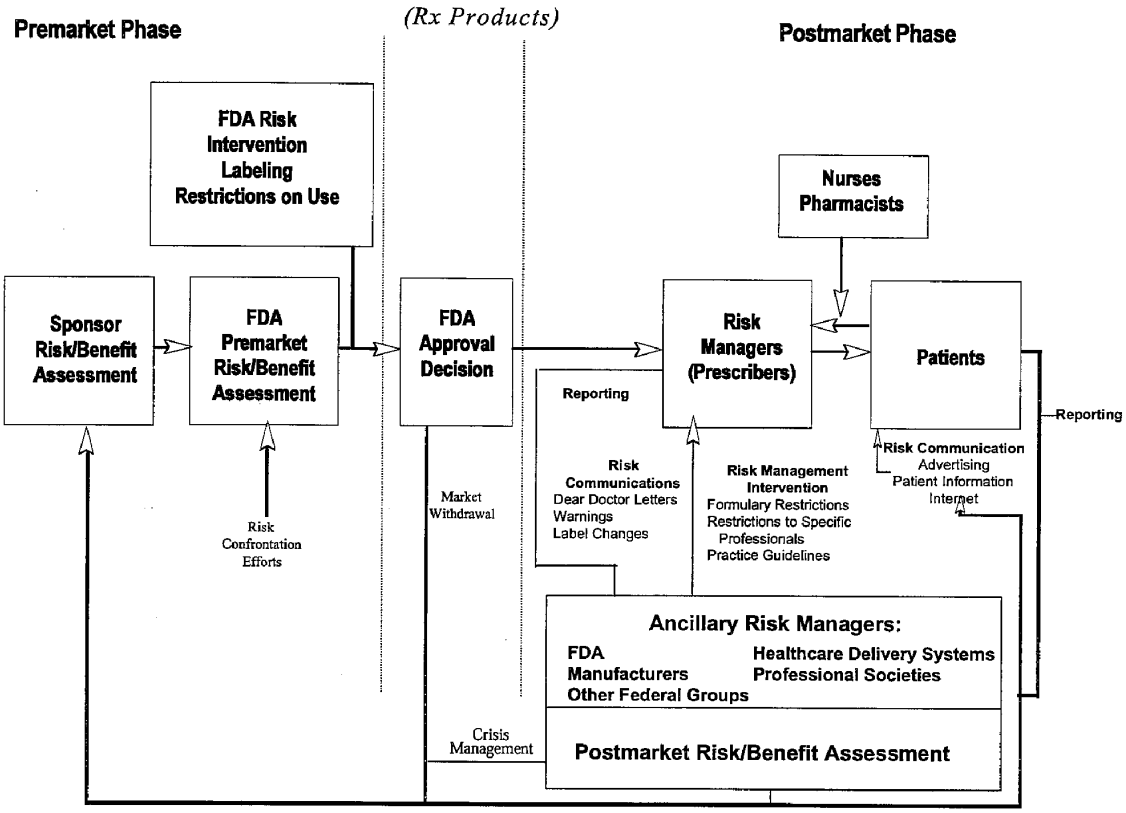
SECTION 8
RISK MANAGEMENT

8.0 RISK MANAGEMENT

8.1 Introduction to Risk Management

The system used to manage the risks presented by medical products during their pre-market and post-market phases involves many different parties with various, and sometimes different, interests. Each party's goal, however, is limitation of the risk a medical product presents to the patient and the public. It is a complex system, presented graphically in Figure 8.1.

Figure 8.1. Complex System for Managing the Risks of Medical Products



Wishing to simplify and update this risk management system, the FDA established a Task Force in 1999 to reconsider the existing system, identify issues, and recommend solutions (Task Force on Risk Management 1999).

One of the major issues highlighted by the Task Force was that each of the partners within this system lacked clearly defined roles and responsibilities. The Task Force further determined that actions of the participants are not well integrated and coordinated.

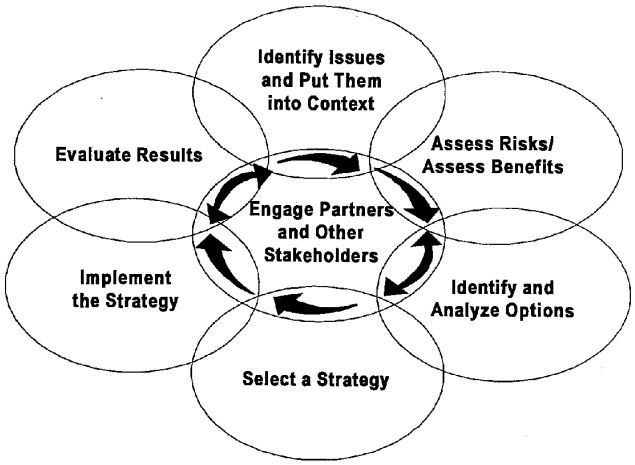
An example is the reporting of adverse events. All pharmacists are trained to identify adverse events, and to report them to the manufacturer, which, in turn, reports them to the FDA. This process is not always effective within the current healthcare environment, in which patients can make several visits to many different physicians, use multiple pharmacies, and take over-the-counter or nutritional products without medical supervision.

Rarely is a thorough medication audit performed on a patient, and consequently, patients may not receive informed counseling regarding potential medication interactions. Resultant adverse events often are not correlated to concomitant medications. While regulations do exist to support counseling of patients by trained pharmacists, many retail pharmacies have addressed this obligation by simply providing written instructions for a given medication, and the opportunity for integration of care is again lost.

Integration of a patient's total care is impossible without all of the care providers working in concert.

The Task Force concluded that "risk confrontation" is key to the effective management of risk associated with medical products. It recommended a simplified model that takes into account the current health care delivery environment (see Figure 8.2).

Figure 8.2. Proposed Risk Management Model



Risk confrontation is the identification of salient risks and the design of methods to address these risks. This model revolves around the participation of relevant partners and stakeholders, that is, interested parties that can contribute to effective risk management. These parties, referred to as the "Interested Community," have to be involved in the risk identification and management processes.

Orphan Medical has embraced and incorporated the conclusions of the FDA Task Force in the design of its risk management system. These are presented in the next sections.

8.1.1 RISK MANAGEMENT OF XYREM USING THE RISK CONFRONTATION MODEL

8.1.1.1 Identify Issues and Put Them Into Context

The first step in the risk confrontation model is to identify issues and understand their real-world implications. Orphan Medical invited stakeholders to participate in a series of meetings, between 1998 and 2001, in order to discuss Xyrem and its potential risks. Stakeholders included in these meetings were:

- Narcolepsy patient organizations
- Narcolepsy patients
- Physicians expert in treating narcolepsy
- Drug abuse experts
- Criminal prosecutors
- Forensics experts
- Sexual assault investigators

- Drug abuse trend experts
- Legislative personnel
- Field law enforcement
- Various law enforcement officers who train other officers in drug recognition issues
- Emergency room physicians
- Toxicologists and Poison Control Center directors
- The National Association of State Controlled Substance Authorities (NASCSA)
- The National Association of Drug Diversion Investigators (NADDI)
- Rape crisis centers and advocates

The objectives of the meetings were to:

1. Identify all of the key risks relating to the use of Xyrem as well as illicit GHB and related chemicals; and to
2. Propose methods to contain the risks identified.

The stakeholders first agreed on the following list of facts and issues.

- Narcolepsy is a disabling disease estimated to affect fewer than 140,000 people in the United States. Since it is a difficult disease to diagnose, only an estimated 75,000 individuals with narcolepsy have received an accurate diagnosis and are receiving treatment.
- Cataplexy, a disabling symptom of narcolepsy, is distinguished by a loss of muscle tone when the patient is confronted by emotional stimulus. It is estimated that the number of diagnosed/treated narcolepsy-with-cataplexy patients in the U.S. is approximately 25,000. Current treatments for cataplexy are limited in their effectiveness and can have troubling adverse effect profiles, leading to their discontinuation by some patients.
- Physicians and narcolepsy patients are familiar with the restrictions and risks associated with controlled substances. Schedule II and IV medicines are typically used in the attempt to control the symptoms of narcolepsy.
- The results of clinical trials in which Xyrem was evaluated indicate that it is safe and efficacious when used to treat narcolepsy.
- Illicit use of GHB and related chemicals is growing, with serious physical consequences to users being identified (Zvosec 2001).
- The sources of illicit GHB and related chemicals range from home made products and “reagent kits” sold on the Internet to two industrial chemicals, of which 100 million gallons were produced in the US last year (Caruso 1997). Illicit GHB and related chemicals can also be obtained as nutritional supplements from health food stores. All illicit products vary in purity, content, and dose.
- Xyrem has never been reported as a source of abused GHB by toxicologists, ER personnel, or law enforcement personnel.

- Poly-drug use is common in the abuser population (Galloway 2000), with little known about drug interactions among various illicit drugs. Use of alcohol in combination with GHB is common, leading to dangerous, potentially synergistic, effects (McCabe 1971).
- In general, toxicologists, emergency medicine personnel, and other medical personnel lack knowledge of GHB and related chemicals and training in how to treat their misuse, especially when ingested with alcohol or other illicit drugs.
- Law enforcement personnel also usually lack knowledge and training in how to identify illicit GHB and related chemicals.
- State laws addressing illicit GHB and related chemicals are not uniform. Differences also exist between federal and state laws.
- Within the Interested Community, very little scientific information regarding abuse of GHB, drug diversion investigations, law enforcement training, identification, activities, and state efforts dealing with controlled substances exists, and even less is shared.
- Currently, diversionary activities are difficult to identify and investigate due to the lack of integration in pharmacy reporting systems.
- Often investigations are initiated many months after a crime occurs, owing to the need to collect extensive data. Thus, illicit use is simply "caught" versus prevented.
- Widespread distribution of controlled substances through community pharmacy increases the potential for diversion.
- Sexual assault investigation protocols do not include screening or testing for illicit GHB and related chemicals.
- Most hospital diagnoses are presumptive. Very few laboratories identify or quantify GHB, GBL and 1,4-Butanediol in blood or urine. These drugs are not part of routine drug screening methodologies in hospitals.
- Urine screening for illicit GHB and related chemicals is not specific enough to distinguish between the ingested agents: all are identified as GHB.
- Available on-line and other information resources that report sanctions of physicians accused of diversion are not used by appropriate parties.
- Legislation has reduced the illicit use of GHB-containing products, however, readily obtained chemicals such as GBL and 1,4BD are increasingly being used as substitutes.
- Further state legislation is needed to apply penalties to the misuse of these substitute sources of GHB.

After identifying these facts and issues, the groups reached these conclusions:

- Xyrem should be made available for patients who need it, but must be handled responsibly by all involved parties.
- A comprehensive approach, involving key stakeholders and partners, is needed to manage the risk that Xyrem could become a source of abused product while allowing access to it by patients whose conditions can be improved by its medicinal properties.
- To reduce the threat to public health posed by illicit GHB, information about GHB must be shared within and among the scientific, medical, and law enforcement communities.

8.1.1.2 Assess Risks/Assess Benefits

The second step in addressing risk management, as described by the FDA Task Force, is to assess the overall benefits and risks of a given medical product. Elsewhere in this document, the medical need for Xyrem is presented, as are data regarding the safety and efficacy of Xyrem.

It should noted that after review of controlled trials assessing Xyrem in narcolepsy patients, the FDA asked Orphan Medical to initiate a Treatment IND. By definition, Treatment IND protocols are granted only when medicines under clinical evaluation treat patient populations whose medical condition is "life threatening or debilitating" and where no acceptable therapeutic alternative exists.

The medical need, efficacy, safety, and Treatment IND information was also shared with the stakeholders and partners that Orphan Medical involved in the development of its risk management approach.

The law enforcement stakeholders involved were initially skeptical about the need for this medication, but, upon learning about narcolepsy and the clinical results of Xyrem, these parties agreed that the therapeutic need for Xyrem was compelling. They continue to be very concerned, of course, about the use of illicit GHB and related chemicals and asked that Orphan Medical address both the potential for inappropriate prescribing of Xyrem and the potential for diversion, two factors which could contribute to the complexity of the illicit GHB drug environment.

Other stakeholders voiced concern about the addictive potential of illicit GHB and related chemicals and whether there is a risk of addiction among narcolepsy patients from their use of Xyrem. Orphan Medical has, and will continue to share, information it has about the abuse or addiction potential of Xyrem. The Abuse Liability and Overdosage section in this document addresses these issues. Orphan Medical has also pledged to assist, where it can, efforts to evaluate the abuse and addictive properties of other GHB related compounds. All of the stakeholders understand that these compounds do not fall under the responsibility of the Company, but that the Company's current and future data may be helpful in efforts to contain the risk presented by these illicit compounds.

All stakeholders agreed that it was important for Orphan Medical to consider risk management solutions that will allow Xyrem to reach the intended population of narcolepsy patients while minimizing the risk that Xyrem may be obtained by those seeking to misuse it.

8.1.1.3 Identify and Analyze Options

Orphan Medical presented to the stakeholders options it could have followed to date, but were dismissed since the options did not combine the goals of providing Xyrem to those who need it, managing risk associated with Xyrem in a responsible manner, and

assisting the stakeholders where possible to reduce the risk of illicit GHB and related chemicals.

Clearly, Orphan Medical could have chosen to ignore risk issues around illicit GHB and related chemicals, and instead focus solely on the medical use of Xyrem. It could have attempted to shift the focus of attention to problems with alcohol, Ecstasy, amphetamines, Rohypnol and other club drugs with greater frequency of use and levels of abuse than GHB. It could have designed its risk management system in a manner that assumes physicians, patients and pharmacists will work together to minimize risks once Xyrem is approved.

Instead, Orphan Medical has invested substantial resources to address issues around Xyrem, and around illicit GHB and related chemicals that are not, strictly speaking, the Company's responsibility. Along with stakeholders and partners, Orphan Medical has pro-actively developed approaches and solutions to these issues. These were arrived at through consideration of possible alternatives available to Orphan Medical, listed below.

8.1.1.3.1 Distribution Options

- Use a traditional pharmaceutical distribution model that relies on current controls to prevent, minimize, and prosecute diversion.
- Establish a specialty distribution model that includes customized controls to meet the needs of the stakeholders.

8.1.1.3.2 Scheduling Timing Options

- Wait for Xyrem approval and scheduling designation at the time of NDA approval, the customary administrative approach.
- Prior to the Xyrem NDA submission, support and move for the legislative scheduling of Xyrem, illicit GHB and related chemicals, which allows greater control over these compounds and allows prosecution of illicit use sooner.

8.1.1.3.3 Scheduling Designation Options

- Support Schedule II designation that allows prescription monitoring and strong penalties for illicit use, but entails a much broader distribution system, thereby creating many more points of potential diversion.
- Support Schedule IV designation that permits use of a centralized mail order-based distribution system serving small patient populations, but offers minimal penalties for illicit use.
- Support Schedule III designation that allows for centralized mail order-based distribution to small patient populations, and offers greater penalties for illicit use.
- Support the HHS recommended "bifurcated schedule" of Schedule I/Schedule III, that allows central, mail order-based distribution to small patient populations, and offers the strongest possible penalties for illicit use.

8.1.1.3.4 Prescribing Options

- A system that allows investigation of inappropriate use/action based on verification and/or identification of:
    - A patient's diagnosis
    - A physician's appropriateness
    - Prescription and dispensing of an appropriate dose
    - Appropriate frequency of prescription
    - Inappropriate use

- A system that relies on state or federal authorities to investigate based on their verification and/or identification of:
    - A patient's diagnosis
    - A physician's appropriateness
    - Prescription and dispensing of an appropriate dose
    - Appropriate frequency of prescription
    - Inappropriate use

- A prescription system that relies on the physician, patient, and pharmacist to oversee verification and/or identification of:
    - A patient's diagnosis
    - A physician's appropriateness
    - Prescription and dispensing of an appropriate dose
    - Appropriate frequency of prescription
    - Inappropriate use

8.1.1.4 Select a Strategy

The fourth step identified by the Task Force in the risk confrontation model is to select a strategy. After much discussion with stakeholders and partners, and consideration of alternatives, Orphan Medical has developed the following risk management strategy. (The key elements of this strategy are in italics.)

8.1.1.4.1 Strategy Selected

Confront issues of risk regarding Xyrem and co-develop risk management solutions with other stakeholders.

Pharmaceutical companies often seek to minimize the perception of risk associated with their products by highlighting problems with other products or allowing risk management of products to be addressed by other stakeholders, such as physicians or pharmacists once the product is commercially available. Orphan Medical concluded this approach was not appropriate for Xyrem.

A closed distribution system has been designed to address risk management of Xyrem. In addition to assigning responsibility for some risk management to the traditional

stakeholders, the system also places more than usual responsibility on the patient, state authorities, and federal authorities.

Assist stakeholders in confronting the risks associated with illicit GHB, and related chemicals.

The risks associated with illicit GHB and related chemicals originate from the distribution of raw chemicals, home-made formulations, and the sales of nutritional supplements and of "reagent kits" over the Internet. Most pharmaceutical companies would refuse help to efforts to curb these risks since there is little that the pharmaceutical company, physicians, and pharmacists can do in regard to illicit GHB. Orphan Medical, however, has pledged its help to efforts to contain the public risk associated with illicit GHB and related chemicals. The Company has shared its data with NIDA, forensic science groups, toxicologists and emergency medicine physicians. Orphan Medical is involved in collaboration and sponsorship of studies relating to abuse pharmacology.

Orphan Medical has tried to set an example of how a company can help advance the science and understanding of an abuse substance and work with physicians, drug abuse specialists, law enforcement and other stake holders to better address risks posed by illicit substances.

8.1.1.4.2 Development Option Selected

Develop Xyrem for a small patient population where adequate therapy does not exist, understanding its importance in that population.

While conventional wisdom in the pharmaceutical industry is to develop a medication for the largest possible indication, Orphan Medical's mission is to develop and market pharmaceuticals of high medical value for patients with rare diseases for which few, or inadequate, therapeutic alternatives exist. Larger pharmaceutical companies typically ignore such diseases and conditions because the potential revenue is inadequate to generate acceptable returns.

Orphan Medical, on the other hand, has conducted trials and collected data that it believes demonstrate Xyrem's safety and efficacy in this small patient population. Xyrem will be marketed only for the approved label claim, with DDMAC (FDA's Division of Drug Marketing, Advertising and Communications) having "jurisdiction" over promotional activities.

8.1.1.4.3 Scheduling Timing Option Selected

Pro-actively support, prior to any approval of Xyrem, the legislative scheduling of GHB compounds, including Xyrem, illicit GHB and related chemicals, to allow greater control and prosecution of misuse.

Traditionally, consideration of a medication's schedule status occurs during the NDA review and its definitive schedule is designated at the time of approval. Due to the

widespread availability of illicit GHB and its growing chemical abuse in the late 1990's, many states began to legislatively schedule GHB. In those states which enacted GHB scheduling initiatives, the "street use" quickly shifted from GHB to GBL, 1,4BD or other related chemicals. Due to the metabolism of these agents in the body to GHB, these agents were used not only to make illicit GHB, but eventually they were simply ingested in order to obtain a "GHB-like" effect. Thus, well-intentioned legislation was ultimately ineffective since it was too narrow and did not also include GHB precursor chemicals.

Orphan Medical, along with stakeholders, concluded it would be in the best interest of the overall risk management of Xyrem to support Federal legislation to schedule GHB and related chemicals. Orphan Medical worked with other interested parties and stakeholders to help obtain legislation as quickly as possible. In early 2000 President Clinton signed into effect PL 106-172, The Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 (Public Law 106-172).

8.1.1.4.4 Scheduling Designation Option Selected

Support congressional scheduling based on the HHS recommended "bifurcated schedule" of schedule I/schedule III that allows for central, mail order-based distribution of Xyrem to a small patient population, and also provides for the strongest possible penalties for illicit use.

One of the main issues raised by stakeholders was the application of the schedule that would apply the harshest penalties possible for the illicit use of GHB and related chemicals, yet allow access to Xyrem for narcolepsy patients who need it. PL 106-172 followed the recommendations of FDA and as presented to the DEA by the Department of Health and Human Services on May 19, 1999 (Satcher, written communication).

This bifurcated schedule made illicitly used GHB a Schedule I substance and provided Schedule III designation for medicines containing GHB that might be approved by the FDA in the future. It is important to note that the Schedule I provisions apply to approved products if they are used illicitly.

The HSS report, submitted to the DEA by David Satcher, M.D., Ph.D., Assistant Secretary for Health and Surgeon General, is based on a document prepared by FDA's Drug Abuse Evaluation Staff. That document includes an eight-factor analysis regarding the recommended scheduling of Xyrem. The following information is excerpted from that documen (US Department of Justice 1997).

> "GHB products are currently being studied under FDA authorized investigational new drug applications. None of the reports of actual abuse of GHB that support the scheduling recommendation in part I has involved GHB that was diverted from an authorized study. Moreover, given the ease with which GHB can be synthesized from readily available materials, it is considerably less likely that these authorized studies will become a source for unlawful use or abuse of GHB. In essence, the widespread availability of clandestinely produced GHB decreases the

> abuse liability and potential for abuse of the products being studied in authorized research programs and well-supervised clinics. For this reason, a GHB product or substance that is the subject of an authorized protocol and is being studied under a carefully designed research protocol has "low potential for abuse relative to drugs or other substances in schedule III." (Emphasis added.) (see U.S.C. 12 (b)(4)(A)".

8.1.1.4.4.1 Medical Use

Dr. Satcher's report goes on to address the medical use of GHB:

> "A GHB product, however, has recently been granted a protocol under 21 CFR 312.34 to allow for expanded, treatment use of the product in patients who suffer from cataplexy associated with narcolepsy. In this instance the study and development of a GHB product is sufficiently far along to suggest that authorized formulations of GHB may be considered as having a "currently accepted medical use with severe restrictions" under the CSA (see 21 U.S.C. 812 (b)(2)(B); see also 47 FDA 281241, June 29, 1982)".

8.1.1.4.4.2 Physical or Psychological Dependence

Dr. Satcher also states,

> "There is no well-developed evidence from clinical studies to suggest that GHB leads to psychological dependence. The few available anecdotal case reports suggest only mild withdrawal symptoms that may be indicative of 'low risk of physical dependence.' Similarly, from these few anecdotal reports, instances of escalation of GHB dose, increased frequency of use, and continued use despite adverse consequences, are only suggestive of dependence production. There is no evidence to suggest that abuse of GHB leads to 'severe' dependence (see 21 U.S.C. 812 (b)(2)(C)). When compared to substances in Schedules II and III, GHB's physical and psychological dependence producing effects appear to be 'limited' (see 21 U.S.C. 812 (b)(4)(C))."

The Assistant Secretary for Health and Surgeon General concludes:

> "Formulations of GHB currently are being studied under FDA-authorized INDs. At least one sponsor's formulation has been granted Orphan Drug status under section 526 of the Food, Drug, and Cosmetic Act, and is available under a treatment use protocol under 21 CFR 212.34. None of the reports of actual abuse of GHB that support the Schedule I recommendation has involved GHB diverted from an authorized study. Given the ease with which GHB can be synthesized from readily available materials, it is unlikely that authorized studies will become a source of GHB for abuse. Rather, the abuse potential of GHB, when used under an

> authorized research protocol, is consistent with substances typically controlled under Schedule IV. Information on the dependence producing effects of GHB is limited, but can suggest that its potential for physical and psychological dependence is also consistent with control under Schedule IV". (Emphasis added.)
>
> "Authorized formulations of GHB, however, do not meet the 'accepted medical use' criteria set forth in Schedule IV. At best, an authorized formulation of GHB is far enough along in the development process to meet the standard under Schedule II of a drug or substance having a 'currently accepted medical use with severe restrictions.' Under these circumstances, FDA recommends placing authorized formulations of GHB in schedule III, a level of control higher than Schedule IV to take into account the lack of an accepted medical use and a level of control lower than schedule II to take into account the abuse and dependence liability findings for authorized formulations of GHB." (Emphasis added)

Stakeholders, potential specialty medications distribution partners, drug diversion investigators, State Boards of Pharmacy, legal experts and others were consulted on the issue of scheduling. They strongly supported a schedule III designation because it allows for a "closed loop" distribution system. A "closed loop" system provides for the confirmation of the shipment and receipt of medicine. Prescribing information, including frequency and dosing data, can be accessed from a single source. With this system, Xyrem's distribution can be monitored and controlled relatively easily and accurately since product is distributed from a single location, unlike a typical pharmaceutical distribution system that allows for widespread distribution through multiple retail pharmacies.

Such a centralized, mail order-based system is very well suited to minimize diversion and related risk issues. Narcolepsy is limited in its incidence so the number of patients is easily managed. Moreover, since the disease is chronic, prescriptions are repetitive and usage can be monitored for unusual patterns.

In practice, some state pharmacy laws do not allow for mail order distribution of Xyrem. (Mail order is legal, but prescriptions for Schedule II agents have to be submitted in person.) The Schedule III designation was necessary to implement this system of direct-to-patient delivery. The closed distribution system for Xyrem, along with the physician and patient education components of the program, will be addressed at length later in this document.

Another issue addressed in PL 106-172 was the "listing" of the industrial chemical GBL, requiring special reporting by chemical manufacturers. Unfortunately, this legislation did not address other related chemicals. Orphan Medical is actively supporting efforts on a state-by-state basis to include GHB precursor chemicals in various analog and sexual assault statutes[1].

[1] various state analog laws

8.1.1.4.5 Prescribing Options Selected

Confront risk by targeting promotional and selling efforts to those physicians (and physician specialties) identified as most likely to treat narcolepsy patients, and develop a system of responsible distribution that includes physician and patient education programs to help minimize physician off-label prescribing and patient misuse of Xyrem.

Certain stakeholders asked if Orphan Medical could somehow control who prescribes Xyrem, and control how Xyrem is prescribed. Orphan Medical cannot dictate or directly limit who prescribes Xyrem as it does not have accrediting jurisdiction over physicians. Further, it cannot limit the indications for which Xyrem might be prescribed, as this would constitute an imposition on the practice of medicine, for which Orphan Medical is not licensed.

Orphan Medical can, however, attempt to address this issue by prospectively identifying and targeting those physicians and physician specialties most likely to treat narcolepsy. This will be accomplished by utilizing a number of research sources and analyzing selected data. (Note that, because narcolepsy is a rare disease with a small patient population, most research sources provide limited information and/or data. Furthermore, these sources of information and data are highly unreliable because survey sample sizes are small. However, certain assumptions can be made.)

The first source consulted was the American Board of Sleep Medicine (ABSM). This organization issues certificates of special knowledge in sleep medicine to physicians and PhDs in related fields. The knowledge base of sleep medicine is derived from many disciplines, including neuroanatomy, neurophysiology, respiratory physiology, pharmacology, psychology, psychiatry, neurology, general internal medicine, pulmonary medicine, pediatrics, and others. As of February 2001, there were 1,517 professionals identified by ABSM as certified sleep specialists.

According to the American Medical Association (AMA), many clinicians practice sleep medicine under their primary specialty, such as neurology, pulmonology, psychiatry. Sleep medicine, however, is not listed as one of the 24 major board specialties recognized by the AMA, and only 48 physicians within the United States have identified themselves to the AMA as practicing sleep medicine. While this group of physicians is certainly qualified to prescribe Xyrem, it clearly does not treat the entire narcoleptic population.

The National Disease and Therapeutic Index (NDTI), identifies physician specialties that prescribe medications for a given disease. The NDTI data, like the ABSM information, report the involvement of numerous medical specialties in treating narcolepsy. NDTI data for 1999 and 2000 (January-June) identified the following specialties that prescribe medication for patients with a diagnosis of narcolepsy: neurology, pulmonary diseases, psychiatry, family practice, osteopathic medicine, internal medicine, and general practice.

IMS HEALTH Information Services, through its National Prescription Audit information, tracks prescribers of Provigil (modafinil). Since Provigil is indicated for the treatment of daytime sleepiness associated with narcolepsy, it could be presumed that Provigil prescribers are physicians treating narcolepsy patients. Again, it was noted that the number of medical specialties is large; Provigil prescribers are classified as follows: neurology, pulmonary diseases, psychiatry, internal medicine, sleep medicine, and 24 other specialties.

All of these data sources corroborate; that is, physicians who practice sleep medicine, diagnose and treat sleep disorders (narcolepsy, in particular), and prescribe medicines for these disorders fall within a defined range of medical specialties. As part of its marketing strategy, and consistent with its risk management goals, Orphan Medical has identified, within this group of specialties, key physicians on whom to focus initial marketing and sales efforts.

Prior to the launch of Xyrem, these physicians will be checked with the AMA and with the National Prescribers Databank (NPD) to determine if they are medical license holders and further licensed to prescribe controlled substances. Because the NPD is updated quarterly, State Medical Boards will be searched on-line to determine if disciplinary actions have been taken against any of these physicians which have not yet been reported to the NPD database. If any of the physicians has had privileges revoked, the central database will be flagged and the physician will be removed from Orphan Medical's list, with no mailings or detail calls made to them. In addition, the central pharmacy will be instructed not to fill prescriptions received from such physicians. These database checks (AMA, NPD and State Medical Boards available on-line) will periodically occur to ensure that physician eligibility has not changed.

At the launch of Xyrem, each of the key physicians identified by Orphan Medical will receive a traditional "detail call" from an Orphan Medical sales representative. During this call, a Xyrem Physician Success Program℠ will be reviewed with the physician and left behind. This educational program outlines the prescription and distribution process for Xyrem. DDMAC-approved information, regarding the benefits and risks of Xyrem in the intended patient population, will also be provided to these physicians.

Because a single, central pharmacy will handle distribution of Xyrem, as well as its educational materials, it will be possible to keep consolidated records of which physicians and patients have received educational materials on Xyrem. In addition, pharmacy data on prescribing physicians will be collected. It will be the pharmacy's role, not Orphan Medical's, to share with appropriate state and federal authorities the data regarding the prescribing of Xyrem. Available data, including physician name, physician specialty, and frequency of prescribing will assist appropriate authorities in an investigation, should one become necessary. The centralized, real-time nature of these data will allow for rapid identification in the rare case of diversion.

The second issue raised around the risk management of Xyrem is that of "off label" prescribing. It is important to note that an NDA holder has the responsibility to

manufacture and promote a medication consistent with its label claim. All promotions are subject to FDA review, and U.S. laws permit no off-label promotion.

Orphan Medical is a manufacturer and marketer, not a pharmacy or distributor. Orphan Medical will sell Xyrem to the specialty pharmacy, which is then responsible for filling prescriptions according to the laws governing the practice of pharmacy in each state.

According to stakeholders in the areas of pharmacy practice and law, there is no state or federal territory in which confidentiality laws allow for a manufacturer to know the name of a given patient or the dose of a given prescription. Orphan Medical has no legal means to ascertain if a given physician has accurately diagnosed a patient's disease. Nor is the pharmacist in a position to approve or disapprove of the use of Xyrem in a given patient. The practicalities of how prescriptions are filled in the U.S. do not allow for a specialty pharmacy to "police" the practice of medicine by a given physician. The role of the central pharmacist will be to fill the prescription; perform a medication audit to determine what other ethical medications, over the counter products, and nutritional supplements the patient may be taking; and given the doctor-patient-pharmacist relationship, enter into a dialog with the physician about the treatment of a given patient if appropriate.

Fortunately, the current system used in the U.S. for managing the risks associated with controlled substances allows for appropriate stakeholders to police individual physician and patient behavior. The Xyrem system preserves this important feature.

In every state in the U.S., a pharmacy is required by law to cooperate with state and federal authorities, including State Medical Boards, DEA and FDA, in any investigation dealing with physician or patient behavior. The controlled substance tracking system has been designed to provide data on both patient use and physician prescribing of controlled substances.

According to the stakeholders familiar with drug diversion, however, the current systems do not work prospectively; they identify inappropriate use long after it happens. Consider the "patient" who is an abuser, seeking various narcotics. This patient may visit an emergency room one day and be prescribed a narcotic, which is filled at a local pharmacy. This same patient may travel to a neighboring town the next day and be prescribed a second narcotic, which is filled at that local pharmacy. This cycle could be repeated in town after town for a long period of time before triplicate prescription forms identify the situation. If the patient is able to obtain different identification for each visit this activity may never be caught.

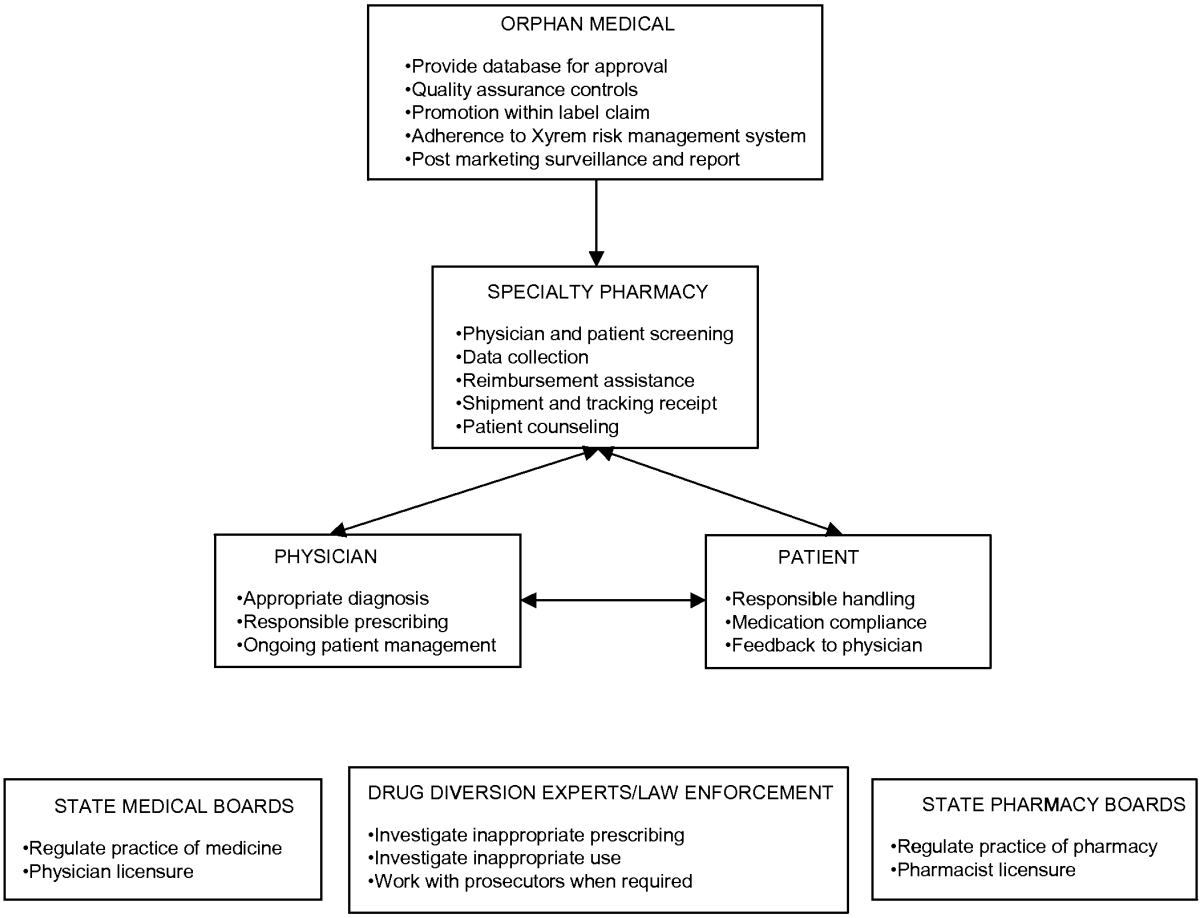
The Xyrem risk management system ensures that the centralized pharmacy will identify patients who are attempting to duplicate prescriptions. All data collected will be available to state and federal authorities, on whatever timeframe they determine to be appropriate. This allows law enforcement agencies to more easily fulfill their responsibility for which they have the training and authority to perform. Incidentally, individuals caught trying to manipulate health care systems for illicit purposes as described above will be subject to Schedule I penalties as outlined in PL 106-172.

This briefing book contains an 8 minute video demonstrating the specific prescription process for Xyrem. Viewing it will aid in understanding the systems Orphan Medical will use to fulfill its stated risk management goals:

- **Make Xyrem available in a responsible manner to patients who need it;**
- **Keep Xyrem out of the hands of those who would use it illicitly; and**
- **Provide responsible assistance to law enforcement investigation and prosecution efforts if illicit use occurs.**

Figure 8.3 describes the roles and responsibilities of each of the involved parties in the Xyrem risk management system.

Figure 8.3. Xyrem: Risk Management Roles and Responsibilities



Stakeholders involved in developing this system strongly support that a risk management system similar to Orphan Medical's be required of any manufacturer who submits an ANDA (generic application) or NDA for any GHB-containing product.

The Xyrem risk management system has been designed to confront risk through responsible distribution as well as through patient and physician education programs. Details of this program follow.

The Xyrem risk management system has been designed with the input of stakeholders to confront and minimize the potential risk of both unintended and intended misuse of Xyrem.

Starting from the Risk Confrontation model outlined by the FDA Task Force, Orphan Medical developed the Xyrem risk management system. It reflects the input and involvement of stakeholders and partners in the identification of risk issues, of potential solutions, and of the final selection of strategies. FDA and DEA input on the program has been sought and has not yet been received.

Bulk drug for Xyrem is manufactured at a single site and it is formulated into finished product at a separate, single site. From there, finished Xyrem is shipped to a central pharmacy.

Each of these facilities meets FDA and DEA requirements for controlled substances: the bulk drug manufacturer meets Schedule I requirements; the drug product manufacturer meets Schedule I and Schedule III requirements; and the central pharmacy is compliant with Schedule III requirements. Each facility is designed to provide secure storage of controlled substances.

Using a central pharmacy is more costly than using conventional distribution channels and systems. Using a single pharmacy also eliminates the opportunity to "fill the retail distribution pipeline." (Generally, pipeline sales of pharmaceuticals are significant, and generate initial sales.) Orphan Medical is foregoing this pipeline opportunity because it feels Xyrem can be better managed through a single pharmacy, rather than on the shelves and loading docks of, perhaps, thousands of pharmacies and distribution centers around the country.

Receiving, storage, and shipping controls are in place to ensure that the amount of Xyrem shipped from the manufacturer is equal to that received at the pharmacy. Discrepancies are investigated and reported appropriately. Xyrem, once received at the specialty pharmacy, goes into a secure holding area dedicated solely to storage of Xyrem and accessible only to authorized employees. Measures such as cages, security alarms, cameras and key cards are used to ensure security. On a weekly basis, the specialty pharmacy determines the amount of Xyrem it is likely to need for fulfillment of prescriptions, and the appropriate amount of product is transferred to "owned inventory".

This is the point at which Xyrem is "sold" by Orphan Medical to the specialty pharmacy. This transfer of ownership allows the specialty pharmacy to collect confidential data such as patient names and medication doses. This is information that Orphan Medical will not have, but the specialty pharmacy can collect because of the doctor/pharmacist/patient relationship.

As was discussed previously, physicians most likely to prescribe Xyrem will be identified and "pre-screened" prior to the launch of Xyrem. When the FDA approves Xyrem, the Xyrem Physician Success Program will be shared with those physicians who have met the screening criteria.

The Xyrem Physician Success Program contains details about Xyrem's unique prescription process, its distribution, the reimbursement program, and physician responsibilities regarding Xyrem. Approximately 25 Orphan Medical sales representatives nationwide will begin making "detail calls" on these physicians. These representatives will have been trained to present efficacy and safety information within the approved label claim as directed by DDMAC. At the first detail call, the sales representative will leave behind the Xyrem Physician Success Program, giving the physician a lasting source of information regarding Xyrem's unique distribution system and special handling process. At no time will samples of Xyrem be carried by sales representatives or left with physicians.

Once a physician decides that Xyrem is appropriate for a given patient, he or she will write a prescription for Xyrem and fax it to the specialty pharmacy. Upon receipt, the specialty pharmacy will verify the physician's eligibility by checking the AMA, DEA, or State Medical Board on-line databases, as previously described. This step will ensure that the prescription was written by a "real" physician with current privileges to prescribe controlled medications.

After physician verification is complete, the specialty pharmacy will contact the physician's office to confirm patient information. By adding this step, the process is likely to "catch" any prescriptions written on stolen or counterfeit prescription pads. During the call, the patient's name, social security number, telephone number and insurance information will also be obtained. The specialty pharmacy will also ask for an assignment of benefits form, so it can work on the patient's behalf to obtain insurance coverage, and for a letter of medical necessity, if it is needed from the insurance company.

While the patient's specific information is needed for insurance purposes, the collection of it by the specialty pharmacy assists in the building of a patient registry which also aids in diversion prevention. The prescribing physician will also be contacted if a prescription appears to be a duplicate or if the dosing frequency appears unusual.

Once the insurance reimbursement is obtained, the Xyrem shipping process begins. The specialty pharmacy will contact the patient to notify him/her of coverage, and arrange a time for a next-day delivery when the patient or his/her designee is to be

present. Xyrem will not be left with anyone other than the patient or the designee (who cannot be a minor), and it will not be left unattended.

Once the shipment designee and time of delivery is determined, the Xyrem prescription and the Patient Success Program℠ is shipped via Federal Express. Federal Express offers real-time tracking so packages can be tracked from point of shipping to point of receipt, and points in-between.

If a shipment becomes lost, the appropriate state/federal authorities will be contacted, and the investigation can begin at the point of loss. If the patient or designee is not available at the location and time designated, the package will not be left on the doorstep, or with a neighbor. Finally, the package will not be returned to the local Federal Express station, but after a same-day redelivery attempt will be returned to the specialty pharmacy.

When the proprietary tracking system shows that the patient has received the shipment, the pharmacist at the specialty pharmacy will contact the patient to:

- confirm receipt of the Xyrem prescription;
- confirm receipt of the Patient Success Program;
- counsel the patient regarding Xyrem administration, dosing and compliance; and
- confirm the patient's understanding of the contents of the Xyrem Patient Success Program and the patient's responsibilities.

This system allows documentation of a patient's receipt of educational materials and communication with the patient about responsibilities and any other matters brought up in the conversation with the pharmacist.

The centrally located, real-time data collected by the specialty pharmacy will be invaluable to the identification of suspicious prescribing or use, and will aid appropriate state and federal investigation and prosecution.

Orphan Medical is grateful for the contributions and efforts of the many stakeholders who have diligently helped identify issues, proposed options, and assisted the company in selecting means to confront and manage the potential risks associated with Xyrem. With their assistance, Orphan Medical has designed a comprehensive system to effectively and responsibly manage risk, while giving narcolepsy patients and their physicians an important medicine to treat this debilitating disease.

SECTION 9
INTEGRATED SUMMARY OF BENEFITS AND RISKS

9.0 INTEGRATED SUMMARY OF BENEFITS AND RISKS

9.1 Background and Rationale for Use of Xyrem® (sodium oxybate) oral solution in the Treatment of Narcolepsy

Narcolepsy is a relatively rare neurologic disease of unknown origin with an incidence of approximately 0.05% (Mignot 1998). It is a debilitating, lifelong disorder following its usual presentation in the second or third decade of life. It is unique in being the only known neurological disorder to specifically affect the generation and organization of sleep (Nishino 1997).

There are currently no therapies approved for the REM related phenomena of narcolepsy, and those currently used clinically (typically the TCA or SSRI antidepressants) are chosen because of REM suppressant properties. This modulation invokes the homeostatic "pressures" to precipitate REM rebound on interruption of therapy, with consequent symptomatic increase in severity, even rarely to status cataplecticus (Scrima 1990, Bassetti 1996). The side effect profile of the tricyclic antidepressants also presents a significant problem. These are mostly due to their anticholinergic effects (dry mouth, tachycardia, urinary retention, constipation, weight gain, blurred vision, sexual dysfunction, tremors) but rarely can extend to severe complications (conduction abnormalities, seizures, exacerbation of glaucoma [Nishino 1997]). The more recent introduction of the selective serotonin reuptake inhibitors (SSRIs) provided a therapeutic alternative to avoid anticholinergic effects, raising the hope of cataplexy control with fewer side effects. In general, however, sleep clinicians have been less impressed with their efficacy in treating the symptoms of narcolepsy.

The mainstay of therapy for excessive daytime sleepiness has been the stimulants, indirect sympathomimetic drugs such as methylphenidate, pemoline, and d-amphetamine that increase the synaptic availability of norepinephrine and dopamine. The rationale for stimulant treatment seeks to maximize alertness at selected times of the day (i.e. work, school, driving) while minimizing side effects and without compromising the potential for satisfactory nocturnal sleep. With all these stimulant agents tolerance develops in up to 30% of cases, more commonly at high doses, and patients may benefit from "drug holidays" of one to two days per week with lower doses or no medication in some patients. The most common side effects include headaches, nervousness, irritability, tremor, insomnia, anorexia, gastrointestinal disturbances and palpitations; however, psychosis, hypertension and myocardial ischemia have been reported (Bassetti 1996). Severe but rare hepatotoxicity is precipitated by pemoline as well.

The recently approved agent, modafinil, is a "wakefulness promoting" agent that is indicated for the treatment of the excessive daytime sleepiness symptoms of narcolepsy. This drug is unrelated both chemically and in its mechanism of action to the other stimulant drugs and has the advantage of an improved side effect profile, as well as less potential for abuse. Its therapeutic response, however, rarely returns the patient to normal values in objective and subjective assessments for daytime sleepiness as was

represented in the randomized blinded trial for modafinil in 283 narcoleptic subjects (U.S. Modafinil in Narcolepsy Multicenter Study Group, 1998).

There is obvious clinical need beyond existing therapies which are clearly divided in efficacy between daytime sleepiness (stimulants and modafinil) and REM suppressant agents (TCAs, SSRIs) that provide limited therapeutic potential for the REM related symptoms of cataplexy, hypnagogic hallucinations, and sleep paralysis for which no approved treatments exist. All have the potential for the development of tolerance as the benefits of treatment wane in time, and although dosage increases provide temporary therapeutic gain, the risk of side effects increases.

Oxybate is a four carbon hydroxy fatty acid that is naturally occurring and widespread in most tissues of the body. Extensive scientific attention has been paid to its central effects and functions. When administered therapeutically as the sodium salt, it is a neuroactive drug with specific effects on sleep architecture. It has been shown to increase slow wave non-rapid eye movement (nonREM or NREM) sleep, with no suppression of rapid eye movement (REM) sleep, and to decrease REM latency (Mamelak 1997, Lapierre 1990).

The unique beneficial effects of sodium oxybate treatment in narcoleptic patients with cataplexy have been previously reported from several open-label, uncontrolled clinical studies (Broughton 1979, Broughton 1980, Scharf 1985, Mamelak 1986, Montplasir 1986). For example, Scharf and colleagues (1985) treated 30 narcoleptic patients for 4 to 30 weeks with average nightly doses of 5 to 7 grams. They reported significant decreases from baseline in the frequency of cataplexy attacks, daytime sleep attacks, hypnagogic hallucinations and sleep paralysis. In addition, sodium oxybate has been shown to produce marked improvement in nocturnal sleep disturbance in narcoleptic patients, with EEG findings supported by subjective improvement (Broughton 1980, Scharf 1985, Montplaisir 1986).

Narcolepsy is a relatively rare disease affecting approximately 0.05% of the general adult population of the United States and in various European countries (Nishino 1997). Review of its prevalence has resulted in Orphan Drug designation by the FDA. This 0.05% prevalence has limited the size of the clinical trial database in the development of Xyrem, along with further patient limitation by the required entry criterion of cataplexy. Whereas excessive daytime sleepiness with sleep attacks affects 100% of narcoleptics, the REM-related symptoms occur with lesser frequency (cataplexy 60-90%, hypnagogic hallucinations and sleep paralysis 30-60% of narcoleptics, as reported by Mitler, 1997).

9.2 Benefits of Xyrem (sodium oxybate) oral solution

The effectiveness of Xyrem in the treatment of narcolepsy has been documented in this application by three basic methods: (1) by patient daily diary records of the occurrence of narcolepsy symptoms along with patient self-rating of daytime sleepiness [e.g., the validated Epworth Sleepiness Scale] (2) by principal investigator rating of overall clinical improvement [e.g., the Clinical Global Impression of Change Rating] and (3) by objective recording of changes in sleep architecture [e.g., overnight PSG,MWT and MSLT].

Taken together these well-established methods have been utilized in four adequate and well-controlled trials (OMC-GHB-2,OMC-SXB-21, Scrima and Lammers) and in one long-term supportive trial (OMC-GHB-3) to validate the benefits of Xyrem in treating the symptoms of narcolepsy. Table 9.1 summarizes the statistical evidence that supports this statement.

9.2.1 CATAPLEXY

Statistical evidence of the reduction in cataplexy incidence has been established in two pivotal trials, OMC-GHB-2, and Scrima.

In OMC-GHB-2, patients represented the broad spectrum of disease severity, with cataplexy ranging in incidence from 2.8/week up to 250/week, but the severity at baseline was well balanced and not statistically different between groups, averaging approximately 34/week. Because of this wide spread and skewed distribution, log transformation was performed when data failed to show normal distribution according to the Wilks-Shapiro Test. Thus, group data are represented as medians rather than the more common means. The median number of cataplexy attacks was approximately 22 per week at the start of double-blind drug treatment in OMC-GHB-2. Therefore, the patients in this trial had moderate to severe cataplexy.

A significant dose-related reduction in the overall occurrence of cataplexy attacks per week is clearly shown in Table 9.1. Statistical reduction relative to baseline was demonstrated across all treatment groups (P=0.0021), but comparison to placebo showed clear efficacy at the 6 g (P=0.0529) and 9 g (P=0.0008) doses. The majority of reduction occurs in the first two weeks of treatment, but response does not maximize in this four-week treatment period.

Another secondary clinical benefit of Xyrem is demonstrated by the data derived from the abrupt cessation of drug after the 4-week treatment period in the OMC-GHB-2 trial. An expected increase in cataplexy incidence followed, showing regression toward, but not exceeding, baseline levels. This lack of acute rebound cataplexy, as occurs with abrupt cessation of tricyclic antidepressants, (described as a consequence of the homeostatic “REM pressure”), separates Xyrem from the medications currently used.

With respect to the Scrima study, the results in Table 9.1 again indicate an appreciable placebo effect in the reduction of the incidence of cataplexy, but this did not reach statistical significance (P=0.117). In contrast, the change from baseline to endpoint for patients receiving 50 mg/kg sodium oxybate (average dose 4.2 g/d) was significant (P=0.007). There were significantly fewer cataplexy attacks/day during sodium oxybate treatment overall compared to placebo (P=0.013) with significant differences at week 3 (P=0.005) and week 4 (P=0.004).

In the Lammers randomized crossover trial in 25 narcoleptics, patients were administered 60 mg/kg/day (average dose 4.7 g/d) or placebo for four weeks, separated by a four-week washout period. This study differs from the previous two in that sodium oxybate treatment was added to existing medications, including anti-cataplectic therapy

in some patients, for an incremental treatment response. Most importantly and in contrast to the patient populations in the OMC-GHB-2 and Scrima trials, the narcoleptic patients in this study presented a much lower cataplexy incidence at baseline (median 5/week). Thus, the Lammers trial represents narcoleptics with relatively mild cataplexy. As reported in the publication of these data (Lammers 1993), the change in cataplexy incidence over the four-week treatment period failed to reach statistical significance but showed a strong trend in favor of the active drug treatment.

The analysis of the published data discussed above employed a non-parametric statistical model that treated each of the two drug administration periods as though they comprised two independent patient samples. When those data were reanalyzed by Orphan Medical using a statistical model more appropriate to a crossover design (ANCOVA) that included treatment order, period, and baseline cataplexy rate, the difference between placebo and oxybate treatment periods was found to be statistically significant (P=0.002).

Strong additional support for the efficacy of Xyrem in cataplexy reduction comes from the GHB-3 open-label extension study, in which 117 patients from the GHB-2 entered a long term open label study, during which daily diary recording of symptoms provided opportunity for longer term efficacy analysis. Patients entered the treatment phase at the 6 g dose, and titrated to clinical efficacy at doses between 3-9 grams. This prolonged treatment period indicated a further marked reduction in cataplexy incidence, with maximal reduction achieved after eight weeks of treatment in OMC-GHB-3, and maintained reduction over the remainder of the twelve-month period. There was no difference in dose response across all doses when expressed as median percentage change from baseline, confirming the appropriateness of the available dose range to optimize clinical response.

In OMC-SXB-21 study, the long-term efficacy of Xyrem was demonstrated in patients who had received treatment with Xyrem for 6 months to 4 years by the return of cataplexy when randomized in blinded fashion to placebo, compared to the blinded continuation of treatment. No change was seen in the incidence of cataplexy attacks in the Xyrem group (median change 0.0 each week), while cataplexy attacks increased in the placebo group by a median of 4.2 in week 1, and 11.7 in week 2. The overall median increase in cataplexy in the blinded study period was 0.0 in the Xyrem group, and 21 in the placebo group. These data strongly support the long-term efficacy of Xyrem in the control of cataplexy in narcolepsy.

In a six-month safety study conducted under the Treatment IND in 185 patients (OMC-SXB-6), treatment with Xyrem was initiated at a 4.5 g nightly dose, added to any existing medications for narcolepsy. This protocol recommended dose titration between 3-9 g/day in 1.5 g increments to optimize clinical response as recorded in a Narcolepsy Symptom Questionnaire. Withdrawal of concomitant anti-cataplectic medications (TCAs or SSRIs) was encouraged once stable Xyrem dosage was reached, unless antidepressant medication was required for treatment of depression. This study established that at stable doses of Xyrem that produce clinical response, the side effect profile does not change when treatment is initiated as concomitant medication, and that

the REM-suppressant antidepressants can be safely and effectively discontinued or decreased in dosage without an increase in the frequency of cataplexy, or the precipitation of rebound cataplexy.

Table 9.1. Summary of Outcomes in Clinical Trials Supporting the Efficacy of Sodium Oxybate

Trial[a]/ Dosage Group (n)	Baseline	Endpoint	Comparison to Placebo *P*-value
Cataplexy Attacks			
OMC-GHB-2 (median attacks/wk; n = 130)			
Placebo (33)	20.5	16.3	—
3.0 g/d (33)	20.0	9.5	NS
6.0 g/d (31)	23.0	8.0	0.0529
9.0 g/d (33)	23.5	8.7	**0.0008**
Scrima (mean attacks/wk — daily x 7)			
Placebo (18/19)	20.3	13.3	—
4.2 g/d (18/19)	20.3	8.4	**0.013**
Lammers (median attacks/wk — daily x 7)			
Placebo (24)	5.5	3.0	—
4.7 g/d (24)	4.0	1.5	NS **(0.002)**[b]
OMC-GHB-3 (median attacks/wk — endpoint = 12 months)			
3.0 g/d (7)	32.85	2.13	**0.016***
4.5 g/d (9)	13.50	0.88	**0.004***
6.0 g/d (24)	23.25	0.55	**< 0.001***
7.5 g/d (14)	33.50	2.76	**< 0.001***
9.0 g/d (21)	34.50	2.67	**< 0.001***
Daytime Sleepiness			
OMC-GHB-2 — Epworth Sleepiness Scale Range 0 to 24 (median)			
Placebo (33)	19.0	17.0	—
3.0 g/d (31)	17.0	16.0	NS
6.0 g/d (30)	17.0	13.5	NS
9.0 g/d (28)	17.0	12.0	**0.0001**
Scrima — MSLT Sleepiness Index: abnormal > 75, borderline 50 to 75, normal < 50 (mean)			
Placebo (20)	88.5	89.6	—
4.2 g/d (20)	88.5	85.8	NS
Lammers — patient rating of severity 0 = no sleepiness, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe (median)			
Placebo (24)	1.50	1.57	—
4.7 g/d (24)	1.67	1.16	**0.028 (0.034)**[b]

(continued)

Table 9.1. Summary of Outcomes in Clinical Trials Supporting the Efficacy of Sodium Oxybate

Trial[a]/ Dosage Group (n)	Baseline	Endpoint	Comparison to Placebo *P*-value
Daytime Sleepiness (continued)			
OMC-GHB-3 Epworth Sleepiness Scale Range 0 to 24 (median — endpoint = 12 months)			
3.0 g/d (7)	17.00	13.00	**0.019***
4.5 g/d (9)	19.00	15.00	**0.005***
6.0 g/d (24)	16.50	12.00	**< 0.001***
7.5 g/d (14)	18.00	11.50	**< 0.001***
9.0 g/d (20)	17.50	13.00	**< 0.001***
Inadvertent Naps/Sleep Attacks[c]			
OMC-GHB-2 (median naps/attacks/day)			
Placebo (33)	1.50	1.07	—
3.0 g/d (33)	1.93	1.14	NS
6.0 g/d (31)	1.45	0.92	**0.0497**
9.0 g/d (33)	1.27	0.50	**0.0122**
Scrima (mean sleep attacks/day)			
Placebo (17)	2.8	2.1	—
4.2 g/d (17)	2.8	1.9	NS
Lammers (median sleep attacks/day)			
Placebo (24)	1.83	2.14	—
4.7 g/d (24)	2.17	1.36	**0.001 (<0.001)**[b]
Number of Awakenings/Night[c]			
OMC-GHB-2 (median)			
Placebo (33)	2.05	2.14	—
3.0 g/d (33)	2.88	2.57	NS
6.0 g/d (31)	2.93	2.57	NS
9.0 g/d (33)	2.89	2.18	**0.0035**
Scrima (mean)			
Placebo (17)	3.0	3.7	—
4.2 g/d (17)	3.0	2.4	**0.042**
Lammers (median)			
Placebo (24)	2.71	3.31	—
4.7 g/d (24)	3.39	2.00	**NS (0.011)**[b]

(continued)

Table 9.1. Summary of Outcomes in Clinical Trials Supporting the Efficacy of Sodium Oxybate

Trial[a]/ Dosage Group (n)	Baseline	Endpoint	Comparison to Placebo *P*-value
Clinical Global Measures of Change[d]			
Trial	**Non-Responders[e]**	**Responders[f]**	**Comparison to Placebo p-value**
OMC-GHB-2 – Investigator's Clinical Global Impression of Change in Severity			
Placebo (34)	23 (68%)	11 (32%)	—
3.0 g/d (30)	16 (53%)	14 (47%)	NS
6.0 g/d (31)	15 (48%)	16 (52%)	NS
9.0 g/d (30)	6 (20%)	24 (80%)	**0.0002**
Lammers — Patient's Global Therapeutic Impression of Change			
Placebo (24)	22 (92%)	2 (8%)	—
4.7 g/d (24)	9 (38%)	15 (63%)	**<0.001 (<0.001)[b]**
OMC-GHB-3 Investigator's Clinical Global Impression of Change in Severity			
3.0 g/d (7)	1 (14%)	6 (86%)	—
4.5 g/d (8)	1 (13%)	7 (88%)	—
6.0 g/d (24)	1 (4%)	23 (96%)	—
7.5 g/d (14)	1 (7%)	13 (93%)	—
9.0 g/d (21)	3 (14%)	18 (86%)	—

[a] OMC-SXB-6 did not measure change from baseline numerically and is not included in this presentation.

[b] *P*-value reported by Lammers (1993) followed in parentheses by *P*-value obtained by reanalysis of data by Orphan Medical, Inc. using ANCOVA.

[c] OMC-GHB-3 did not present number of naps/sleep attacks/week or number of awakenings/night.

[d] Scrima did not have a clinical global measurement of change and is not included in this presentation.

[e] Non-responders in OMC-GHB-2 and OMC-GHB-3 = "minimally improved," "no change," "minimally changed," and "much worse"; in Lammers = "no beneficial effect."

[f] Responders in OMC-GHB-2 and OMC-GHB-3 = "very much improved" and "much improved"; in Lammers = "beneficial effect."

* Comparison of endpoint to baseline for open-label trials only; double-blind placebo-controlled trials comparison is oxybate-treated vs placebo.

Epworth Sleepiness Scale measures sleep propensity based on the retrospective report of the subject's dosing behavior in 8 everyday situations.

— = not applicable. MSLT = multiple sleep latency test. NS = not statistically significant, p > 0.05.

Data Source: Trial reports: OMC-GHB-2 — in-text Tables 10, 12, 13 and Summary Tables 20 and 22; Scrima — Tables 6A, 7A, 8A, 23; Lammers — 14a, 16a, 18a; OMC-GHB-3 — Tables 10, 16, 23. Publication: Lammers 1993.

9.2.2 EXCESSIVE DAYTIME SLEEPINESS

The measures employed to monitor excessive daytime sleepiness (EDS) in the Orphan-sponsored clinical development program have been the validated and widely-used patient representation of daytime feeling of somnolence, the Epworth Sleepiness Scale (ESS) and patient recordings in daily diaries of the number of inadvertent naps or sleep attacks occurring each day during daytime.

In the blinded, randomized study in 136 patients (OMC-GHB-2), there was again a clear dose-related ESS decrease across the three doses studied, with this change reaching statistical significance (*P*=0.0001) in patients in the 9 g/day dose group compared to placebo response. These data represent three important considerations: First, stimulant medication was held constant throughout this trial, so the change in daily feelings of somnolence was incremental beyond that of maintenance stimulant medication. Second, in spite of the continued stimulant therapy, the baseline measure in all groups showed severe subjective sleepiness (mean ESS score of approximately 17, maximum ESS score=24) indicating a real need for additional therapeutic options in the treatment of daytime sleepiness. Lastly, this incremental improvement has been sufficient to improve some patients in all three treatment groups to a reduced ESS score no longer in the defined range for narcolepsy (13 to 24). Approximately one quarter of the patients in the 9 g/day dosage group achieved Epworth scores in the normal range ($\leq$ 10).

The second component of daytime sleepiness, the number of inadvertent sleep attacks during the day, were also significantly reduced versus placebo at the 6 g/day dose (*P*=0.0497) and the 9 g/day dose (*P*=0.0122).

In OMC-SXB-20, the objective measure of Maximal Wakefulness Test (MWT) was employed on the day following overnight polysomnographic recording. This study was primarily conducted to define the dose-related EEG characteristics of Xyrem, but again supported the efficacy of Xyrem to reduce the symptom of daytime sleepiness by the objective measure of increased sleep latency under standardized soporific conditions. The mean (SD) sleep latency time in minutes increased from 4.5 (6.01) minutes at baseline by 3.7 (7.68) minutes after 4 weeks of 4.5g/day dosing, and by 6.1 (6.82) minutes at the 9g/day dose. Both of these changes were statistically significant, and represent incremental increases beyond the effects of maintained stimulant therapy.

In the Scrima trial, efficacy measures for excessive daytime sleepiness included the objective measure of Multiple Sleep Latency Test (MSLT) and the number of daytime sleep attacks. In this small group of twenty patients, statistically significant changes were not observed although both measures showed a positive trend with respect to oxybate.

In the Lammers Study, a patient assessment of sleepiness during the day was recorded on a 5-point scale in daily diaries. This measure showed significant improvement in the oxybate treatment phase (*P*=0.028) compared to placebo. Daytime sleep attacks were

again significantly reduced (*P*=0.001) further confirming efficacy at this dose of 60 mg/kg (average actual dose = 4.7 g/d).

In the OMC-GHB-3 follow-on study in 117 patients continuing from OMC-GHB-2, the subjective assessment of somnolence represented by the Epworth Sleepiness Scale mirrored the changes seen in cataplexy, with maximal changes across all doses seen after eight weeks of treatment, and then sustained across the 12 months of treatment. This sustained response strongly supports this parameter as a representation of pharmacodynamic significance, since one would certainly expect subjective measures of less significance to regress toward baseline over such a prolonged time course. Because the patients were titrated to clinical effect, no significant differences were seen amongst the dose groups from 3 to 9 g/day.

9.2.3 OTHER SYMPTOMATIC BENEFITS

Sleep paralysis was recorded in relatively low incidence in all controlled trials, so no meaningful analysis was feasible. In both the Lammers and Scrima trials, hypnagogic hallucinations were reduced in a statistically significant manner (p=0.008 in both trials). In the OMC-GHB-2 & 3 studies, a consistent trend in the reduction of hypnagogic hallucinations was seen that did not reach a level of significance.

9.2.3.1 Clinical Global Improvement

Finally, in OMC-GHB-2 and in the Lammers study, the clear clinical benefit of Xyrem therapy in narcolepsy was confirmed by two measures of overall assessment, one by the clinician and the second by the patient. In OMC-GHB-2 the Clinical Global Impression of Change (CGIc) was the instrument used by the clinical investigator to assess the overall change in disease severity at the end of the blinded four-week treatment period compared to an assessment of disease severity recorded at the end of baseline. The change in status utilized a standard seven-point rating scale from “very much worse” to “very much improved”. Based on the CGIc rating, only patients rated as “very much improved” or “much improved” were classified as responders, with all other classifications grouped as non-responders. A clear dose response was seen for this parameter with a 32% responder rate for placebo-treated patients, 47% and 52% in the 3 g and 6 g groups, respectively, and an 80% responder rate for patients in the 9 g high dose Xyrem group. Only the 9 g group responder rate was statistically significantly different from the placebo group (*P*=0.0002).

In addition, this same CGIc rating instrument was continued through to the twelve-month assessment in OMC-GHB-3. Even though this was an open-label study, there was a clear indication of high responder rates across all doses, sustained over time, when Xyrem was titrated to optimal clinical effect.

A different means of assessing overall clinical response was used in the Lammers crossover study, where the patient’s opinion on the overall benefit of the double-blind medication was recorded (as a dichotomous Global Therapeutic Impression: “beneficial effect” versus “no beneficial effect”) at the end of each four-week treatment period.

Sixty-four percent of the patients (16 of 25) reported overall beneficial effect following sodium oxybate treatment. In comparison, after placebo treatment, only 8% reported beneficial effect (2 of 25). This difference was highly significant (*P*=0.001).

9.2.4 BENEFICIAL CHANGES IN SLEEP ARCHITECTURE

Pre- and post-treatment polysomnogram (PSG) analyses were not included in the OMC-GHB-2 trial but were a part of both the Scrima and Lammers trials. Orphan Medical did not have access to the Lammers PSG raw data and, therefore, was not able to include the PSG data in the full clinical report in this application. Thus, the statements below regarding Lammers' findings with respect to PSG-based sleep architecture are based solely upon his published paper (Lammers 1993).

In the Scrima trial, polysomnographic recordings at the end of baseline and again at the end of the active and placebo treatment periods yielded very useful objective data regarding the beneficial effects of sodium oxybate on sleep architecture. Sleep consolidation was confirmed by enhancement of both the depth (increased slow wave sleep) and continuity of sleep. Compared to placebo, treatment with sodium oxybate increased slow wave sleep (especially Stage 3) with a correspondingly significant decrease in light (Stage 1) sleep. The number of objectively measured awakenings decreased significantly (*P*=0.042). This enhanced sleep continuity was supported by the significant reduction in stage shifts associated with oxybate treatment. Lastly, oxybate did not suppress REM sleep, a characteristic of other hypnotic drugs such as the benzodiazepines.

In the OMC-SXB-20 study, overnight polysomnographic studies demonstrated the dose-related effects on sleep architecture. There was the characteristic increase in slow-wave sleep (Stage 3 & 4) across all four doses, reaching significance at the 9.0 g/night dose, and a reduction in Stage 1 sleep. Delta power, a derived index of all slow wave signals, showed a dose related increase that was highly significant on the first night of dosing at 4.5 g as well as after 2 weeks of dosing at 6 g, 7.5 g and 9 g/night. A dose-related decrease in the number of nocturnal awakenings was recorded, which was significant at the 7.5 g and 9.0 g/night Xyrem doses.

Unlike previous studies, a decrease in total REM sleep duration at all 4 doses followed an initial acute increase at 4.5 g dosing. No significant change in REM latency was observed.

A decreasing trend in the number of shifts in sleep stages was seen, but total sleep time and time awake after sleep onset did not change.

In the publication of the Lammers trial, several effects of sodium oxybate on PSG sleep parameters were reported (Lammers 1993). Compared to placebo, sodium oxybate significantly reduced the number of awakenings from, and the percentage of wakefulness during, REM sleep. During oxybate treatment the amount of nocturnal slow wave sleep also was increased considerably and to a significant degree (*P*=0.053). Other PSG parameters were not significantly altered by oxybate treatment.

These sleep EEG effects are consistent with and supportive of the open-label published trials previously discussed at the beginning of this section.

9.3 Observed and Potential Risks of Xyrem® (sodium oxybate) oral solution

9.3.1 SAFETY

9.3.1.1 Adverse Event Profile

The overall safety profile of sodium oxybate during the controlled, double-blind and open-label trials in narcolepsy has been favorable, with most adverse events reported as mild to moderate in severity, and not considered to be serious. The most frequently reported adverse events included headache, nausea, dizziness and pain (without causality association). When the occurrence of adverse events was considered in terms of dose at onset of the event, there were no apparent differences across the proposed therapeutic dosage range from 3 to 9 grams per day.

There are 181 patients included in the three randomized, blinded, controlled trials. OMC-GHB-2 is the largest parallel design trial of 136 patients and patients were assigned to the treatment groups of 3 g, 6 g, 9 g or placebo in blinded fashion, without regard for physical characteristics or disease severity, and, as in proposed clinical practice, without any dose titration. One hundred of the patients reported one or more adverse events during the treatment period. Many occurred within the first few days of initiation of double-blind medication and were not reported again during the study period. The adverse events that suggested a dose relationship included nausea, vomiting (only reported in the 6 and 9 g dose groups), dizziness, and enuresis. Although not statistically dose-related, headache was a prominent adverse event (including the placebo group). Enuresis is of special interest, since this and, more rarely, somnambulance (sleepwalking) have been uniquely associated with sodium oxybate therapy.

In the Scrima Trial of crossover design, 20 patients received 50 mg/kg and placebo in divided dose at night for 29 days. In general, most adverse events occurred either with similar frequency during placebo and oxybate treatment or only once during the trial with the exception of dizziness (four events on active treatment, none with placebo). The most common events with oxybate were headache (n=5), dizziness (n=4), nervousness (n=3), and somnolence (n=3). Most events were of mild severity, with no deaths or discontinuations, or serious adverse events.

In the Lammers Study of crossover design, 25 patients received active drug treatment in a nightly divided dose of 60 mg/kg for 28 days. Sodium oxybate was well tolerated with adverse events few in number and mild in severity, with only 3 of 6 events occurring during active drug therapy.

In the uncontrolled extension trial, OMC-GHB-3 patients could continue the study for up to 24 months. This was analyzed in detail for the 12-month duration as in the initial

protocol and, in summary, from up to 18 and 24 months. Patients entered the study at the 6 g dose and were titrated to clinical efficacy at doses between 3 g and 9 g, with dose titration generally achieved in 2 to 5 weeks. By the end of the trial, >75% of patients had titrated to dosages between 6 g/d and 9 g/d, while stimulant medication dosage was maintained.

Of the 117 patients receiving drug, 109 reported any adverse event in the first 12-month treatment period. The most common events were headache (33.3%), nausea (28.2%), viral infection (27.4%), dizziness (26.5%), pain (25.6%) and somnolence (19.7%). Of these events, only dizziness occurred across treatment groups at a statistically significant level (*P*=0.015), but was not a dose-related event, since most events occurred in the lower dose groups. Weight decrease occurred in five patients (3 in 7.5 g group, 2 in 9 g group).

In the second 12 months of the study (to two years exposure), no additional patients experienced adverse events.

Overall, a positive safety profile of long-term Xyrem administration was observed. Adverse events appeared to initiate within the first 12 months of drug exposure, and the great majority (> 90%) were classified by the investigators as mild or moderate. There was no dose relationship for severity.

In the OMC-SXB-6 Treatment IND Protocol, 185 patients enrolled, and started Xyrem at 4.5 g in divided dose at night as additional therapy for narcolepsy. Dose was titrated to optimize clinical response with the option to gradually withdraw TCAs or SRIs, while maintaining stimulant medication constant. The majority of patients (70%) were receiving doses $\geq$ 6 g/d by the time of their last observation. In this trial 144/185 (78%) of patients reported adverse events over the 6-month treatment period and these were rated as mild to moderate in 114 patients (62%) and severe in 30 patients (16%), with possible association with drug rated in 53% of patients overall.

There were no apparent dose related trends for adverse events. Most frequently reported over the 6-month period were headache (22%), nausea (16%), pharyngitis (11%) and sleep disorder (10%). Six patients reported an event coded in the COSTART dictionary as “convulsion”, but all of these were cataplexy events and, therefore, part of the disease symptomology. Weight variation was reported in 5 patients, 3 with weight increase and 2 with weight loss.

Of the adverse events that occurred with a frequency of $\geq$ 5% overall or in any one-dose group, only headache (6 patients) was classified as severe in $\geq$ 3 patients for the overall population. There was no apparent dose-relationship for severity.

Of the adverse events classified as “sleep disorder” the majority were at 4.5 to 6 g dosage at onset, and mostly represented somnambulism (sleep walking), with 12 patients reporting 13 episodes, and 2 reporting somniloquence (sleep talking).

Thirteen patients reported urinary incontinence, all as single episodes except for 1 patient (2 episodes) and all representing enuresis except for 2 reports that were unclassified in terms of temporal diurnal relationship.

The longer-term treatment IND study (OMC-SXB-7) into which patients transferred from previous trials (OMC-GHB-3, OMC- SXB-6, or Scharf IND patients) provides longer-term evidence of safety. Patients entering this trial had previously received sodium oxybate for up to 2 years in GHB-3, for 6 months in OMC-SXB-6, or for up to 16 years under the Scharf IND. Of the 145 patients enrolled in this trial to the date of interim cut-off of December 31, 1999, 44 (30%) had 1 or more adverse events, with 7 (5%) reporting severe adverse events, but only 13 (9%) having adverse events considered possibly related to trial medication. Two patients reported serious adverse events, one leading to patient discontinuation, and no deaths occurred.

The same profile of adverse events was seen in this trial with the most common adverse events reported as nausea (4%), sleepwalking, vomiting, back pain and pain (each 2%). The majority of reported adverse events were classified by the investigator as mild (45%) or moderate (39%). Again, there was no dose relationship in the severity of adverse events.

9.3.1.2 Scharf Report

Orphan Medical was aware of the long experience of Martin Scharf, PhD, Cincinnati, in the use of sodium oxybate. He treated 143 patients with the drug during a period of over 16 years under his Investigator IND. Orphan Medical was granted access to this database by Dr. Scharf and we have included this data to provide a profile of long-term clinical experience with sodium oxybate. This data was collected by the site more in the form of clinical records than as drug development research and, hence, there exists some compromise in interpretation (i.e. laboratory measures were generated from many different laboratories, dose titration extended to as high as 12.5 g/day [greater than 9 g in four patients]), but this data does provide useful experience in long-term treatment exposure. The exposure to drug includes 121 patients with data $\geq$ 6 months, 104 for $\geq$ one year, 74 $\geq$ 5 years and 46 $\geq$ 10 years.

During the study, any adverse event was reported by 136 (95.1%) patients, with a higher evidence of reporting in the first 6 months (87.4%) than in the remaining treatment period (77.6%). This suggests that long-term exposure to sodium oxybate is not associated with higher levels of adverse events.

Many of the adverse events were those expected as a temporal relationship with a long-term clinical study, the most common being associated with frequent symptomology (flu syndrome, headache, viral infection, accidental injury, pain, nausea, pharyngitis and rhinitis). For the entire study, 44% of the adverse events occurred in only 1 or 2 patients and, hence, does not support a strong association with sodium oxybate.

Many of the frequent adverse events were judged not related to study medication by the investigator. In the first 6-month treatment period, the reports of dizziness and nausea

were frequently assigned as related (8.4% and 5.6%, respectively). All instances of sleep disorders (9.1%), mainly somnambulism, were considered related to treatment. When this time period is compared to the similar time period in the long-term studies conducted by Orphan Medical to create accurate comparative temporal relationship, the adverse event profile was very similar in incidence and profile.

For the continued long-term treatment period beyond 6 months, all instances of sleep disorders [40, (28%)] and urinary incontinence [31, (21.7%)] were considered treatment related.

The term "convulsions" was used to code events reported in 9 patients, but 5 of the 9 patients had events that were more appropriately coded as "cataplexy", and, therefore, symptomatic of the primary disease of narcolepsy. Four patients had events that were correctly coded as convulsions. At least one of these patients had a history of seizures prior to oxybate treatment and one patient had a known intracranial lesion. There was no dose response relationship evident.

In 1991, a 49-year old female patient in the study developed clinical symptoms of arthritis, after treatment with sodium oxybate continuously for over 5 years at an average nightly dose of 6 g. An anti-nuclear antibody (ANA) test and two repeat tests were all positive raising concern for the possibility of drug-related lupus. She was withdrawn from the drug with a subsequent fall in ANA titers, followed by an increase again 1 year later.

At this time, Dr. Scharf began to collect ANA profiles on all patients active in the ongoing study. Over the next 2 years, 19 of 65 patients were shown to have ANA elevations ranging from 1:40 to 1:2560. Some of these elevations were intermittent and no correlation was found between ANA titer positivity and duration of oxybate treatment, age or gender. Antihistone antibodies were also determined for 15 of the 19 ANA-positive patients. Only 1 patient showed a "borderline" positive result.

These data indicate that long-term use of sodium oxybate may result in elevations in ANA antigen profiles without the corresponding increase in antihistone antigens that is characteristic of most reported cases of drug-induced lupus. Secondly, narcoleptic patients with positive ANA findings did not present or subsequently develop symptoms suggestive of lupus-related disease. Lastly, no patients in the Scharf long-term study have developed systemic lupus erythematosus during treatment with sodium oxybate for over 16 years.

9.3.1.3 Clinical Laboratory Test Evaluations

In consideration of blood chemistry values in the five clinical trials discussed, mean changes for all parameters were small and similar across all 5 doses of sodium oxybate and placebo. Similar observations were made for hematology values, where changes were again small and similar across all 6 treatment groups.

A slight increase in urinary pH was seen in OMC-GHB-2, where this change was postulated to relate to the urinary excretion of the sodium load sourced from Xyrem (in this sodium salt, 18.23% by weight of each dose is sodium).

When considering specific values, shifts from baseline to last observation occurred in $\geq$ 10% of patients for calcium and total bilirubin. A shift from normal to low calcium was seen in 14 of 132 patients in whom this was measured over 1 year as in OMC-GHB-3 and OMC-GHB-2. This laboratory value shifted significantly from normal to abnormal (low) within the 6 g dose group, but was considered probably due to natural variability as there was no observed dose effect and the change was not considered clinically significant.

Of 23 patients with a normal serum calcium at baseline in OMC-GHB-3 that recorded a value lower than the normal range, 15 patients recorded a subsequent serum calcium within the normal range while still on Xyrem therapy, confirming laboratory variability rather than study medication. In a further 8 patients, values remained in the hypocalcemic range, in spite of normal renal function, proteins and phosphate levels, with no clinically significant reports to explain the finding. In all cases, the reduction was mild and would not be considered clinically significant.

A shift from normal to high values was seen in some patients with respect to glucose blood levels, but since these were frequently non-fasting levels, clinical interpretation is difficult.

9.3.1.4 Deaths

There has been one death (suicide) reported in the studies conducted by Orphan Medical. This death occurred from overdose of multiple drugs not involving Xyrem, and was considered unrelated to study medication. No deaths were reported in the Scrima or Lammers studies. This includes 366 patients, plus 144 subjects or patients in the pharmacokinetic/drug interaction studies. Subsequent to the cut-off date of data included in the NDA, a second suicide death has occurred in a patient with a long history of depressions and progression to bipolar disorder.

During the 16-year period of the Scharf trial, 11 patients died. These deaths were causally related to: 5 deaths from cardiovascular-related causes, 5 deaths from malignancy (3 lung, 1 colon, 1 bladder). One death resulted from a boating accident (study medication discontinued 4 months prior to the accident). A significant prior history of contributory disease was present in all 5 cardiovascular related deaths. In 2 of the patients succumbing to malignancy, a prior medical history of the malignancy was known. No symptoms were recorded prior to diagnosis of the malignancy for the remaining two patients. None of the deaths were considered as causally related to study drug.

9.3.1.5 Serious Non-Fatal Adverse Events

In the randomized, controlled trials, there was one serious adverse event (OMC-GHB-2), and 17 recorded during the longer term, open-label studies. Of these, 2 patients reported the SAEs prior to beginning sodium oxybate therapy.

The SAE's classified as related to study medication occurred in 5 patients (1 in OMC-GHB-2, 1 in OMC-GHB-3, and 3 in OMC-SXB-6). In the OMC-GHB-2 study, a female patient randomized to the 6 g dose experienced a severe confusional episode in the afternoon of the 7th day after her 6 g dose of Xyrem the preceding night. This episode resulted in hospitalization where she was treated with haloperidol, and the episode resolved. She was permanently discontinued from the study, and the event was categorized as possibly related to study drug.

Another patient in OMC-GHB-3 on 9 g dosing experienced severe agitation in the middle of the night on day 678 of treatment, leading to temporary cessation of treatment. The event resolved spontaneously.

A third patient in the OMC-SXB-6 experienced dizziness, confusion, nausea, vomiting, vertigo and asthma on day 99 of treatment at the 9 g dose. This patient was permanently discontinued from the trial.

Another patient in OMC-SXB-6 experienced a possibly related event at the 4.5g dose on day 170. The episode was coded as thinking abnormal, apnea, and unconsciousness. He collapsed soon after the first nightly dose (un-witnessed) recognized by the sound of hitting the floor. He was transferred to the hospital, requiring intubation and ventilation. He soon regained consciousness and respiratory depression resolved. Extensive neurological and cardiac assessment failed to identify a cause. Final expert opinions suggested some type of cardiac or neurological event, most likely cataplexy with resultant head injury, but with possibility of overdose. Symptoms resolved without sequelae, but he was permanently discontinued from the study.

The last report also came from OMC-SXB-6 and the patient was permanently discontinued from the trial on day 66 because she reported pregnancy, an exclusion criteria. Forty-two days later she experienced a spontaneous abortion which was rated by the investigator as "possibly" related to Xyrem.

In the Scharf patients, a total of 205 serious adverse events were reported by 54 patients over 16 years, representing 155 unique SAEs. However, the evidence for recurring SAEs was minimal, and the majority of events appeared consistent with the illness profile of older patients with narcolepsy and cataplexy.

Twelve serious adverse events were judged by the investigator to have been related to study medication. These 12 events occurred in 6 patients and 6 of these events were associated with higher doses than recommended as the therapeutic range (11.3 g, 12 g, and 3 instances of overdose at 18 g and 1 further event considered probably related to a high dose). These events were classified as overdose (2 instances), comatose, stupor,

unsuccessful suicide attempt, and potential overdose. One of these patients had associated hypoxemia, one had an accidental fall down a flight of stairs with consequent injuries, and one had "convulsive like seizures" and urinary incontinence. As several of these SAEs imply acute major psychiatric illness, this will be addressed separately in this report.

9.3.1.6 Discontinuations Due to Adverse Events

There were 38 withdrawals due to 1 or more AEs in the seven clinical trials excluding the Scharf database. These included 37 patients on sodium oxybate, 1 patient receiving placebo and, of those on drug, 32 experienced AEs considered related to trial medication. Four of these have been described in the SAE section, including the patient incorrectly listed as withdrawal due to pregnancy (protocol violation) with subsequent spontaneous abortion 42 days later. In these discontinuations due to AEs classified as related to study medication, there was no dose relationship seen, with 17 of the 32 events occurring at doses of 3-4.5 g/d, and 15 reported at doses of 6, 7.5, or 9 g/d.

Many of these events are related to the established side effect profile of sodium oxybate, such as dizziness, nausea, urinary incontinence, and headache. Others relate to other components of sleep disorders such as somnolence and movements during sleep (periodic limb movements), COSTART listed as hyperkinesias.

One subject also withdrew from one of the pharmacokinetic studies (OMC-SXB-11) investigating the effect of a high-fat meal on the bioavailability of Xyrem. This event consisted of respiratory depression, severe obtundation, and fecal incontinence when administered 4.5 g Xyrem as a single dose after an overnight fast. This patient responded to simple supportive measures, but chose not to continue in the second portion of the study.

In the Scharf study, 19 patients discontinued treatment with sodium oxybate because of an adverse event. These included eight patients whose symptoms were associated with their subsequent deaths, the attempted suicide, the 6 patients listed earlier as SAEs, 1 patient with difficulty sleeping and a psychiatric problem, elevated ANA titer, hypertonia, swelling and weight loss.

9.3.1.7 Drug Interactions

Orphan Medical sponsored three separate drug interaction studies evaluating the effects of Xyrem on co-medication and vice versa (Zolpidem, Protriptyline and Modafinil). The 3 co-medications chosen represent 3 classes of drugs (hypnotics, antidepressants and stimulants) commonly used in the treatment of narcoleptic symptoms. These studies concluded that sodium oxybate had no clinically important effect on the pharmacokinetics of these medications. Conversely, these 3 co-medications do not have any clinically significant impact on oxybate pharmacokinetics.

Invitro studies with pooled human liver microsomes show that oxybate does not significantly inhibit or enhance the activities of the human P450 isozymes: CYP1A2,

CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A. Given this fact and that the degradation of GHB is mediated by enzyme systems not related to the P450 oxidative systems, the lack of in-vivo drug-drug interactions are not surprising.

No reports of interactions with other concomitant medications were recorded during the drug development program. The clinical safety experienced with the wide range of medications, the expected lack of metabolic interaction resulting from independence from the cytochrome P450 oxidative enzyme system, and the fact that oxybate is an endogenous substance provide a satisfactory risk profile in terms of drug-drug reactions.

Special consideration should be given to interaction with alcohol. Animal data suggests that potential synergy resulted from coadministration of alcohol and GHB on the sleep time in rats (McCabe 1971). Kinetic interactions have been suggested by Vree (1975,1978), and so the warning must be issued that concomitant use of alcohol with Xyrem must be avoided.

9.3.1.8 Vital Signs and Electrocardiograms

No significant changes in vital signs or ECGs from baseline to the end of double-blind treatment were found in the four treatment groups (Placebo, 3, 6, and 9g/day) in OMC-GHB-2. Dose-related decreases detected in body weight and blood pressure were not considered to be clinically significant. Likewise, in the 6 PK studies conducted in healthy subjects, no clinically significant changes were observed in heart rate, respiration rate, or blood pressure.

9.3.2 SPECIAL CONSIDERATIONS

9.3.2.1 Seizurogenesis and Incontinence

Since enuresis has been an event reported in several of the studies (15 events in 8 patients in OMC-GHB-2, 51 events in 13 patients in OMC-GHB-3, 33 patients in the Scharf database), it is considered worthy of special address. In addition, 1 patient in OMC-GHB-2 reported fecal incontinence (considered due to diabetic diarrhea), as did 1 subject in the effect-of-food PK study (described earlier), and 1 patient in the Scharf trial.

At the time of review by FDA of OMC-GHB-2 in October 1998, FDA suggested that a relationship of incontinence and seizurogenesis should be considered and, hence, investigation was initiated into these early patients. This was done by:

- A questionnaire to all Investigators to review any observed abnormal nocturnal observations suggestive of seizures, urologic history preceding oxybate therapy, and any new neurologic symptoms.

- Correlation of any other CNS AEs correlating with incontinence (either urinary or fecal) that could be related to seizures.

- Subjecting 6 patients who had reported incontinence to overnight EEG (full-montage) recording at 9 g Xyrem dosing. These recordings were then referred to Nathan E. Crone, M.D., Neurologist, Johns Hopkins Medical Case, along with case reviews.

- Discussions with Martin Scharf, Ph.D. and Mortimer Mamelak, M.D., University of Toronto, Canada, regarding this long-term prior experience with sodium oxybate therapy.

In animal studies at high dose, GHB has been associated with EEG changes and behavioral presentation of symptomatology representing absence-seizure-like states. This has been developed as a model for absence seizures by Snead (1978) in primates, when high doses of GHB (600mg/kg) were administered intravenously. Myoclonus has been described as an occasional accompaniment of anesthesia induction with GHB intravenously.

In review of the data, there was no evidence to support seizurogenesis in our clinical trials. No bed partner has ever reported a seizure-like event in the treated patients. When the full-montage EEG studies were conducted in the patients with an incontinence history with Xyrem, it was serendipitous that 1 patient had urinary incontinence during the recording. Neither in this case nor with the other patients was there EEG evidence of seizure activity. There was no correlation with other CNS AE's that would correlate with incontinence to suggest neurologic disorder. Finally, 2 patients in the OMC-SXB-10 pharmacokinetic study at 4.5 g dosing as a single dose, experienced enuresis while under observation, and no seizure activity was seen. Pre-existing nocturia was a frequently reported symptom in these patients in their questionnaire.

Hence, in spite of the potential for partial seizures at doses far in excess of the human therapeutic dose in primates (when administered intravenously), there is no support for a relationship between seizures and the incontinence reported in this NDA submission, or from literature reporting human experience in therapeutic doses. Some associated seizure or tonic-clonic activity has been associated with presentation of some overdose and abuse experiences, where polypharmacy is common, and dose relationship determinations are impossible.

9.3.2.2 Psychopathology

The reporting of depression, and acute psychiatric symptomatology, such as frank psychosis, intentional overdose and suicide in the long-term studies, prompts a review of the literature associating psychopathology with narcolepsy as a disease. An association between psychopathology and narcolepsy was proposed by John Sours in 1963 when he reviewed clinical records of patients admitted to a New York hospital in the period from 1932 to 1964 that were coded under categories of hypersomnia, somnolence and narcolepsy. He identified eight patients with schizoid personality disturbances and another ten patients that developed frank schizophrenic psychoses that required prolonged hospitalization. Similar association was established in 1985 with an eleven-year sex- and age-matched review at the University of Iowa by James Wilcox that concluded a relationship between narcolepsy and psychosis. Such associations

have led to discussions as to whether psychiatric findings are epiphenomenal to, or inherent in the expression of narcolepsy.

A review of the emotional and psychosocial correlates of narcolepsy in fifty adults by Kales in 1982 indicated a "high level of psychopathology compared to controls", but he concluded that this resulted primarily as a reaction to the disorder and its effects.

An association between the HLA antigens related strongly to narcolepsy-cataplexy (HLA-DR2, DQ1) and its subdivision HLA-DR15, DQ6 has been suggested with schizophrenia. Douglass (1991, 1993) found that in 56 schizophrenic patients and 56 controls, the incidence of narcolepsy-associated antigens was 3.89 times higher in the schizophrenic patients. Also, that the patients with the narcolepsy-associated antigens had more hospitalizations and higher Brief Psychiatric Rating Scale scores, suggesting a severity association.

As was suggested by Kales, studies using self-report as well as traditional psychiatric measures have found significant depression among narcoleptics. People newly diagnosed with narcolepsy have reported that depression was the personality change they noted at disease onset (Broughton 1976). Recurrent episodes of depression have been reported by 51% of people with narcolepsy (Broughton 1984).

Seven hundred narcoleptics chosen randomly from the patient rolls of the American Narcolepsy Association were surveyed (response rate = 61.4%) with anonymous responses to the Center for Epidemiologic Studies Depression Scale (CES-D), indicating again that a high proportion of narcoleptics (49%) were experiencing depressive symptoms.

Analeptic-induced paranoid psychoses have been reported to occur in the treatment of narcolepsy (Leong 1989). Certain predisposing factors, such as pre-treatment paranoid ideation, family history of psychosis, significant head injury, or previous excessive use of stimulants, may provide "triggers" for psychiatric progression from long-term high dose stimulant therapy (Pawluk 1995).

Patient status in narcolepsy is obviously a complicated and dynamic representation of:

- Disease-associated psychosocial morbidity.
- Stimulant-induced changes and "trigger" influences
- Stress variations in daily life.
- Treatment-related co-morbidities

Such a possible commonality in pathogenesis and biochemical mechanism must be included in assessment of adverse events in a narcoleptic population and, in this context, there is little support for an association between sodium oxybate and the precipitation of the acute psychopathology recorded during the clinical trial periods.

9.3.2.3 Abuse Liability

There has been no evidence of tolerance development requiring dose escalation to maintain clinical efficacy in our clinical trials, and hence it has been possible to exclude suggestion of dose escalation for reasons of social pleasure. Absence of kinetic tolerance with chronic dosing was established in an appropriate study in narcoleptic patients. Although drug abuse has emerged as a significant public health issue for GHB wherein dose escalation both in terms of total dose and frequency of dosing is a real issue, we have seen no evidence of any such tendency in our clinical studies. Strict drug compliance has been monitored, and neither non-prescribed dose escalation nor diversion of clinical trial supplies was evidenced. As with the stimulant medications routinely used by narcoleptics, there was no documentation of euphorogenic properties at therapeutic doses used over the long periods of administration. No withdrawal symptomatology was reported following abrupt discontinuation of therapy.

Pre-clinical studies of the abuse potential using standard animal models have not yielded a picture of a highly abusable substance, but minimal human testing has yet been done. It is therefore difficult to separate the pharmacologic contributions to the public health problems of abuse from the sociologic issues, particularly in light of the ease of clandestine manufacture, the ease of access to starting materials, recipes, and "kits" for home manufacture via the Internet, and the wide availability and use of precursor chemicals such as gamma butyrolactone, and 1,4-butanediol.

9.4 Conclusions

Sodium oxybate offers a new and major therapeutic improvement in the management of narcolepsy when titrated to optimal clinical effect between the doses of 3 and 9 g nightly in divided dosing. It has great facility to reduce the incidence of cataplexy and, in combination with stimulants, reduce the subjective feelings of daytime somnolence. The added benefit in the reduction of inadvertent naps/sleep attacks was established in two double-blinded studies, with useful effects on the other ancillary REM-related symptom of hypnagogic hallucinations. Prolonged, sustained efficacy was established in the long-term study, OMC-GHB-3, and by the OMC-SXB-21 protocol.

The primary beneficial effects of sodium oxybate on sleep architecture previously described in the literature were confirmed in the Scrima trial, where a decrease in the number of awakenings, decreased Stage I with increased slow wave sleep, and a decrease in the number of stage shifts was measured in this double-blinded, placebo-controlled study. This confirms the increased delta-wave sleep seen in the OMC-SXB-20 protocol, where a clear dose-response increased in Stage 3,4 sleep along with a dose-related increase in delta power was established. The objective measure of Maximal Wakefulness Test increase confirmed the effects of Xyrem on daytime sleepiness that had been extensively measured by use of the Epworth Sleepiness Scale.

These benefits of therapy are seen in relation to low potential risks when used under prescribed medical care. Since the proposed dosing regimen requires therapy initiation at the low dose of 4.5 g in divided dose nightly with slow titration to achieve optimum

clinical benefit, the side effects that are usually mild (most frequently nausea, dizziness, headache, with occasional enuresis and somnambulism in susceptible individuals), can be minimized relative to clinical benefit. These benefits are offered as an alternative to the current off-label treatments of tricyclic and SSRI antidepressant medications used in addition to the stimulant medications. Sodium oxybate is the first drug product with the therapeutic potential to bridge the duality of treatments used to manage the symptoms of narcolepsy that are conceptually divided into the two mechanistic presentations of excessive daytime sleepiness and the ancillary REM-related symptoms of hypnagogic hallucinations, sleep paralysis and cataplexy.

SECTION 10
LIST OF REFERENCES

10.0 LIST OF REFERENCES

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Dayton T. Reardan Ph.D et al.

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

Docket No.:	101.031US9	Serial No.:	13/592,202
Filed:	August 22, 2012	Due Date:	N/A
Examiner:	Lena Najarian	Group Art Unit:	3686
Customer No.:	21186	Confirmation No.:	5805

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We are transmitting herewith the following attached items (as indicated with an "X"):

X Supplemental Information Disclosure Statement (2 pgs.), Form 1449 (1 pg.) Copies of Cited References (17).

If not provided for in a separate paper filed herewith, please consider this a PETITION FOR EXTENSION OF TIME for sufficient number of months to enter these papers and please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
Customer No.: 21186

By: / David D'Zurilla /
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Attorneys for Plaintiff
Jazz Pharmaceuticals, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **v.** **AMNEAL PHARMACEUTICALS, LLC,** **Defendant.**	**Civil Action No. _____** **(Filed Electronically)**

FED. R. CIV. P. 7.1 DISCLOSURE STATEMENT

Pursuant to Fed. R. Civ. P. Rule 7.1, counsel for Plaintiff Jazz Pharmaceuticals, Inc. certifies the following:

1. The full name of the party represented by me is: Jazz Pharmaceuticals, Inc.

2. Jazz Pharmaceuticals, Inc. is a wholly-owned subsidiary of Jazz Pharmaceuticals plc, which is a publicly traded company.

Dated: January 18, 2013

By: s/ Charles M. Lizza

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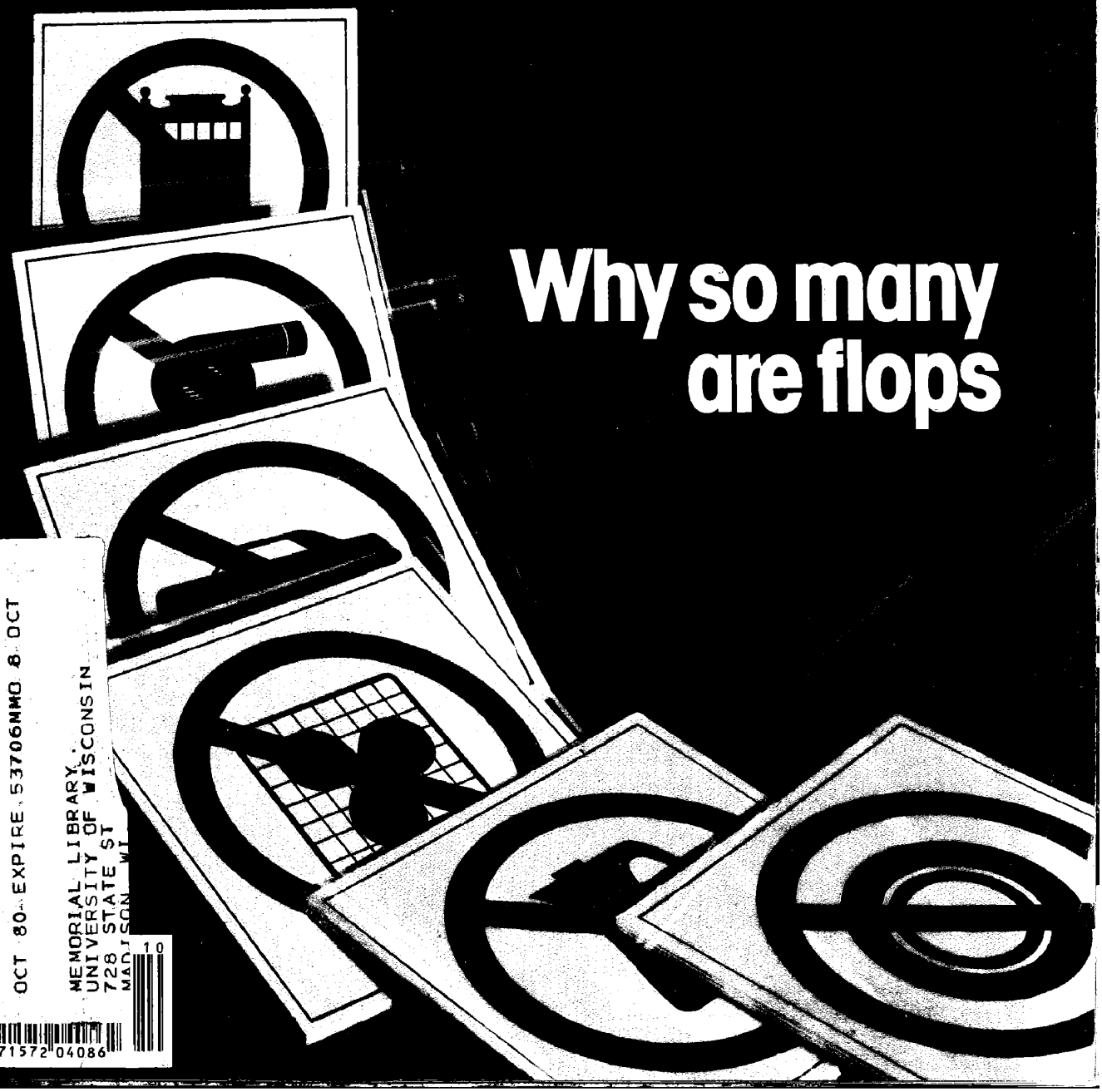
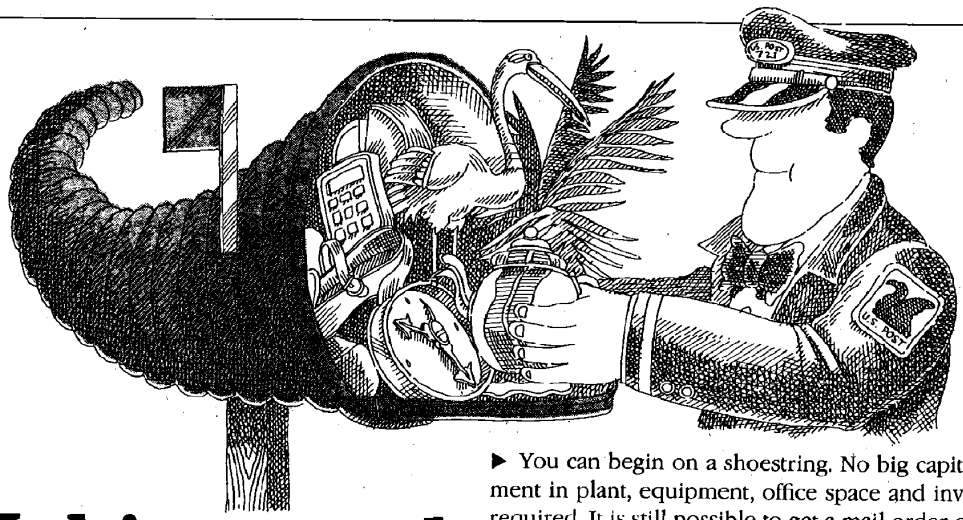
Changing Times

Does your medical insurance cover enough?
Home video equipment • Floating-rate mortgages
Making good in your own mail-order business



Why so many are flops



Making good in your own mail-order business

This year 100 billion dollars' worth of goods will be sold by mail. No wonder the business tempts entrepreneurs. If you see yourself in it, get the facts first.

THE MAIL-ORDER business traces its origin to the 1872 catalog of a merchant named Aaron Montgomery Ward. Since then mail-order has become a multibillion-dollar industry and produced its share of rags-to-riches stories. It still appears to offer as much opportunity for new ventures as ever. Now, the rising cost of gasoline and the decline of service in retail stores are the reasons cited for pushing direct-marketing sales past 100 billion dollars this year—and the increasing availability of sophisticated electronic systems may enable more and more customers to view merchandise and order it via their TV screens.

What allure this field has for an entrepreneur!

▶You can start a mail-order business from your basement recreation room in your spare time. As long as your advertising, catalogs, brochures and letterhead look professional, your company will appear as substantial as the biggest firms in the business.

▶ You can begin on a shoestring. No big capital investment in plant, equipment, office space and inventory is required. It is still possible to get a mail-order operation off the ground for under $1,000.

▶ The variety of products and services that can be successfully sold by mail-order is seemingly infinite—food, needlecraft, educational courses, jewelry, clothing, furniture, coins, luggage.

▶ You can test the water quickly. Within 60 days after your ad appears in a publication that is a valid test medium, the volume of orders will give a good clue to the ultimate success or failure of your venture.

▶ It's an efficient business. You can reach a national market with a single ad. You need no nationwide sales force or distribution network. You can keep tight control over your business because customer response is almost immediate.

▶ With the right product or service, the right marketing touch and smart planning, you could emulate those operators who built part-time ventures into multimillion-dollar enterprises in as little as five or six years..

Now the other side of the coin.

▶ Starting a mail-order firm is a high-risk proposition. The people who achieve quick success are the exception. Says Hubert Bermont, head of his own consulting, publishing and mail-order firm, "It takes guts, fortitude and creative ability to succeed. If you aren't comfortable with an up-and-down financial existence, don't get into the business. Don't risk more than you can afford to lose; you shouldn't invest your last $600 in this business any more than you'd take it to the racetrack."

The most successful mail-order operators readily admit their share of failures. Joe Sugarman started his JS&A National Sales Group in 1971 with $12,000 borrowed from friends. He lost money on his first ad. Had his second ad bombed, he would have been wiped out. It didn't, but later, in the midst of his success, he attempted to market a $1,500 laser-beam mousetrap. The world did not beat a path to his door. In fact, not a single customer showed up.

▶ You must contend with customer resistance and legal

restrictions. No matter how valid your offer or how good your products, people are basically skeptical of dealing through the mail. All direct-sales letters are "junk mail." Many people consider unsolicited mail an intrusion on their privacy. And they feel doubly so about sales pitches via telephone.

One consequence of this skepticism is laws that specifically regulate the conduct of mail-order businesses. There are continual rumblings about new laws, too. Since access to customers through the mail or by telephone is crucial in this business, major restriction of that access could be devastating for people in the mail-order field.

What you need to know to get started

Contrary to the adage that "a little knowledge is a dangerous thing," a little may be all you need to launch a mail-order venture. Ted Nicholas, whose mail-order marketing of his own book grew into self-help publishing and business service companies, says that if he had known beforehand all the problems, he probably would never have gotten into the business. As he puts it, if you take the time to amass too much knowledge, you won't ever start, yet if you begin with too little knowledge, you're almost bound to fail.

Fortunately, good information about all phases of the mail-order business is widely available. The sources listed in the box on the next page are a sampling. You could learn a lot about launching a mail-order firm by studying one or more of the books on the subject, by attending seminars or courses, or by working for an existing mail-order firm. Here are the major elements for success.

Advertising. Successful advertising—in publications, on TV, by direct mail or by telephone—is the linchpin. Unless your sales pitch sounds the right chords to the right audience, it won't produce the response you'll need. Some mail-order operators hire professional copywriters to create their ads and sales letters. Some of those who have taken on the task themselves have done so without experience and without exactly understanding what they were doing. If the ad worked, they figured they had done it right; if it didn't, they either gave up or kept tinkering with the ad until it chanced to work.

The format and even the wording of presumably successful ads that run repeatedly in a variety of publications are widely imitated, but the imitations are not necessarily effective. Subtle aspects of the most successful mail-order ads often escape the inexperienced eye. The creators of top ads usually have a special knack for designing ads and selecting products that gives them an edge on competitors.

Deciding what to sell. There is probably a mail-order market for almost any product or service you might come up with. The type of product doesn't appear to be as important as the seller's ability to sense what and where the market for it is. Nevertheless, astute mail-order entrepreneurs aim to come up with something unique, especially in the beginning. You should also have reasonably exclusive distribution rights to whatever you sell. Many mail-order operators start with a product they have created themselves, such as a book or a new gadget. Some scout the world for undiscovered products from small manufacturers with whom they can arrange exclusive rights to sell in the U.S. Finally, you must have access

Beware the fast-buck promoters

As in any field of business, there are scams in mail-order. The relative ease with which you can start a mail-order operation makes many of the schemes sound plausible. But beware of ads for mail-order deals that promise big bucks for little or no investment, that guarantee your success or that make starting a mail-order business sound too easy. Some questionable come-ons have taken these approaches.

- *"We'll do it for you."* A firm promises, for a small price, to set you up in a mail-order business. Or you are invited to share in the profits of a "successful" mail-order operation through cooperative mailings and advertising. Or a firm offers to sell you everything you need for your own mail-order business—ready-made "proven successful" ads you can place in publications, the "hottest" customer mailing lists, catalogs of merchandise "guaranteed to sell."

  Question: Why would the creator of mail-order ads, mailing lists and catalogs that are profitable want to let you and thousands of others in on the deal? The truth is, they wouldn't unless their profits come not from selling mail-order products but from collecting dollars from aspiring mail-order operators.
- *Catalogs for sale.* A firm offers to sell you merchandise catalogs on which your name and address are printed, which you then send to people on mailing lists (your own or those you can purchase from the catalog promoter). The pitch is that you can sit back and wait for orders to flow in.

  Catalogs are an essential part of a mail-order business, but their design and content must he tied to the image you have created for your operation. Mailing another firm's catalogs, which are also being mailed by who knows how many others, is not a smart way for you to launch a mail-order business.
- *Drop shipping.* You'll encounter this term frequently. It means that you rely on a supplier to fill orders for you. There is nothing inherently wrong with a drop-shipping arrangement. You don't necessarily have to manufacture, or even stock, every item you advertise. But if you will rely on a supplier to drop-ship, it had better be one you have carefully investigated and with which you have a solid contract that protects you and your customers.

Getting rich quick is no more certain in the mail-order business than in any other venture. You'll soon learn to spot the come-ons that really are too good to be true.

to an ample supply of whatever you have chosen to sell so the mail orders produced by your advertising can be sent to your customers as promptly as possible.

Preparing for repeat customers. When mail-order companies fill an order, they usually enclose ads for some of their other products. In the business this is known as a bounce back. Since the bounce-back offer gets a free ride in the customer's parcel, any orders that come from it are bound to be more profitable than those gained from costly advertising.

In addition, mail-order firms send sales letters and catalogs several times a year to people who have ordered from them before. These repeat orders are the heart of the business. Top mail-order operators say they don't expect to make a profit on the sale that pulls in the customer's initial order. All they hope to achieve with those sales is to cover their costs and build a mailing list—of people who presumably trust the firm, like its products and can be counted on to respond to follow-up pitches for other products.

Though you may launch your mail-order business with a single product, it will pay to have additional products in mind and readily available for bounce-back offers. Several successful entrepreneurs *Changing Times* interviewed started out with a single product and no thought to the importance of a bounce back. But they soon caught on, and their advice now is, "Don't do as I did, do as I say: Plan ahead for additional offers to your proven customers."

Minding the store. There is no way to escape tedious bookkeeping and cost-computing paperwork in any kind of business. In mail-order meticulous records that show which ads produced the most orders, which price sells best, the response rate on follow-ups and the like are more vital than to a conventional retailer. Analyzing those statistics to learn who your customers are, where they live, when they order, how they order (by mail or phone, for instance) and how they pay (by personal check or credit card) is how you sharpen and improve your selling techniques.

Knowing the mail-order law. You must be mindful of several federal regulations and the trade rules of the state in which your business is based. A Federal Trade Commission rule that can result in stiff penalties prohibits false and misleading advertising. Federal law bars misleading representations and fraud perpetrated through the mail. Armed with a court order, postal authorities can hold up mail intended for what they believe are fraudulent operators until the issue is decided.

Another FTC mail-order rule stipulates that if goods are not delivered to customers within 30 days (or other time period promised in the ad), the customer has the right to cancel. You can get a copy of the rule from the FTC, Washington, D.C. 20580. Reputable mail-order operators are supersensitive to this rule. "Worrying that your shipments will be lost in the mail is the greatest anxiety you face in this business," says one.

The experts agree that because of general distrust of mail offers, prompt fulfillment of orders is crucial to success. After all, the customers haven't seen the merchandise. They haven't seen your office or plant. If the order doesn't arrive promptly, the typical customer is primed to exclaim, "Aha, I've been ripped off!" And he will complain to the Better Business Bureau, FTC, Postal Service and to any consumer complaint agency he can think of. In 1979 the Postal Service received 42,000 nonreceipt complaints; 40,000 of them were resolved. Many firms make it a policy to send a second shipment without question when a customer complains he didn't receive his order.

If your firm does get orders to customers quickly, you will begin to earn their confidence and, consequently, the repeat business that brings in the profits. □

WAYS TO LEARN THE BASICS

There is a wealth of excellent information about the mail-order business readily available, much of it in local libraries. Also check colleges and universities in your area for courses on marketing, general business management, advertising and design. The following resources contain the kinds of data you need to get started in your own mail-order business.

Books

- *How You Too Can Make at Least $1 Million (But Probably Much More) in the Mail-Order Business,* by Gerardo Joffe (Advance Books, 779 Bush St., Box 7584, San Francisco, Cal. 94120; $14.95 hardcover; also distributed by Harper & Row). The author, a former mining engineer with a Harvard M.B.A., launched a mail-order firm, sold it to Time Inc. for over $1,000,000 and then began another mail-order business called Henniker's, which he still operates.
- *How to Start and Operate a Mail-Order Business,* by Julian L. Simon (McGraw-Hill; $24.95 hardcover). Third ed. The author, a professor of economics and marketing at the University of Illinois at Urbana, started and sold his own mail-order firm.
- *Money in Your Mailbox: How to Start and Operate a Mail-Order Business,* by L. Perry Wilbur (Reston Publishers; $14.95 hardcover). The author is a consultant and university instructor and has operated his own mail-order business.
- *How to Self-Publish Your Own Book & Make It a Best Seller,* by Ted Nicholas (Enterprise Publishing, Inc., 725 Market St., Wilmington, Del. 19801; $14.95 hardcover, $4.95 paperback). The author's businesses include publishing, business services and advertising.
- *The Successful Consultant's Guide to Authoring, Publishing & Lecturing,* by Hubert Bermont (Bermont Books, 815 Fifteenth St., N.W., Washington, D.C. 20005; $25 hardcover). The author is a consultant, publisher and mail-order businessman.

Trade periodicals

- *Direct Marketing* (224 Seventh St., Garden City, N.Y. 11530; $27 per year). This monthly magazine is considered the bible of the mail-order industry.
- *The Importer* (c/o East Asia Publishing Co., Ltd., 2-11 Jingumae, 1-Chome, Shibuya-ku, Tokyo 150, Japan).
- *Asian Sources* (c/o Trade Media Ltd., P.O. Box K-1786, Kowloon Central, Hong Kong).
- *Made in Europe* (P.O. Box 174027, D-6, Frankfurt/Main, 17 West Germany).

Civil Initial Pleadings (Attorney/Credit Card) USE CASE 33-1

2:33-av-00001 PLAINTIFF v. DEFENDANT

U.S. District Court

District of New Jersey [LIVE]

Notice of Electronic Filing

The following transaction was entered by LIZZA, CHARLES on 1/18/2013 at 8:44 PM EST and filed on 1/18/2013

Case Name: PLAINTIFF v. DEFENDANT
Case Number: 2:33-av-00001
Filer:
Document Number: 17041

Docket Text:
COMPLAINT - Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC (Filing fee $ 350 receipt number 0312-4781268.). (Attachments: # (1) Exhibit A - G, Part 1, # (2) Exhibit A - G, Part 2, # (3) Corporate Disclosure (Re Complaint only), # (4) Civil Cover Sheet) (LIZZA, CHARLES)

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Original filename:n/a
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Original filename:n/a
Electronic document Stamp:
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Document description: Corporate Disclosure (Re Complaint only)
Original filename:n/a
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VIA UNITED PARCEL SERVICE

December 7, 2012

Jazz Pharmaceuticals, Inc.
Attn: Legal Department
3180 Porter Drive
Palo Alto, CA 94304

RE: Notice of Paragraph IV Certification of U.S. Patents 6,780,889, 7,262,219, 7,668,730, 7,765,106, 7,765,107, 7,851,506, 7,895,059 and 8,263,650, Concerning ANDA 203631 for Sodium Oxybate Oral Solution, 500 mg/mL

To Whom It May Concern:

Pursuant to 21 U.S.C. § 355(j)(2)(B)(ii)(I), AMNEAL PHARMACEUTICALS, LLC ("AMNEAL"), whose address is 440 US Highway 22, No. 104, Bridgewater, NJ 08807-2477, hereby provides the following notice of Paragraph IV certification of invalidity and/or non-infringement concerning U.S. Patent Nos. 6,780,889, 7,262,219, 7,668,730, 7,765,106, 7,765,107, 7,851,506, 7,895,059 and 8,263,650 (referred to herein as the "Orange Book Listed Patents").

1. Pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(I) and 21 C.F.R. § 314.95(c)(1), AMNEAL hereby notifies you that it submitted to the U.S. Food and Drug Administration ("FDA"), and the FDA has received, an Abbreviated New Drug Application ("ANDA") that contains data from bioavailability or bioequivalence studies for, and which seeks approval to engage in the commercial manufacture, use, and/or sale of, Sodium Oxybate Oral Solution, 500 mg/mL, before the expiration of the Orange Book Listed Patents. We understand that the Orange Book Listed Patents are owned by Jazz Pharmaceuticals, Inc. ("Jazz"). We also understand that Jazz is the holder of the new drug application ("NDA") under § 505(b) of the Act in connection with Sodium Oxybate Oral Solution (Xyrem®).

2. Pursuant to 21 C.F.R. § 314.95(c)(2), AMNEAL's ANDA has been designated No. 203631 by the FDA.

3. Pursuant to 21 C.F.R. 314.95(c)(3), the "established name" of the proposed drug product is Sodium Oxybate Oral Solution, which is sold under the trademark Xyrem®.

4. Pursuant to 21 C.F.R. § 314.95(c)(4), the active ingredient is Sodium Oxybate, the strength is 500 mg/mL, and the dosage form is an oral solution.

5. Pursuant to 21 C.F.R. § 314.95(c)(5), AMNEAL identifies the Orange Book Listed Patents, as being unenforceable, invalid, and/or not infringed, either literally or under the doctrine of equivalents, by the manufacture, use, sale, offer for sale, and/or importation of the drug product for which ANDA No. 203631 has been submitted by AMNEAL.

6. On information and belief, NDA No. 21-196, for Sodium Oxybate Oral Solution, which was submitted to the FDA pursuant to 21 U.S.C. § 355(b)(1) and, according to public FDA records, was approved by the FDA on July 17, 2002, included a list (or was amended to include a list) identifying the Orange Book Listed Patents, apparently because Jazz believed the patents "could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."

7. Please be warned of the following. It is an antitrust violation to assert a patent known not to be infringed. *Loctite v. Ultraseal*, 781 F.2d 861 (Fed. Cir. 1985). As such, the attached Detailed Factual and Legal Basis of Non-Infringement and/or Invalidity ("Detailed Statement") has outlined in the necessary detail that the Orange Book Listed Patents are not, and cannot be, infringed by the subject matter described in the ANDA. As such, your pursuit of an infringement action may be deemed to be an antitrust violation. In addition, it is an antitrust violation to assert a patent known not to be valid. *Handgards v. Ethicon*, 601 F.2d 986 (9th Cir. 1979). If you launch any patent infringement lawsuit, either now or later, AMNEAL may pursue the appropriate remedies against you, including seeking fees, costs, and sanctions for potential violations of Rule 11 (of the Civil Procedure Rules), exceptional case and frivolous suit statutes under the patent laws, and for violations of the antitrust laws, plus any remedy the court deems fit to award.

8. We reserve the right to allege the same, similar, different or new theories of non-infringement and/or invalidity, and nothing in this Notice Letter or Detailed Statement shall be construed as to limit our rights to make any allegation in any subsequent litigation regarding any issue.

9. Pursuant to 21 U.S.C. § 355(j)(5)(C), this Notice Letter includes an Offer of Confidential Access to Application. As required by § 355(j)(5)(C)(i), AMNEAL offers to provide confidential access to certain information from its ANDA No. 203631 for the sole and exclusive purpose of determining whether an infringement action referred to in § 355(j)(5)(B)(iii) can be brought.

Section 355(j)(5)(C)(i)(III) allows AMNEAL to impose restrictions "as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information." That provision also grants AMNEAL the right to redact its ANDA in response to a request for Confidential Access under this offer.

As permitted by statute, AMNEAL imposes the following terms and restrictions on its Offer of Confidential Access:

(a) AMNEAL will permit confidential access to certain information from its proprietary ANDA No. 203631 to attorneys from one outside law firm representing Jazz; provided, however, that attorneys from such firm do not engage, formally or informally, in patent

prosecution for Jazz. Such information (hereinafter, "Confidential AMNEAL Information") shall be marked with the legend "HIGHLY CONFIDENTIAL—OUTSIDE COUNSEL'S EYES ONLY."

(b) The attorneys from the outside law firm representing Jazz shall not disclose any Confidential AMNEAL Information to any other person or entity, including Jazz's employees, outside scientific consultants, and/or other outside counsel retained by Jazz, without the prior written consent of AMNEAL's counsel H. Keeto Sabharwal, Esq.

(c) As provided by § 355(j)(5)(C)(i)(III), Jazz's outside law firm shall make use of the Confidential AMNEAL Information for the sole and exclusive purpose of determining whether an action referred to in § 355(j)(5)(B)(iii) can be brought and for no other purpose. By way of example only, the Confidential AMNEAL Information shall not be used to prepare or prosecute any future or pending patent application by Jazz or in connection with any filing to or communication with the FDA relating to AMNEAL's ANDA No. 203631. Jazz's outside law firm agrees to take all measures necessary to prevent unauthorized disclosure or use of the Confidential AMNEAL Information, and that all Confidential AMNEAL Information shall be kept confidential and not disclosed in any manner inconsistent with this Offer of Confidential Access.

(d) The Confidential AMNEAL Information disclosed is, and remains, the property of AMNEAL. By providing the Confidential AMNEAL Information, AMNEAL does not grant Jazz's law firm any interest in or license to the Confidential AMNEAL Information.

(e) Jazz's law firm shall, within thirty-five (35) days from the date that it first receives the Confidential AMNEAL Information, return to H. Keeto Sabharwal, Esq. all Confidential AMNEAL Information and any copies thereof. Jazz's law firm shall return to H. Keeto Sabharwal, Esq. all Confidential AMNEAL Information before any infringement suit is filed by Jazz, if suit is commenced before this 35-day period expires. In the event that Jazz opts to file suit, none of the information contained in or obtained from any Confidential AMNEAL Information that AMNEAL provides will be included in any publicly-available complaint or other pleading.

(f) Nothing in this Offer of Confidential Access shall be construed as an admission by AMNEAL regarding the validity, enforceability, and/or infringement of any U.S. Patent. Further, nothing herein shall be construed as an agreement or admission by AMNEAL with respect to the competency, relevance, or materiality of any such Confidential AMNEAL Information, document, or thing. The fact that AMNEAL provides Confidential AMNEAL Information upon request of Jazz shall not be construed as an admission by AMNEAL that such Confidential AMNEAL Information is relevant to the disposition of any issue relating to any alleged infringement of the Orange Book Listed Patents, or to the validity and/or enforceability of said patents.

(g) The attorneys from Jazz's outside law firm will acknowledge in writing their receipt of a copy of these terms and restrictions prior to production of any Confidential AMNEAL Information. Such written acknowledgement shall be provided to H. Keeto Sabharwal, Esq.

(h) This Offer of Confidential Access shall be governed by the laws of the State of New York.

Section 355(j)(5)(C)(i)(III) provides that any request for access that Jazz make(s) under this Offer of Confidential Access "shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in [this] offer of confidential access" and that the "restrictions and other terms of [this] offer of confidential access shall be considered terms of an enforceable contract." Thus, to the extent that Jazz request(s) access to Confidential AMNEAL Information, it necessarily accepts the terms and restrictions outlined above. Written notice requesting access under this Offer of Confidential Access should be made to:

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By providing this Offer of Confidential Access to Application, AMNEAL maintains the right and ability to bring a Declaratory Judgment action under 28 U.S.C. §§ 2201 *et seq.*, pursuant to 21 U.S.C. § 355(j)(5)(C).

AMNEAL PHARMACEUTICALS, LLC

By: _____
Candis Edwards
Senior Vice President – Regulatory Affairs

amneal
PHARMACEUTICALS

ADMINISTRATIVE OFFICES
440 US HIGHWAY 22 EAST, SUITE 104
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VIA UNITED PARCEL SERVICE

December 12, 2012

Jazz Pharmaceuticals, Inc.
Attn: Legal Department
3180 Porter Drive
Palo Alto, CA 94304

RE: Notice of Paragraph IV Certification of U.S. Patent 8,324,275, Concerning ANDA 203631 for Sodium Oxybate Oral Solution, 500 mg/mL

To Whom It May Concern:

Pursuant to 21 U.S.C. § 355(j)(2)(B)(ii)(I), AMNEAL PHARMACEUTICALS, LLC ("AMNEAL"), whose address is 440 US Highway 22, No. 104, Bridgewater, NJ 08807-2477, hereby provides the following notice of Paragraph IV certification of invalidity and/or non-infringement concerning U.S. Patent No. 8,324,275 (referred to herein as the "Orange Book Listed Patent").

1. Pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(I) and 21 C.F.R. § 314.95(c)(1), AMNEAL hereby notifies you that it submitted to the U.S. Food and Drug Administration ("FDA"), and the FDA has received, an Abbreviated New Drug Application ("ANDA") that contains data from bioavailability or bioequivalence studies for, and which seeks approval to engage in the commercial manufacture, use, and/or sale of, Sodium Oxybate Oral Solution, 500 mg/mL, before the expiration of the Orange Book Listed Patent. We understand that the Orange Book Listed Patent is owned by Jazz Pharmaceuticals, Inc. ("Jazz"). We also understand that Jazz is the holder of the new drug application ("NDA") under § 505(b) of the Act in connection with Sodium Oxybate Oral Solution (Xyrem®).

2. Pursuant to 21 C.F.R. § 314.95(c)(2), AMNEAL's ANDA has been designated No. 203631 by the FDA.

3. Pursuant to 21 C.F.R. 314.95(c)(3), the "established name" of the proposed drug product is Sodium Oxybate Oral Solution, which is sold under the trademark Xyrem®.

4. Pursuant to 21 C.F.R. § 314.95(c)(4), the active ingredient is Sodium Oxybate, the strength is 500 mg/mL, and the dosage form is an oral solution.

5. Pursuant to 21 C.F.R. § 314.95(c)(5), AMNEAL identifies the Orange Book Listed Patent, as being unenforceable, invalid, and/or not infringed, either literally or under the doctrine of equivalents, by the manufacture, use, sale, offer for sale, and/or importation of the drug product for which ANDA No. 203631 has been submitted by AMNEAL.

6. On information and belief, NDA No. 21-196, for Sodium Oxybate Oral Solution, which was submitted to the FDA pursuant to 21 U.S.C. § 355(b)(1) and, according to public FDA records, was approved by the FDA on July 17, 2002, included a list (or was amended to include a list) identifying the Orange Book Listed Patent, apparently because Jazz believed the patent "could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."

7. Please be warned of the following. It is an antitrust violation to assert a patent known not to be infringed. *Loctite v. Ultraseal*, 781 F.2d 861 (Fed. Cir. 1985). As such, the attached Detailed Factual and Legal Basis of Non-Infringement and/or Invalidity ("Detailed Statement") has outlined in the necessary detail that the Orange Book Listed Patents are not, and cannot be, infringed by the subject matter described in the ANDA. As such, your pursuit of an infringement action may be deemed to be an antitrust violation. In addition, it is an antitrust violation to assert a patent known not to be valid. *Handgards v. Ethicon*, 601 F.2d 986 (9th Cir. 1979). If you launch any patent infringement lawsuit, either now or later, AMNEAL may pursue the appropriate remedies against you, including seeking fees, costs, and sanctions for potential violations of Rule 11 (of the Civil Procedure Rules), exceptional case and frivolous suit statutes under the patent laws, and for violations of the antitrust laws, plus any remedy the court deems fit to award.

8. We reserve the right to allege the same, similar, different or new theories of non-infringement and/or invalidity, and nothing in this Notice Letter or Detailed Statement shall be construed as to limit our rights to make any allegation in any subsequent litigation regarding any issue.

9. Pursuant to 21 U.S.C. § 355(j)(5)(C), this Notice Letter includes an Offer of Confidential Access to Application. As required by § 355(j)(5)(C)(i), AMNEAL offers to provide confidential access to certain information from its ANDA No. 203631 for the sole and exclusive purpose of determining whether an infringement action referred to in § 355(j)(5)(B)(iii) can be brought.

Section 355(j)(5)(C)(i)(III) allows AMNEAL to impose restrictions "as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information." That provision also grants AMNEAL the right to redact its ANDA in response to a request for Confidential Access under this offer.

As permitted by statute, AMNEAL imposes the following terms and restrictions on its Offer of Confidential Access:

(a) AMNEAL will permit confidential access to certain information from its proprietary ANDA No. 203631 to attorneys from one outside law firm representing Jazz; provided, however, that attorneys from such firm do not engage, formally or informally, in patent prosecution for Jazz. Such information (hereinafter, "Confidential AMNEAL Information") shall be marked with the legend "HIGHLY CONFIDENTIAL—OUTSIDE COUNSEL'S EYES ONLY."

(b) The attorneys from the outside law firm representing Jazz shall not disclose any Confidential AMNEAL Information to any other person or entity, including Jazz's employees, outside scientific consultants, and/or other outside counsel retained by Jazz, without the prior written consent of AMNEAL's counsel H. Keeto Sabharwal, Esq.

(c) As provided by § 355(j)(5)(C)(i)(III), Jazz's outside law firm shall make use of the Confidential AMNEAL Information for the sole and exclusive purpose of determining whether an action referred to in § 355(j)(5)(B)(iii) can be brought and for no other purpose. By way of example only, the Confidential AMNEAL Information shall not be used to prepare or prosecute any future or pending patent application by Jazz or in connection with any filing to or communication with the FDA relating to AMNEAL's ANDA No. 203631. Jazz's outside law firm agrees to take all measures necessary to prevent unauthorized disclosure or use of the Confidential AMNEAL Information, and that all Confidential AMNEAL Information shall be kept confidential and not disclosed in any manner inconsistent with this Offer of Confidential Access.

(d) The Confidential AMNEAL Information disclosed is, and remains, the property of AMNEAL. By providing the Confidential AMNEAL Information, AMNEAL does not grant Jazz's law firm any interest in or license to the Confidential AMNEAL Information.

(e) Jazz's law firm shall, within thirty-five (35) days from the date that it first receives the Confidential AMNEAL Information, return to H. Keeto Sabharwal, Esq. all Confidential AMNEAL Information and any copies thereof. Jazz's law firm shall return to H. Keeto Sabharwal, Esq. all Confidential AMNEAL Information before any infringement suit is filed by Jazz, if suit is commenced before this 35-day period expires. In the event that Jazz opts to file suit, none of the information contained in or obtained from any Confidential AMNEAL Information that AMNEAL provides will be included in any publicly-available complaint or other pleading.

(f) Nothing in this Offer of Confidential Access shall be construed as an admission by AMNEAL regarding the validity, enforceability, and/or infringement of any U.S. Patent. Further, nothing herein shall be construed as an agreement or admission by AMNEAL with respect to the competency, relevance, or materiality of any such Confidential AMNEAL Information, document, or thing. The fact that AMNEAL provides Confidential AMNEAL Information upon request of Jazz shall not be construed as an admission by AMNEAL that such Confidential AMNEAL Information is relevant to the disposition of any issue relating to any alleged infringement of the Orange Book Listed Patent, or to the validity and/or enforceability of said patents.

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AMNEAL PHARMACEUTICALS, LLC

By: _____
Candis Edwards
Senior Vice President – Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

Wednesday, June 6, 2001

8:15 a.m.

Holiday Inn
Bethesda, Maryland

PARTICIPANTS

Claudia H. Kawas, M.D., Consultant and Acting Chairman
Sandra Titus, Ph.D., Executive Secretary

MEMBERS:

Ella P. Lacey, Ph.D., Consumer Representative,
LaRoy P. Penix, M.D.
Richard D. Penn, M.D.
Gerald Van Belle, Ph.D.

CONSULTANTS:

Gustavo C. Roman, M.D.
Jerry S. Wolinsky M.D.

XYREM CONSULTANTS:

VOTING:

Pippa Simpson, Ph.D.
Carol Falkowski, Ph.D.

NON-VOTING:

Christine A. Sannerud, Ph.D.
Jerry Frankenheim, Ph.D.
Jo-Ellen Dyer, Ph.D.

ON PONE-LINK - NON-VOTING:

Ronald Chervin, M.D.
Christian Guilleminault, M.D.

FDA:

Robert Temple, M.D.
Russell Katz, M.D.
Ranjit Mani, M.D.
John Feeney, M.D.
Deborah B. Leiderman, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. KAWAS: Good morning, everyone, and welcome to the Wednesday, June 6, 2001 meeting of the Peripheral and Central Nervous System Advisory Committee. My name is Claudia Kawas, and I think we can begin with introductions, please, perhaps over by Dr. Temple's side.

DR. TEMPLE: Bob Temple, I am the Office Director.

DR. KATZ: Russ Katz, Division of Neuropharmacological Drug Products, FDA.

DR. FEENEY: John Feeney, neurology team leader, FDA.

DR. MANI: Ranjit Mani, medical reviewer, Neuropharm., FDA.

DR. LEIDERMAN: Deborah Leiderman, Director, Controlled Substance Staff, FDA.

DR. SIMPSON: Pippa Simpson, University of Arkansas Medical Sciences, biostatistician.

DR. FALKOWSKI: Carol Falkowski, drug abuse researcher, Hazelden Foundation.

DR. ROMAN: Gustavo Roman, Professor of Neurology at the University of Texas, San Antonio.

DR. WOLINSKY: Jerry Wolinsky, Professor

of Neurology, University of Texas, Houston.

DR. TITUS: Sandy Titus, FDA, the administrator of the Peripheral and Central Nervous System Committee.

DR. PENN: Richard Penn, neurosurgeon at the University of Chicago.

DR. LACEY: Ella Lacey, professor emerita, Illinois University, Carbondale, Illinois.

DR. VAN BELLE: Gerald Van Belle, Department of Biostatistics, from the University of Washington.

DR. PENIX: LaRoy Penix, Associate Professor of Neurology at Moorehouse School of Medicine.

DR. SANNERUD: Christina Sannerud, Drug and Chemical Evaluation Section, Drug Enforcement Administration.

DR. DYER: I am Jo Dyer, with the University of California, San Francisco and the San Francisco Poison Control System, California.

DR. FRANKENHEIM: Jerry Frankenheim, pharmacologist, National Institute on Drug Abuse.

DR. KAWAS: Today we have met to discuss the consideration of Xyrem, proposed to reduce the incidence of cataplexy and to improve the symptom

of daytime sleepiness for persons with narcolepsy. The main focus of the deliberations will also be on risk management issues.

If we could ask Dr. Titus to begin with the conflict of interest statement?

Conflict of Interest Statement

DR. TITUS: Before I begin the conflict of interest statement, I just want to announce that we have two people on line with us, Dr. Chervin and Dr. Guilleminault. They are both in a room listening to us and will participate with us on the mikes.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The special government employees participating in today's meeting have been screened for interests in Orphan Medical's Xyrem and for interests in the products and sponsors deemed by the agency to be competing. Based on the agency's review of each participant's response to the conflict of interest screening, it has been determined that there is no potential for a

conflict of interest with regard to this meeting.

With respect to FDA's invited guests, there are reported affiliations which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Ronald Chervin would like to disclose for the record that he has a contract with Cephalon to study Provigil, but not for use in narcolepsy. He is the principal investigator, however, no funds from Cephalon, present or past, have contributed to his personal salary and none have been made available for his non-research related use. Further, in previous years Dr. Chervin was a co-investigator with Cephalon in a narcolepsy clinical trial.

Christian Guilleminault has been the administrator of the Sleep Disorder Clinic in Palo Alto, California, where the study of Xyrem was performed by a team of researchers.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon. Thank you.

DR. KAWAS: Thank you very much, Dr. Titus. We will begin with Dr. Russell Katz, of the FDA, who will give us the FDA overview of the issues. I want to point out to the committee members that they have much of the materials that they will be seeing during this meeting in front of them.

FDA Overview

DR. KATZ: Thanks, Claudia. First, I would like to welcome the committee back. You were here just a few months ago so I appreciate your coming back so soon.

We have a number of invited guests who are augmenting the committee today, and many of them are experts in the evaluation of issues related to drug abuse, and I would just like to welcome them, in particular Drs. Simpson, Sannerud and Frankenheim.

We have two other experts who will actually be speakers later this morning. Dr. Dyer

will speak on her experience with GHB use and misuse in cases she has seen, and Dr. Falkowski will talk about the epidemiology of GHB abuse in the United States.

Finally, as Dr. Titus mentioned, we have two acknowledged experts in sleep disorders who are attending the annual sleep meetings in Chicago, but who have agreed to sit in a hotel room for however long this takes and participate by phone. So, Drs. Guilleminault and Chervin, wherever you are, thank you. Thanks for being here.

As you know and as you have heard, today we will ask you to discuss NDA 21-196, which was submitted by Orphan Medical for the use of Xyrem, gamma hydroxybutyrate or better known as GHB, for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy.

GHB is a simple molecule and it is ubiquitous in mammalian tissues, its function though is not really well known. Its relevant regulatory history goes back to about 1990, and prior to that date it was freely available in health food stores. But in 1990 the agency began to receive reports of widespread recreational use in a number of different types of folks, for a

number of different types of reasons, or GHB and began to get numerous reports of serious adverse events associated with its misuse.

It was not entirely clear that all of these events were necessarily related to GHB. It was difficult to interpret some of these reports because there were concomitant medications that were unreported and it wasn't entirely clear whether or how much GHB was in a particular preparation that someone had taken. Those sorts of issues made it difficult to completely interpret the reports, but many of the reports were of events that were known to be consistent with GHB's effect as a potent CNS depressant, including things like respiratory depression, coma and other decreased levels of consciousness. So, it was reasonable to believe that GHB was at least in part responsible for some of these reports.

As a result of these reports, the agency withdrew GHB from health food shelves and made it illegal to use. However, illicit use continued and continues to this day, not only with GHB but with two related drugs which are precursors, GBL and 1,4-butanediol, and there have been similar reports of serious adverse events associated with the use

of those products.

So, against this background of use, the investigation of GHB as a treatment for cataplexy began. Based on the results of a single trial performed by the sponsor and their commitment to perform additional trials, the sponsor was granted a treatment IND in December of 1998. For those of you unfamiliar with a treatment IND, it is basically a mechanism to permit use of an investigational drug outside the context of a controlled trial for a serious disease for which there aren't other available treatments. It is usually granted relatively late in the development of a drug so that by the time you grant it you have some reasonable idea, based on controlled data, that the drug is probably effective and reasonably well tolerated.

Just another relevant piece of history, in 2000 Congress passed a law which placed GHB in Schedule I and also placed it into Schedule III for any approved uses that may be granted.

The NDA that we are discussing today was submitted in September of 2000 by the company, and it contains the results of four controlled trials which the sponsor believes establish substantial

evidence of effectiveness for cataplexy and excessive daytime sleepiness in patients with narcolepsy. It also contains, obviously, safety experience.

I just want to talk about the safety experience for just a little bit. As you know from the briefing documents, much of the safety data in the application was not generated by the company but by an individual investigator under his own individual investigator IND. This is Dr. Scharf, and he is an acknowledged expert in the use of GHB and he has been treating patients under his IND for about 16 years. His data comprise almost 30 percent of the patient safety database in the NDA. If one looks at patient time, his experience constitutes about 70 percent of the total patient exposure.

As part of a routine investigation of the NDA to look at source documents, the agency investigators found that they were unable to locate some critical source documents of Dr. Scharf's IND, and it was difficult to confirm the sponsor's submission of Dr. Scharf's data. However, subsequent to that, Dr. Scharf has made extensive efforts to provide the additional source documents

and agency investigators have reinspected that data. I believe the conclusion of that investigation is that we find that the records, for the most part, do support the sponsor's descriptions of Dr. Scharf's data. And, we believe we can make certain statements about that data at this point.

We were particularly interested in the 80 or so patients that Dr. Scharf treated that did not move on into the company's treatment IND. He treated a total of 143, or thereabouts, patients, 60 of whom went into the sponsor's treatment IND. So, we had a good idea of what was happening to those patients but there were about 80 that didn't and who were basically discontinued from treatment under Dr. Scharf's own IND.

So, except for a handful of patients, we believe we know why those 80 patients discontinued and their status. I believe we can say reasonably comfortably say that nothing catastrophic that we don't know about happened to those patients but, unfortunately, we have relatively little well-documented data regarding other less serious adverse events in that cohort of 80. Other than patient diaries, we have essentially no

documentation about exactly what dose those patients took and for how long.

I have gone into this at some depth because the safety experience in the NDA is relatively small as compared to a typical NDA, and that is by agreement. This is an orphan product. Based on the sponsor's estimated prevalence of cataplexy of about 25,000, it received orphan designation and one wouldn't necessarily expect that a safety database of a typical size, which is somewhere in at least 10000 to 2000 patients in the typical NDA, would be submitted in an orphan application. So, we agreed with the sponsor that about 500 patients treated for appropriate durations, at appropriate doses would be acceptable.

But, given the relatively small database and some of these residual questions about a reasonable proportion of it, that is to say Dr. Scharf's data, that may take on some additional meaning and we would like you to think about that as the day goes on.

In addition to the safety and the effectiveness data which is required in an NDA of course, the sponsor has proposed a detailed risk

management program, and that has three goals: to inform patients and physicians about the risks of GHB; to minimize the risks to those patients; and also to minimize the likelihood that subjects for whom the drug has not been prescribed will be exposed to it. This latter point not only refers to diversion and its use illicitly by folks who shouldn't be taking it, but also to the accidental use of GHB in the home, perhaps by small children, and you will hear how GHB is administered and what form it is prepared in, and we think that is a potential risk. So, we would like you to think about that as the day goes on too.

As far as the risk management program, you will hear about it in great detail from the company but, in brief, it consists of a couple of sort of major components. One is that the product will be made available through a central pharmacy and will be shipped directly to the patient at home. Physicians and patients will also receive detailed materials about the risks and the appropriate use of the drug after the first prescription is filled. Actually, they will receive those materials initially and all subsequent refills of prescriptions will be contingent upon patients and

physicians documenting that they have read these materials, and they understand the risks and how to take the drug appropriately.

All patients and physicians will be entered into a registry, and there will be close surveillance instituted to ensure that untoward events are minimized, for example, to ensure that patients don't go from doctor to doctor trying to get refills of prescriptions that are inappropriate.

So, with these data and against the background of misuse of GHB out in the population at large, we bring you today's application and we will ask you to formally vote on three questions. One is whether or not you think that substantial evidence of effectiveness has been submitted for the indications that the sponsor has proposed, that is to say, cataplexy and excessive daytime sleepiness in patients with narcolepsy. If you find that they haven't, we would be very interested to know whether or not you feel that substantial evidence has been submitted for either of those two indications.

While you listen to the effectiveness data, we would like you to pay particular attention

to the question of dose and for which dose you think evidence of effectiveness has been submitted. If you find there is substantial evidence of effectiveness for a particular indication, we need to ask you whether or not GHB can be considered safe in use given appropriate labeling. Now, we are not going to discuss necessarily the specifics of proposed labeling but, nonetheless, we ask you to think of it in that context.

Again, in assessing the safety of the product, we ask you to concentrate on at least the question of what dose you have found to be effective and whether or not there is sufficient safety experience at that dose for the drug to be approved.

Finally, we want to take a formal vote on the question of whether or not you think it is required or should be required that the drug be approved only with the risk management program of some type, not necessarily the one specifically proposed by the company. Obviously, the company has proposed a risk management program but we need to know whether or not you think it is mandatory that it be approved with such a program in place. If you do, we have a number of questions that we

would like you to discuss -- not necessarily take a formal vote on but discuss with regard to a risk management program and some of the provisions that the sponsor has proposed.

There are some aspects of the program that they have proposed that we would like you to pay particular attention to and discuss. For example, there is some considerable sympathy in the agency for including a provision in the risk management program that would restrict the use of the drug to patients with whatever indication you believe has been supported, that is to say, to restrict as much as possible off-label prescribing. That is one possibility.

There is also some enthusiasm internally for physicians and patients to document that they have reviewed the relevant materials before the first prescription is filled. So, we would like you to think about that as well as we talk about the risk management program.

So, as you can see from the agenda, the company is going to present the safety and effectiveness data, after which Dr. Mani, from the Division, will come up and present briefly some of our views about the data you will have just heard.

Specifically, I believe we have some different views about the evidence submitted for establishing a claim for excessive daytime sleepiness in narcolepsy, and there may be other additional safety issues that we would like to bring up at that time, in particular the question of an event that has been called sleep walking.

I think with that as background, I will turn it back to Dr. Kawas. Thank you.

DR. KAWAS: Thank you, Dr. Katz. Orphan Medical presentation is to follow. Dr. David Reardan, Orphan Medical?

Orphan Medical Presentation

DR. REARDAN: Hi. Good morning. Good morning, ladies and gentlemen, members of the committee and FDA.

[Slide]

My name is David Reardan, and I represent Orphan Medical as head of regulatory affairs. Orphan Medical is a small, 60-person firm, dedicated to the development of orphan drugs. We have obtained marketing approval for six orphan products from FDA since we were founded, in 1994.

The firm became involved with Xyrem when approached by FDA that same year, and Xyrem was

designated an orphan drug in 1994. Today we will share with you the data that has been collected with respect to the efficacy and safety since our IND was submitted, in 1996.

[Slide]

Dr. Mignot, director of the Narcolepsy Institute at Stanford University, will present a picture of a narcoleptic patient and the serious medical need such patients have for new therapeutic treatments.

Dr. Houghton is the chief medical officer and chief operating officer at Orphan Medical, and he will present next on the efficacy that has been collected. Dr. Houghton was chair of anesthesia and critical care in Australia.

Dr. Black, director of the Stanford Sleep Clinic and an investigator for several trials, will share with you the EEG pharmacology of Xyrem. Dr. Houghton will then present the safety data and finish up with a benefit/risk assessment.

Following presentations by two FDA invited speakers with respect to GHB abuse, Dr. Balster, director of the Institute for Drug and Alcohol Studies at the Medical College of Virginia, will share with you his views on abuse liability.

Since there is public abuse of GHB and its analogs, the company has developed a risk management program for Xyrem that will be presented by Patti Engel, our vice president of marketing and sales.

[Slide]

In addition to those presenting today, the following experts are available in the audience to answer questions from the committee or FDA: Dr. Emsellem, Dr. Hagaman and Dr. Ristanovic are all directors of their respective sleep institutes, and have been investigators in our clinical trials. Dr. Okerholm is a consultant in the area of pharmacokinetics and drug metabolism; Dr. Reno in the area of toxicology; and Dr. Richard Trout, who is a professor emeritus in statistics from Rutgers, is here if there are any statistical questions.

[Slide]

This is the chemical structure of sodium oxybate, more commonly known as gamma hydroxybutyrate, or GHB. Notice that it is a simple 4-carbon hydroxy fatty acid and, as such, quite easy to synthesize. In fact, kits have been illegally promoted on the Internet for its manufacture. If an amino group were to replace

this alcohol functional group at position 4, you would have GABA, gamma aminobutyric acid, another CNS active chemical. Oxybate is a natural compound in the human body.

[Slide]

Gamma hydroxybutyrate was first discovered in the 1960's by Dr. Labore, in France, and was investigated as an analog for GABA. It was found to have hypnotic properties and was first approved in France, and later a few other countries of Europe, as an adjunct in anesthesia. It was used in labor and delivery for quite a few years. The injectable form is still available today in parts of Europe.

In the 1970's initial work was begun in Canada to test its properties in narcolepsy. Following initial promise for use in patients with narcolepsy two controlled trials were conducted by independent investigators, one in the U.S. and one in The Netherlands. In 1994, due to the promising investigator trials, FDA Office of Orphan Products approached Orphan Medical to consider the compound for development.

Since there was no patent protection and the market was very small, no other firms were

willing to consider the development of GHB for narcolepsy at the time. Orphan Medical agreed to sponsor this medication. Our new drug application was submitted in October of 2000 and was designated by FDA for priority review.

The clinical development has been fairly straightforward and all controlled trials conducted to date have shown sodium oxybate to be effective and safe for the treatment of narcolepsy. This project has been made more difficult because of the abuse situation.

[Slide]

Let me explain why Xyrem is not going to be a factor in the abuse of GHB and its precursors. Orphan Medical was aware abuse existed at the time the company agreed to sponsor development of Xyrem. At this same time, Internet was burgeoning. Due to its ease of synthesis and ready availability of precursor chemicals, GHB was initially an easy target for promoters of illegal drugs.

But GHB is not the only problem. GBL and 1,4-butanediol are precursor chemicals that can be easily converted to GHB and are, in fact, converted to GHB in the human body. These precursors are widely available as bulk chemicals and are being

illegally used in the United States, and the abuse problem is growing.

Federal legislation, enacted in 2000, helped to control the availability of GHB and GBL but not 1,4-butanediol and other precursor chemicals that can be used for the same purpose. In many states, even with GHB schedules, GBL and 1,4-butanediol are not controlled.

We believe that approval of Xyrem for use by patients with narcolepsy will not add to the general abuse problem of GHB and its numerous precursors.

[Slide]

The proposed indication for which we are asking FDA for marketing approval is to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy.

[Slide]

Narcolepsy fits the definition of orphan disease in the United States, with less than 200,000 patients. There are estimated to be about 135,000 patients, of which 55 percent are diagnosed, with about 24,000 seeking treatment for cataplexy.

[Slide]

I would now like to introduce you to Dr. Emmanuel Mignot, from Stanford. Dr. Mignot has been widely published in this area and is considered one of the premiere international experts on narcolepsy. He has not participated in any of our clinical trials.

Medical Need

DR. MIGNOT: It is my privilege to talk to you today about narcolepsy. I have been working on narcolepsy for about 15 years, both at the level of basic research as well as clinical care. I am a medical doctor and I see patients with narcolepsy.

[Slide]

I am going to try to summarize in a few minutes really a lot of data about narcolepsy and how it impacts people.

[Slide]

First, I would like to start briefly by reviewing the symptoms of narcolepsy. Narcolepsy is usually associated with 5 different symptoms. The most disabling and the most problematic in patients with narcolepsy is sleepiness. Patients with narcolepsy are sleepy all the time; tired; they have sleep attacks; they cannot stay awake for a long period of time, and it is usually why they

come to see the doctor. They just cannot live a normal life. Especially in work conditions, as you probably know, it is very difficult -- you have to be awake all day long and it is a major problem in narcolepsy.

Now, it is not enough to diagnose narcolepsy. Narcolepsy is not just sleepiness and there are a lot of other medical conditions that are associated with sleepiness. Patients with narcolepsy also have a series of symptoms that correspond to the fact that they go very quickly into rapid eye movement sleep. As probably many of you know, rapid eye movement sleep is a stage of sleep that only occurs 1.5 or 2 hours after you fall asleep where you are actively dreaming but your body is completely paralyzed and you have these rapid eye movements.

Patients with narcolepsy go into REM sleep extremely quickly, sometimes in a few minutes, and that leads to a series of symptoms where patients sometimes are half way through REM sleep, being still awake. Consequently, they may experience odd symptoms that we call the dissociated REM sleep event, abnormal REM sleep event. Those are cataplexy, hypnagogic hallucinations and sleep

paralysis.

An example is cataplexy. When a patient gets emotionally excited, typically when they are happy, they meet a good friend, sometimes when they are angry but most often when they are joking, in a nice environment and happy about something, they may feel suddenly weak; they become paralyzed; sometimes they fall down to the ground, completely paralyzed and they cannot move. In very rare cases they may even go into REM sleep. We believe somehow being emotionally excited stimulates the paralysis of rapid eye movement sleep that every one of us experiences during sleep, except that in patients with narcolepsy it may occur in the middle of the day in response to emotion.

Also, when they fall asleep they sometimes have hallucinations because they go so quickly into REM that sometimes they dream while they are still awake. I remember a patient, for example, who every night would fall asleep and he would see someone coming and strangling him. Or, they may hear people talking; or see people walking in the room. It can be very frightening and it can be a very terrible experience for patients with narcolepsy.

Another symptom of abnormal REM sleep that patients with narcolepsy have as well is called sleep paralysis. When they wake up from a nap or when they fall asleep, sometimes they again go so quickly into REM and disassociated REM sleep events that sometimes they may be paralyzed from REM but still be awake. Basically, they would wake up from sleep and they cannot move, not even their little finger. It can be very scary. It lasts a few minutes and then finally they can move. Some patients with narcolepsy have multiple episodes of sleep paralysis when they nap during the day, and so forth, and that is another very bothersome symptom.

Finally, patients with narcolepsy, contrary to what people way, don't sleep too much; their main problem is that they just cannot stay awake. They fall asleep very quickly in many circumstances, but they are unable to stay asleep for a long period of time. In fact, patients with narcolepsy don't sleep 20 hours a day. What happens is that at night they don't sleep well. Often that is another symptom that is very bothesome. They fall asleep very quickly at night but after one hour they cannot sleep again. They

are just awake and cannot sleep.

Then, all these symptoms are quite severe and, of course, affect the lives of patients. And, since GHB is recommended in cataplexy, which is muscle atonia triggered by emotion, I will just show you a quick video of a patient with cataplexy.

This is a boy, a 9-year old. Narcolepsy usually starts during adolescence and here the clinicians are trying to make him laugh to just try to elicit the symptom, and you see he is falling down and he is completely paralyzed and he is losing his muscle tone. Some of these patients have that many time per day and it can be extremely socially disabling. You can imagine being at a party or being with some friends and having this happen to you. In this kid it was particularly severe.

Most cases of narcolepsy start during adolescence but occasionally it starts as early as 5 years of age. It peaks around 15 years of age. It is often extremely problematic because I am sure you realize when you have this type of thing happening to you and sleepiness at school, especially when you are 15 years old, when you are an adolescent, it really wrecks your life apart,

especially when it is not properly diagnosed.

[Slide]

There have been a number of studies, and I won't have time to review them, that have shown that the quality of life of patients with narcolepsy is extremely impaired, as much as depression, epilepsy or other reference conditions in almost all the scales that you look at. Clearly, it is a very socially disabling disorder.

[Slide]

It is also, of course, a disorder that impacts just your daily life. For example, driving -- patients with narcolepsy have a very increased rate of accidents and sometimes many of them refuse to drive just because of falling asleep or having cataplexy while driving.

[Slide]

We have objective tests for diagnosing narcolepsy. In fact, it is not just a psychological disorder. You can actually use a test like the Multiple Sleep Latency Test, where you ask patients to come to the sleep lab. You check that they sleep normally and the following day you ask them to nap every two hours and you measure how fast they fall asleep. You see,

normally people won't fall asleep or nap in the middle of the day, or they would fall asleep with a 15-minute latency in the dark. A patient with narcolepsy, as soon as you switch off the light, they are sleeping. In a few minute latency, they are asleep. So, we have objective ways to show that these people have a problem.

[Slide]

Also, in this nap you see that they go very quickly into REM sleep. Normal people won't have REM sleep before one hour after falling asleep, but patients with narcolepsy will go straight into REM. You can actually demonstrate -- we call that sleep onset REM period -- that patients with narcolepsy have all this sleep abnormality and REM abnormality using sleep testing.

[Slide]

Current treatment for narcolepsy is completely symptomatic. We don't treat the cause of the disease; we only treat the symptoms. Typically, the treatment now uses two drugs, two lines of drug. A patient with cataplexy will be treated usually with two drugs. One is a stimulant which would be a classical amphetamine-like

stimulant or this more recent drug that was just approved that is called modafinil, Provigil, which works on sleepiness. It will keep a patient awake but will never normalize him; it only improves him. And, they all have a lot of side effects. You know, the stimulants can even produce psychosis in some rare cases but, of course, they raise blood pressure. They produce psychological changes. They have a lot of other side effects.

We all know now that they all increase dopamine in the brain. We have done a series of studies which have shown that. Even modafinil, the most recent drug -- we know now that it works by increasing dopamine in the brain. And, they don't have anything different from each other so some of them are definitely safer than others.

For the antidepressants, for the treatment of cataplexy -- this works well on sleepiness but it doesn't work on cataplexy or nightmares, or hallucination or sleep paralysis. For this you use antidepressants. Why? Because antidepressants depress REM sleep and they also suppress cataplexy and all the other abnormal dreaming that patients with narcolepsy have. The problem is they also have a lot of side effects. Actually, the new

SSRI, they don't work as well as the old tricyclines. Often you even have to use the old tricycline antidepressants because norepinephrine uptake inhibition seems to be the mode of action of these drugs, more than serotonin. They don't really work that well and, of course, they have a lot of side effects and a lot of different problems.

[Slide]

Finally, I want to stress again that we need new treatments for narcolepsy just because all the treatments we have now just don't make people normal. They just help them to be better. You can best illustrate that using the MSLT/MWT, which is a slightly different test where, instead of measuring how fast people fall asleep in the dark, you ask people to try to stay away in the dark and you see that normal people can stay awake. They don't fall asleep in 20 minutes, whereas patients with narcolepsy fall asleep very dramatically after a few minutes in the dark.

Even if you treat them with modafinil which is a very good treatment for narcolepsy, which was recently approved, you improve them but they never become normal. Then, it is clear that

what we have is not enough. We just need better, and this would be the same for amphetamines. Even high dose amphetamines don't normalize these patients. That has been shown by multiple studies.

[Slide]

We have worked for more than 15 years trying to find the cause of narcolepsy, and recently we have isolated the gene for narcolepsy in a canine model where the disease is genetically determined, and we found that it was a receptor for a norpeptide that is called hypocretin. We found that in humans with narcolepsy it is not like dogs with narcolepsy; it is not the receptor but a peptide called hypocretin which is expressed in about 10,000 cells in the brain, here in the hypothalamus, which is missing in patients with narcolepsy.

This is brain tissue of a patient with narcolepsy. You see here is the normal; everything is gone. If you measure in the cerebrospinal fluid, this is a normal level in a normal person, or in patients with MS or other neurological symptoms, and you see in all patients with narcolepsy that this hypocretin molecule is gone. We know now that the cause of narcolepsy is not

dopamine or norepinephrine, which is the current treatment for narcolepsy, which are stimulants and antidepressants acting through these neurotransmitters, and probably replacing this hypocretin would be an ideal treatment for narcolepsy. But this finding was only made one year ago and it is going to take probably 10 years or many years before we actually have a treatment based on this new discovery.

[Slide]

To summarize the medical need, I think I have convinced you that narcolepsy is a serious and disabling condition that needs treatment, and these patients are in desperate need of better treatment. As you will see from the presentation afterwards, GHB is one of the effective treatments which helps a lot of people. So, current treatments like amphetamines and antidepressants don't work well in terms of efficacy. They have a lot of side effects. They all work the same way but they don't act on the cause of the disease and, clearly, we know that GHB, even though it probably doesn't act on hypocretin, acts differently from other drugs. And, it is one more drug that would be available to help a lot of patients with narcolepsy.

Finally, even though there have been numerous, very recent developments that are very exciting in the hypocretin area, unfortunately, you all know it takes a long time until drugs are available and it is going to take probably many years until this available.

This is a very quick summary of what we know about narcolepsy to date. Thank you.

DR. REARDAN: Thank you, Dr. Mignot. Dr. Houghton will now present the data which has been assembled in support of the efficacy of Xyrem. Dr. Houghton is a qualified anesthesiologist, with 18 years of clinical experience in critical care medicine and numerous years experience in pharmaceutical drug development. Bill?

Efficacy

DR. HOUGHTON: Good morning.

[Slide]

I am sorry to start with such a complex diagram but this just outlines the pattern of studies that we will be talking about this morning. On the left-hand side here are the 4 controlled studies on which the assessment of efficacy will be based, but what is unusual about this program is that patients, in an uncommon way, move to

extension protocols. So, as Dr. Katz pointed out, even though the total database may be small, the total duration of exposure of patients is quite promising.

The first study that I will talk about is entitled OMC-GHB-3, and the patients, at the completion of this short-term treatment study did progress to a long-term, open label study and then had the opportunity to move into one of the treatment IND protocols, with some of them still participating in that study.

A second contributor to that protocol was the patients who completed the first 6-month safety treatment IND protocol, and the significance of all of that is that it was from this protocol that the patients are represented in the long-term pivotal blinded efficacy study that supports the long-term efficacy of Xyrem.

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The first and pivotal study is a randomized, double-blind, placebo-controlled, parallel group, multi-center trial comparing the effects of three doses, 3 g, 6 g and 9 g of orally administered Xyrem with placebo for the treatment of narcolepsy. As I mentioned, this was a study

conducted in 136 patients in 16 centers.

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The primary efficacy parameter was the change in the number of total cataplexy attacks in the last two weeks of the treatment period compared to the two weeks of the baseline period.

Secondary efficacy parameters that were considered included complete and partial cataplexy attacks; daytime sleepiness; inadvertent sleep attacks during the day; hypnagogic hallucinations; sleep paralysis; and a clinical global impression of change.

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Patients naive to sodium oxybate therapy were chosen with a bona fide diagnosis of narcolepsy for at least 6 months. They were required to have a record of a polysomnograph or Multiple Sleep Latency Test within the last 5 years to exclude other causes of daytime sleepiness, and particularly sleep apnea.

They were required to have a history of daytime sleepiness and cataplexy for at least 6 months, and recurrent daytime naps that occurred almost daily in the preceding 3 months.

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The overall study design was divided into 5 stages. Firstly, there was a screening period in which the patients were required to qualify for entry criteria and then withdrawn from their existing anti-cataplectic medications over a 4-week period to avoid rebound phenomena which were considered a safety consideration. At the end of this withdrawal period they entered a washout period, which was determined by at least 5 times the half-life of their preceding drug to remove any effects of those drugs. However, if patients weren't on any cataplectic medications, they were still required to remain 5 days in that washout period to familiarize themselves with the use of diaries.

They then proceeded to a baseline period of 2 to 3 weeks, using daily diary recording to establish the severity of their disease and to confirm that they had reached a stable stage in their disease. They then entered a 4-week blinded, randomized treatment period, with a visit at 2 weeks, a telephone call the day after commencing treatment, and then safety telephone calls 3 times a week during the treatment period, at the end of which they were abruptly withdrawn from drug and

followed up 3 to 5 days later to assess any rebound phenomena and any adverse experiences that may have ensued.

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As is shown here, the patient groups were very evenly balanced at baseline. They represented a fairly severe group of narcoleptics, with an average incidence of cataplexy of around 34 per week at baseline.

There was a dose-response relationship across the doses based on median change in the total number of cataplexy attacks that, when compared to placebo, approached significance at the 9 g dose, with a p value of 0.0529, and achieved highly significant change at the 9 g dose.

[Slide]

This dose relationship is clearly shown in the plot of median change from baseline in the number of cataplexy attacks per week, and the spread of the data is demonstrated as the quartile lines around these median values.

[Slide]

A more clinically relevant presentation of the data is the percentage change in the number of cataplexy attacks from baseline. This was

calculated as the distribution of percentage change values for each individual patient and is again presented as the medians. This representation clearly shows that the major change in cataplexy occurs in the first 2 weeks, but with ongoing change in the subsequent 2 weeks, as represented in 2 of the dose groups.

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Secondary efficacy variables included assessment of excessive daytime sleepiness using the validated Epworth Sleepiness Scale which rates the patient's feeling of daytime somnolence by scoring on a scale of 0-3 the probability of falling asleep in the circumstances of 8 common life scenarios. This results in a potential maximum score of 24.

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This slide demonstrates a clear dose-related reduction in the Epworth Sleepiness Scale, reaching a significant level of 0.0001 in the 9 g group compared to placebo. This change was incremental beyond the effects of stable dosing of stimulants because stimulant medications were maintained constant throughout the study. In all Xyrem-treated groups some patients improved beyond

the defined narcolepsy range, with some patients in the 6 g and 9 g groups actually improving into the normal range as rated by the Epworth Sleepiness Scale.

The second component of daytime sleepiness, the number of inadvertent naps during the day, was also significantly reduced compared to placebo in the 6 g group and 9 g dosing.

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The severity of the disease at baseline was rated by the principal investigator according to the following validated scale. Then, at the end of the treatment period a blinded global impression of change according to the rating shown here was made, rating from very much improved through no change to very much worse.

[Slide]

Assignment of these modal values indicated a primary distribution of the placebo patients mainly to no change or minimally improved, but there is an obvious predominance of assignment in the 9 g dose to very much improved and much improved.

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Because of the complexity of presenting

these assigned categories, a post hoc simplification was applied to group the patients that showed clear clinical improvement into a responder group, and all others were called non-responders. This again displays the dose-response trend in the categorical data, with a clear statistical difference between the 9 g group and the placebo group.

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Other secondary measures that achieved significant change included the number of awakenings at night, subjective sleep quality, morning alertness, the ability to concentrate. Hypnagogic hallucinations and sleep paralysis, which had a much lower incidence at baseline, showed a non-significant trend towards improvement.

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The next study that I would like to present is the study that was suggested by the FDA to provide evidence of long-term efficacy of Xyrem based on the return of cataplexy following the cessation of long-term treatment with the active drug.

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Patients entered this blinded, randomized

study from the long-term open-label study I showed you initially having completed the GHB-2 protocol and proceeded into the GHB-3 protocol for periods up to 2 years, or from the initial treatment IND protocol. This provided assessment of potential adverse consequences of the abrupt withdrawal of long-term therapeutic doses of Xyrem as well.

Patients having taken the drug for 6 months to 3.5 years were screened, and after blinded randomization entered a single blind baseline period in which daily diaries were used to record the severity of their cataplexy. They then entered a double-blind phase of 2 weeks wherein they were randomized in a 50 percent ratio to either continued, unchanged dose of Xyrem in a blinded fashion or to placebo. Randomization was performed in a centralized manner to ensure equal representation of dosing in the comparative groups.

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The primary efficacy variable was the change in the number of cataplexy attacks in the double-blind period compared to baseline. There was a median change of zero in the Xyrem group but, as seen, there was a marked increase in the incidence of cataplexy in those randomized to

placebo. This was highly significant.

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When the median change from baseline by week was calculated, you can see that there was a step-wise increase in cataplexy which supported the long-term efficacy of the drug in a statistically significant manner, but they represent a gradual return of cataplexy rather than an acute rebound phenomenon.

[Slide]

I will now present very briefly some supportive data from 2 early controlled, crossover design studies that have been published, and for which Orphan Medical purchased the databases and included in the NDA submission.

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The first was a study conducted by Dr. Lawrence Scrima, then of the University of Arkansas, in 20 patients, 10 males and 10 females, using a dose of 50 mg/kg, much lower than some of those in the previous studies and equivalent to about 3.5 g per day in a 70 kg man.

Following the withdrawal of anticataplectic medications, he recorded a baseline period during which the patients were required to

have a minimum of 10 cataplexy attacks, then were randomized into an initial treatment period of 29 days, followed by a washout period of 6 days, and then crossed over to the alternate treatment, again followed by a washout of 6 days. Stimulants were continued throughout this study and all patients were actually transferred to methylphenidate as their stimulant.

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The primary efficacy measures are identified, with the average number of cataplexy attacks compared to baseline and objective sleepiness index as determined by the Multiple Sleep Latency Test. This was to represent a measure of daytime sleepiness.

Because of logistic issues in the study conduct and methodologic issues in design and definition, this is presented as supporting data only to represent cataplexy response at a lower dose. As can be seen, this patient group again represented a reasonably severe narcoleptic population. They had a baseline measure of 20 cataplexy attacks per week. There was an initial fairly significant placebo response, as was shown in the previous studies, but by week 3 and week 4

statistically significant differentiation between placebo and active treatment was shown, and there was a statistically significant overall response in the study. There was no significant change in the sleepiness index as the measure of daytime sleepiness, however, in this study.

[Slide]

The second study that I will present very briefly was conducted by Dr. Lammers, in The Netherlands. It is, again, a randomized, blinded, crossover design study in 24 narcoleptics. The other significant difference in this study was that concomitant medications for both cataplexy and excessive daytime sleepiness were continued throughout the study.

Following a 1-week baseline to establish disease severity, the patients were randomized to a 4-week treatment period at a dose of 60 mg/kg in divided nightly doses, followed by a washout period of about 3 weeks, and then a baseline period of 1 week again preceding a second treatment period of 4 weeks.

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As is obvious here, the severity of cataplexy during the baseline period was much lower

in this study, potentially the consequence of continued anticataplectic medication in some patients. But, again, there is a significant response. According to the statistical plan which was very scant that was represented in the published study, and agreed to by the FDA, there was an incorrect or unsatisfactory statistical management of this study. The change in cataplexy was not statistically significant. When the results of this study were submitted by Orphan, they were reanalyzed with an ANCOVA analysis as had been applied in the GHB-2 study, and this change was significant according to the ANCOVA analysis.

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Other measures that showed significant improvement included hypnagogic hallucinations and daytime sleep attacks again.

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Although not eligible for determination of efficacy since it is an open-label study, I would like to briefly mention three aspects of the follow-on study to the pivotal GHB-2 study. And, 117 patients chose to participate entering the study at the 6 g per day dose and then slowly titrating to clinical efficacy between the doses of

3 g and 9 g. This study, therefore, represents the proposed clinical use of the drug and, although primarily a safety study, represents some important dynamic information.

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This slide shows the response in cataplexy over the 12-month period. What is surprising is that the maximum nadir occurred at about 8 weeks, and then the sustained efficacy was maintained across the 12 months in all dose groups.

[Slide]

A similar pattern was seen in the Epworth Sleepiness Scale, which shows the same time frame with maximum response at about 8 weeks, and then maintained efficacy over the course of 12 months in this open-label study. What is also interesting to note is that most of the patients in most dose groups were maintained beyond the defined narcolepsy range.

[Slide]

When the distribution of doses to which the patients were titrated is shown, it is seen that 6 g per day is the most common dose, followed by the 9 g dose group.

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This represents the pattern of dosing seen in other open-label studies where doses were titrated to clinical response. What is important to note is that there is not a change in dosing between the 6-month and the 12-month dosing groups, suggesting no tolerance development to maintain the dynamic effects shown.

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This slide represents the cohort of patients that entered the SXB-21 protocol via the GHB-2 and then GHB-3 protocol. Represented here is the incidence of cataplexy for each individual patient at the baseline in GHB-2. They were then maintained in the study I have just shown you over the course of up to 2 years, and this is the incidence of cataplexy of each of the individual patients in the single-blinded baseline in the SXB-21 protocol. When the paradigm of random assignment to placebo is shown, then there is certainly a demonstration of efficacy between those who were randomized to the placebo group in SXB-21 versus those that maintained their Xyrem treatment, which certainly helps to support the efficacy statement in the GHB-3 protocol.

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Finally and to summarize, we have presented data to show efficacy of sodium oxybate to reduce cataplexy in 4-week treatment periods in a dose-related manner that is highly statistically significant at the 9 g dose, and approaching statistical significance at the 6 g dose.

We have presented supportive data demonstrating statistically significant efficacy of the lower doses, and demonstrated statistically significant efficacy in terms of daytime sleepiness, using the Epworth Sleepiness Scale, again at 9 g. In a scale used in the Lammers study at 60 mg/kg daytime sleep attacks were statistically significantly reduced in all 3 studies. We supported the long-term efficacy of Xyrem with return of cataplexy when blindedly assigned to placebo in the SXB-21 protocol.

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I would now like to very briefly summarize the pharmacokinetics studies that were conducted by Orphan Medical.

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In total, we conducted 8 clinical pharmacokinetic studies, including 2 studies in narcoleptic patients and 6 in healthy human

volunteers. This slide lists the 8 pharmacokinetic studies by their primary objective.

The studies included a single dose pilot study in 6 narcoleptics, and a second study in narcoleptic patients comparing acute and chronic dosing over an 8-week period. Normal volunteer studies were conducted to examine the kinetics of Xyrem with respect to gender differences, dose proportionality and the effects of food. Also, 3 drug interaction studies were performed with Zolpiden, protriptyline and modafinil as representatives of the 3 classes of drugs used commonly to treat the symptoms of narcolepsy. Lastly, an in vitro study, using human hepatic microzymes, was conducted to assess the effects of oxybate.

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I will only present the studies that have a significant message, and in very brief summary form. This slide displays the results of the dose proportionality study that compared nightly dose of 4.5 and 9 g given in 2 equally divided doses at bedtime and 4 hours later. A randomized, 2-day crossover design was utilized, and doubling the dose from 4.5 to 9 g resulted in a nearly 4-fold

increase in the area under the time concentration curve. The peak plasma concentration and the time to peak concentration changed significantly with doubling the dose, the latter suggesting capacity-limited absorption. C_{max} was higher after the second dose than with the first nightly dose, as has been seen in other studies with divided dosing.

These findings indicate non-linear kinetics and capacity-limited elimination and absorption, as reported in previously published studies.

[Slide]

The results of the effect of food study are displayed graphically on this slide. In this randomized, crossover study 34 healthy subjects were dosed with 4.5 g of Xyrem on 2 occasions 1 week apart, either after an overnight 10.5 hour fast or immediately following a high fat standardized breakfast. After the high fat meal the peak plasma concentration decreased by almost 60 percent. The median time to achieve peak levels increased from 45 minutes to around 2 hours, and the AUC decreased by 37 percent. All of these differences were statistically significant. The

apparent half-life was not significantly altered. Thus, the presence of food significantly reduces systemic exposure to GHB, a finding not previously reported.

In the 3 volunteer kinetic studies the urinary excretion of Xyrem was measured, and renal excretion was shown to be a minor pathway of elimination, accounting for less than 5 percent of the administered drug.

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As an example of the drug interaction studies, on this slide we present the modafinil results. The upper graph indicates that co-administration of 200 mg of modafinil had no impact on the kinetics of Xyrem. The lower graph demonstrates that 4.5 g of Xyrem had no clinically significant effect on the kinetics of a standard dose of modafinil.

Likewise, in the Zolpiden protriptyline interaction studies, no significant kinetic interactions were found. In the separate in vitro study using human hepatic microzymes, sodium oxybate was found to have no effect on 6 cytochrome p450 enzymes either to inhibit or induce their activity.

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So in summary, Xyrem oral solution is rapidlyh absorbed and eliminated with a half-life of about one hour. The drug displays non-linear, dose-dependent kinetics, indicative of capacity-limited absorption and elimination. Xyrem kinetics are similar in men and women and do not change with chronic administration at therapeutic doses.

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Chronic dosing did not change the kinetics of Xyrem in a patient population, and a high fat meal appreciably delayed absorption and reduced total systemic exposure to the drug. Three separate in vivo drug interaction studies, as well as the in vitro p450 enzyme study, would suggest the probability of significant drug-drug interaction with Xyrem is minimal. Thank you very much.

DR. REARDAN: Thank you. I would now like to introduce Dr. Jed Black, from Stanford University Sleep Center, and he will present on the polysomnographic effects of Xyrem and GHB.

Polysomnographic Effects of Xyrem

DR. BLACK: Good morning, ladies and

gentlemen. I would like to summarize the body of data that has been collected over the past 25 years which characterizes the effects of gamma hydroxybutyrate or sodium oxybate on sleep parameters. I will then speculate briefly on a possible mechanism whereby these effects on sleep result in a robust improvement in daytime narcolepsy symptoms seen with this agent.

This has been a particular focus of my research in sleep over the past years. That is, how does what happens in the brain at night affect various aspects on daytime function and alertness?

It is unexpected that a medication that objectively markedly improves sleep quality also improves measures of daytime alertness as this finding has never been observed with traditional hypnotics or sleep aids. To pursue an understanding of this possible interaction, 6 investigations have been conducted in humans. These studies explored the effect of sodium oxybate on a variety of nocturnal sleep parameters, using electroencephalography during sleep and a laboratory test known as polysomnography.

The first 3 studies found an increase in slow wave sleep. Slow wave sleep, also known as

stages 3 and 4 sleep, is the deepest portion of sleep and correlates positively with functions of daytime concentration, attention and alertness in normal subjects. These studies also reveal a reduction in nocturnal awakenings with GHB.

The more recent studies of Scrima, Lammers and Orphan Medical explored both measures of nocturnal sleep as measured by polysomnography, or PSG, and measures of daytime sleepiness with the Multiple Sleep Latency Test, or daytime alertness with the Maintenance of Wakefulness Test.

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These 2 studies, the design of which has been reviewed by Dr. Houghton, again found significant reductions in slow wave sleep, that is to say stage 3-4 sleep or slow wave sleep, and reductions in nocturnal awakenings. Additionally, the Scrima group reported a reduction in stage 1 sleep, a very light stage of sleep, and the Lammers group noted significant reduction in the percentage of time patients spent awake during nocturnal polysomnography.

[Slide]

The most recent study, a multi-center trial performed at 4 sites with an enrollment of 25

patients, was designed to further explore the effects of sodium oxybate on nocturnal sleep parameters and daytime measures of sleepiness and alertness. In this open-label study patients were kept at a stable stimulant dose throughout the protocol. Cataplexy medications were tapered, followed by a 2-week washout and baseline period. Sodium oxybate was initiated at 4.5 g in a divided nightly dose for 4 weeks, then increased to 6, then 7.5, then 9 g for 2 weeks each. Nocturnal polysomnography and the Maintenance of Wakefulness Test, or MWT, were obtained at the time points noted here.

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This study revealed the expected increase in slow wave, or stages 3-4 sleep, and increase in delta power. Delta power is the measure of the depth of sleep. It incorporates the combination of the amplitude of the slow frequency waves and the prevalence of those waves through the night to produce a single number called delta power. Delta power is another measure found in a variety of animal and human studies to correlate positively with sleep quality. The calculation of this value requires sophisticated processing which was

unavailable for the prior studies. The increments in slow wave sleep and delta power were found to be dose related. Dose-related improvements in daytime alertness and subjective sleepiness were also observed.

[Slide]

The dose-response increase in the number of minutes of slow wave sleep is illustrated in this slide, with an increase from 6 g up to the 9 g dose. The total duration of slow wave sleep increased to over 5-fold that of baseline at the 9 g dose.

It is important to note that while these results are predicted to be dose related, time on medication cannot be factored out as a potential contributor to these increments.

[Slide]

Delta power, which characterizes slow wave activity throughout the entire sleep period, not just during stages 3 and 4, was also found to increase in a dose response fashion with a 50 percent increase noted at the 9 g dose over baseline.

[Slide]

The Maintenance of Wakefulness Test, or

MWT, is a daytime evaluation which places the patient in a dimly lit room in a semi-recumbent position, with nothing to do and with the instruction to remain awake. The duration of sustained wakefulness was measured in this study over 40-minute intervals across 4 periods, spaced 2 hours apart during the day. Substantial dose-related increases in the ability to remain awake were observed at both the 4.5 g and 9 g doses.

[Slide]

As previously noted, the MWT was not performed at the 6 g nor 7.5 g doses in this protocol. Similar marked reductions were found in the Epworth Sleepiness Scale scores. In this measure the individual rates their own potential to fall asleep in a variety of more sedentary daytime activities.

[Slide]

A post hoc analysis of the possible correlations between sodium oxybate-related changes in nocturnal parameters with changes in daytime measures revealed the strongest correlation occurring with delta power and Epworth Sleepiness Scale scores. This was a negative correlation,

such that the greater the delta power, the lower the daytime sleepiness. In addition, trends toward significant correlations between delta sleep and MWT scores, and between slow wave sleep and Epworth and MWT scores were observed.

[Slide]

In conclusion, studies of sodium oxybate's effects on sleep demonstrate increases in measures of restorative sleep, including dose-related increments in slow wave and delta sleep, coupled with and correlated with improvements in measures of daytime alertness and sleepiness.

It is postulated that sodium oxybate works directly to enhance brain neurochemical activity critical to the restorative mechanisms of slow wave sleep and of slow wave activity during the total sleep period. Such enhanced activity may be the cause of substantial improvement in both subjective and objective measures of sleepiness and alertness observed with sodium oxybate in narcolepsy.

DR. REARDAN: Thank you, Dr. Black. Dr. Houghton will now present the safety summary overview of Xyrem and finish up with a benefit/risk assessment.

Safety Overview and Summary of

DR. HOUGHTON: Thank you.

[Slide]

I am sorry to horrify you with this complex diagram again but it is just to outline the 15 studies that will be referred to today as the updated safety database. The Lammers study was excluded because adverse events were not recorded in the classical way and, as Dr. Katz explained, the Scharf study was separated and will be explained again later.

[Slide]

The safety profile was reported based on exposure of 479 narcoleptic patients and 125 healthy volunteers from the pharmacokinetic studies. This represents an exposure of greater than 6 months in 360 patients in total, and greater than 12 months in 296 patients, which represents a total patient-year exposure of 1328 years with the Scharf database included.

[Slide]

When exposures were restricted to the studies other than the Scharf database, 399 narcoleptics and 125 subjects represent exposure in 524 persons. This represents exposure of greater

than 6 months in 296 patients and greater than 12 months in 223 patients, for a total exposure of 330 patient-years.

[Slide]

In the open-label studies patients were titrated between the doses of 3-9 g in divided dose at night. This slide represents the distribution of patients across this defined dose range and, again, identifies the 6 g dose as the most commonly used, followed again by the 9 g dose. In fact, approximately 80 percent of patients were titrated within the 6-9 g range.

[Slide]

In the updated integrated safety database, composed of 402 patients, 399 of whom were treated with active drug and 3 patients received placebo only, it can be seen that 65 percent of patients completed therapy or were ongoing in the treatment IND study. Thirty-five percent have discontinued treatment for the reasons noted here, with 13 percent discontinuing due to adverse events; 2 percent discontinuing because of lack of efficacy; and there were 2 deaths that occurred in the treatment IND studies, both due to suicide.

[Slide]

Across all of these studies, 82 percent of treated patients reported any adverse event, as did 70 percent of patients exposed to placebo. It is important to note that the placebo exposure represents 4 weeks as compared to active drug treatment over a much longer period of up to 4 years. Hence, severe adverse event discontinuations and serious adverse events are significantly greater in the active treatment groups.

[Slide]

When considered in terms of dose at onset, there seemed to be a slight preponderance of incidence in the 9 g group.

[Slide]

This slide represents the most frequent adverse events reported across the integrated database. There was a consistent pattern of events across the study. Nausea, dizziness, sleep walking, are represented here as a partial representation of the term sleep disorder, enuresis and confusion were most frequently considered dose related, while others represent intercurrent illness.

[Slide]

This profile is reinforced by consideration of the controlled trials in which there is represented a balanced exposure to placebo and active medication. Again, dizziness, nausea, pain, sleep disorder, confusion, infection, vomiting and urinary incontinence separate. A dose relationship was shown introduction eh GHB-2 trial for confusion, nausea, dizziness and urinary incontinence.

[Slide]

In the SXB-21 trial the most common adverse events that were reported are shown here. The incidence was very low in this study of patients on long-term treatment, but what is relevant is the data that looks at the possible presentation of a withdrawal syndrome with the abrupt cessation of long-term therapy.

[Slide]

This is in marked contrast to a severe syndrome that is being described in the abuser population who have significantly escalated both dose and frequency of dosing. When we looked at symptoms that could relate to a withdrawal phenomenon, we saw only 2 patients with anxiety in a circumstance of escalating cataplexy, 1 patient

with dizziness, 1 insomnia, 1 sleep disorder that actually in verbatim terms, was increased awakenings, and 1 patient with somnolence as their narcolepsy worsened.

[Slide]

I would like to now address the Scharf database. This was conducted under an investigator IND commencing about 10 years before Orphan's involvement, without any of the rigors of external monitoring, and really represents over 16 years experience in the use of the drug rather than drug development clinical research with regulatory disciplines.

Patients were scattered all over the country and, hence, the data is based primarily on diary recordings without medical review and interpretation, leading to a significant discontinuation rate for lack of compliance. Dose accountability and titration were less clearly defined and less controlled. Patients had less defined entry criteria and represent a broader profile of associated pathologies. On this basis, the study data has been reported separately to the integrated database, as Dr. Katz had suggested.

[Slide]

We will address the Scharf open-label experience in terms of dosing exposure, patient disposition, adverse event incidence over 16 years, and then to try and establish some parity with the integrated database. We have considered the adverse event experience reporting in just the first 6 months of the study.

[Slide]

Patient disposition in the Scharf database is represented in this slide. At the time of database closure 63 patients transferred into the SXB-7 protocol. The FDA expressed concern regarding the accountability of the 80 patients that did not continue. We provided a narrative account for each individual patient, with updated status where possible, in the form of a major amendment. In addition, FDA requested further clarification of adverse events initially deemed uaevaluable, which we have also provided.

Of these 80 patients, 8 continued in the Scharf trial under his treatment IND. The 71 patients who withdrew had received oxybate for from 5 days to 10 years, and the reasons for early withdrawal of the 71 patients were primarily classified into non-compliance, adverse event and

cost.

[Slide]

The adverse event profile reflects the length of the study. The relatively large numbers of viral infection, flu syndrome, pharyngitis, etc. shouldn't be worrisome considering the 16 years duration of the study. However, of particular interest is the unusual incidence of sleepwalking and urinary incontinence and these will be discussed in some detail later.

[Slide]

The most frequent adverse events in the first 6 months of the Scharf trial are shown here. When compared to the integrated safety database, few adverse events separate in incidence. Most notable are somnolence, infection, viral infection and malaise. There were few new adverse events reported after the first 6 months.

The FDA requested further information regarding the following adverse events of particular interest. They were represented by incontinence and convulsions, confusion, neuropsychiatric events and sleepwalking.

[Slide]

I will address incontinence first. In

their review of the GHB-2 trial, submitted in October, 1998, the FDA requested an analysis of adverse event terms for incontinence in association with central nervous system adverse events suggestive of seizure.

[Slide]

We responded by initiating the following: a questionnaire to all investigators to review the history of abnormal nocturnal observations that could be suggestive of seizures; a detailed urologic history preceding oxybate therapy and any new neurologic symptoms.

Examination of the databases for potential correlation between central nervous adverse events that could be related to seizures and incontinence, either urinary or fecal, was undertaken. Review of both preclinical and clinical data in the literature was performed and an overnight EEG recording after a 9 g dose was conducted in 6 patients who had reported incontinence during their oxybate therapy. An expert opinion was provided by Dr. Nathan Chrone, a neurologist of Johns Hopkins University.

[Slide]

The issue as represented is shown here.

Urinary incontinence was presented by 8 patients reporting 15 events in the GHB-2 study, by 13 patients reporting 51 events over the 2-year period of GHB-3, and in the Scharf study by 33 patients reporting 140 events.

When central nervous system events were analyzed for contemporaneous reporting, 2 patients in each of the GHB-2 and -3 trials recorded such events corresponding to episodes of incontinence, as did 7 patients in the Scharf database. Relatively few incontinence events were temporally associated with the CNS adverse events suggestive of seizure. No potential seizure genesis was reported by bed partners in response to specific questions, and many of the partners reported relevant urinary symptoms such as frequent nocturia preceding the Xyrem treatment.

[Slide]

Single events of fecal incontinence occurred in 4 patients in 4 different trials. Association between these incontinence events and central nervous system adverse experiences were present only in 1 patient in the Scharf trial and 1 in the pharmacokinetic SXB-11 trial. In this patient the event of fecal incontinence was

definitely associated with a seizure in a patient with a known pre-study history of seizures. The subject in the SXB-11 effect of food study was a patient who, while significantly obtunded and with respiratory obstructive symptoms, had a brief episode of fecal incontinence.

[Slide]

In conclusion, there was limited support for a relationship between incontinence and seizures from the clinical trials, the prospective EEGs or from the literature.

[Slide]

The vast majority of events that could have been coded as convulsions were actually recorded under the COSTART dictionary as cataplexy events. One patient in the integrated trial database did not represent this classification and he has been investigated by a neurologist for seizure genesis. His fugue state and automatic behavior episodes have been deemed part of his narcolepsy syndrome.

In the Scharf database two patients with definite seizures recorded history of preexisting disease, and two other patients recorded seizure events without definitive diagnosis but with

complicated polypharmacy.

[Slide]

To now address confusion, in the integrated safety database 30 patients or 70 percent reported 48 events recorded as confusion, leading to discontinuation from study in 3 patients. A possible dose relationship was suggested by a review of the entire database. In the Scharf database, again 7 percent of patients reported 15 such events, with no discontinuations and no dose relationship pattern observed.

[Slide]

The coding of confusion embodied a wide range of verbatim terms, as shown here. These do not represent confusion based on a standard medical status examination. They do not differentiate between nighttime events from those of awakening or arousal parasomnias. These events led to no dosage adjustment in 37 instances, but dose was reduced in 4 events, led to temporary discontinuation following 4 events, and 3 patients discontinued permanently because of a side effect of confusion.

[Slide]

When the GHB-2 controlled trial was considered with respect to confusion, the highest

incidence in the databases is represented in this 4-week study by 10 patients. The highest incidence was seen in the 9 g dose, and 6 of the 10 developed during the first week of treatment. Seven of these 10 events were in patients over the age of 50. The difference in this study, of course, was the assigned doses rather than dose titration. It is important to note that 1 event was reported in a placebo patient.

[Slide]

In conclusion, the term represents a symptom report rather than confusion defined in a medical sense by formal mental status examination, and all resolved usually without interruption of therapy or dose modification. Confusion and other associated symptoms are not unexpected with sedating medications. The blinded, controlled trial results suggest that a higher incidence may result without dose titration.

[Slide]

Neuropsychiatric events will now be reviewed. The adverse event database was searched for terms that could represent neuropsychiatric symptoms, and this led to the classification shown in this slide. Fifty-two patients reported 57 such

events in the integrated safety database, of whom 12 discontinued as a result of these events. In the Scharf database 41 patients reported 84 such events, leading to 2 patient discontinuations.

[Slide]

Of these 57 events, 1 occurred while a patient was on placebo. This slide lists the terms examined and some, such as stupor and coma, failed to represent neuropsychiatric events. Many represented symptoms of narcolepsy such as hypnagogic hallucinations COSTART-coded to the term hallucinations. The most frequent was clinical depression, and this represents a symptom rather than a diagnosis of major depressive disorder. Depressive symptoms are frequent accompaniments in narcolepsy, and this is well recorded in the literature. Suicide was attempted in 4 patients with major preexisting psychiatric history, and resulted in death in 2 of these patients. The other representations of psychotic disorders and the patient with manic depressive disorder also occurred in patients with preexisting major psychiatric disease. As is shown, a similar profile of reported symptoms is found in the Scharf database.

[Slide]

In conclusion, most patients with major events had a preexisting psychiatric disorder. Many events do not qualify as neuropsychiatric disorders, as was represented by the terms pointed out. Assignment of causality is very difficult because narcolepsy is associated with depression and even mechanistically there has been an association between psychosis and the central processes in narcolepsy. As Dr. Mignot mentioned, stimulant medications are associated with central nervous system side effects that are represented by neuropsychiatric symptoms. And, it is true to say that in many patients, particularly in the Scharf database, pre-study screenings were deficient.

[Slide]

To lastly address sleepwalking, in the integrated safety database 7 percent of patients reported such events, whereas in the Scharf database 32 percent of patients reported events that were listed as sleepwalking. In the Scharf trial, however, these reports were primarily data listings in patient diaries in response to a specific leading question, listed as a line item in the diary.

[Slide]

The listing of this term did not receive the benefit of medical consideration of a differential diagnosis of somnambulism, and since most patients were not seen by the investigator no clarification was provided. Post hoc consideration was rendered impossible given the lack of information regarding sleep stage, time of night, relationship to drug dosing, and could be representative of any of the differential diagnoses listed on this slide.

[Slide]

In the controlled trials only 3 sleepwalking events were reported, 2 of which occurred on active treatment and 1 occurred in a patient during placebo treatment.

[Slide]

Hence, in conclusion, the incidence in the integrated safety database of 7 percent is not particularly dissimilar to the range reported in the literature for normal patients. This was reported by Dr. Mahowald, of Minneapolis, as between 4-10 percent in a publication in 1998, and between 1-7 percent by Dr. Roger Broughton of Canada.

Diary recording without medical classification represents a potential increased reporting in the Scharf trial. The slight increase in incidence over the general population may certainly be representative of Xyrem effects with increase in slow wave sleep, but REM behavior disorder, common in narcolepsy, mayou be a separate consideration.

[Slide]

To summarize the safety profile of this drug, we based our assessment to date on 604 patients, which represents 524 patients excluding the Scharf database. Dosing was between 3-9 g per day in divided nightly dosing. The common adverse events were certainly headache, unspecified pain, nausea, dizziness, and less common but important adverse events were vomiting, confusion, restlessness, agitation, sleepwalking and enuresis.

[Slide]

All events have been reversible. There were no significant changes in lab values or vital signs identified across the studies. There was no evidence of organ toxicity outside the pharmacologic effects in the central nervous system. There was no diversion or consumption of

clinical trial supplies by any family members during the trials, and there was certainly no evidence of Xyrem diversion in our database.

[Slide]

I would like to conclude with the statement that Xyrem was generally well tolerated.

[Slide]

To commence a risk/benefit assessment, I would like to remind you of the indication proposed by Orphan Medical for the use of Xyrem. That is, to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy.

[Slide]

As has been pointed out, narcolepsy is an uncommon disease, with an incidence of around 0.05 percent and, as such, has been qualified for orphan designation. There are no therapies approved for the treatment of cataplexy. Because of this, the FDA were very kind to apply a priority review to our submission and we are very appreciative of that recognition. Current off-label therapies, so well described by Dr. Mignot, are unsatisfactory. Excessive daytime sleepiness has approved therapies but these do not address cataplexy. There is

clearly a medical need existing beyond the therapies available.

[Slide]

The benefits of Xyrem in the trials presented were based on patient diary recordings, investigator ratings of overall clinical improvement in overall disease severity, and objective measures of changes in sleep architecture and daytime response.

[Slide]

Clinical benefit in the short-term reduction in cataplexy was shown by the dose-related reduction in cataplexy in the GHB-2 and Scrima studies and in the long-term efficacy in the SXB-21. Subjective changes in the Epworth Sleepiness Scale have been well demonstrated, and reduction in daytime sleep attacks have accompanied this change. Early objective Maintenance of Wakefulness Test data supported these changes in daytime sleepiness. The global impression of the investigators for overall changes in disease severity also showed a significant dose relationship.

[Slide]

Xyrem was generally well tolerated when

used in the proposed dose range, with the most common side effects reported including nausea, dizziness, headaches, pain and confusion. Less common but important associated effects include enuresis and sleepwalking, with a possible dose relationship suggested. Although there were 11 deaths in the Scharf trial over 16 years and 2 deaths by suicide in the integrated database, no deaths were associated with Xyrem.

[Slide]

In relation to the specific FDA inquiries, there is a possible relationship between Xyrem therapy and somnambulism but further definition is required. There is a marked discrepancy between the reported incidence in the Scharf study of the 32 percent, recorded solely by diary entry in response to a leading question, and the 7 percent in the integrated database, which is really in the range in public literature for the normal population. In the controlled trials there were only 3 such reports in total, 2 recorded in active treatment and 1 during placebo treatment.

[Slide]

Confusion is also an adverse accompaniment of sedative hypnotic drugs and has been identified

as an occasional side effect of Xyrem. Dose titration may assist in limiting this side effect but it remains an important component of patient and physician education.

[Slide]

The incidence of enuresis with Xyrem treatment supports an association that may be dose related, but any association of these events with seizure activity is very weak. In terms of Xyrem causing seizures at the therapeutic doses, there was no reliable support for such causality. In this regard, the coding to the COSTART dictionary terms of cataplexy as convulsion was confusing. However, there were 2 patients recording seizures with preexisting causes. Two further patients in the Scharf database reported seizures where confounding contributions rendered assignment very difficult. One patient in the Orphan studies represented a complex history of symptoms characterized by fugue state and these symptoms have been attributed to his narcolepsy syndrome.

[Slide]

No significant measures were seen in laboratory measures, vital signs or ECG measures and these changes were comparable across the

treatment groups. There was no evidence of organ toxicity at therapeutic doses that were not part of the central nervous system pharmacology of the drug.

[Slide]

We did not identify any evidence of kinetic or dynamic tolerance in the narcoleptic populations studied and the absence of drug-drug interactions in the 3 classes of drugs commonly used in narcolepsy, along with the absence of either induction or inhibition of the oxybate p450 enzyme system make it possible to predict that drug-drug interactions should be minimal.

[Slide]

Although a serious withdrawal syndrome has been described in the abuser population that relates to escalation in both dose and frequency of dosing, no evidence of withdrawal has been demonstrated in patients maintained on long-term therapeutic doses in narcolepsy. Following abrupt discontinuation of long-term dosing in the blinded study, only 2 patients reported anxiety but in the presence of worsening cataplexy, with 1 patient reporting mild dizziness and 1 report of insomnia.

[Slide]

We have not attempted in any way to minimize the issue of abuse with GHB or its precursors. We recognize that this is a serious problem, but stress the fact that this has been peripheral to the development program in narcolepsy. We have detected no evidence of abuse, diversion or self-escalation of dosing in patients in clinical trials. Great efforts have been applied to working with the appropriate expert bodies to plan a restricted distribution system to support in every way the unique bifurcated scheduling legislated by Congress and to plan physician and patient education to minimize the possibility of diversion. This will be greatly facilitated by the documentation centrally of prescribing and patient use. This will be described in detail to you later.

[Slide]

In conclusion, I would propose that we have established statistically and clinically significant evidence for the reduction in cataplexy, and for improvement in daytime sleepiness when used concomitantly with stimulant medications.

Xyrem is generally well tolerated, with a

safety profile well characterized in this orphan population by long-term exposure. The medical benefits clearly outweigh the risks for a therapeutic agent that may be the first single agent to address the multiple symptoms of narcolepsy. Thank you very much.

DR. REARDAN: I would just like to thank the committee and FDA for your attention. I believe Dr. Mani has some comments, or we are now happy to take questions from the committee.

DR. KAWAS: The FDA will give us a response to the presentation, and then we will probably take a break before we have questions, unless the committee has anything burning they need to ask now. Dr. Ranjit Mani will present for the FDA.

FDA Response to the Presentation

DR. MANI: What I propose to do in the next few minutes is address two issues where our views diverge somewhat from those of the sponsor.

[Slide]

The first is the effect of GHB on measures of daytime sleepiness in narcolepsy.

[Slide]

This overhead illustrates how many

measures of daytime sleepiness there were in the GHB efficacy trials. As you can see, GHB-2 had 3 measures of daytime sleepiness; the Scrima study had 2, of which 1 was primary; and the Lammers study had 2. I will draw your attention to the fact that, with the exception of the Scrima study, the remaining measures were all designated as being secondary.

[Slide]

Because what is considered statistically significant does depend or could depend on the number of comparisons made, I think it is also important to illustrate how many secondary efficacy measures there were in each trial. In the GHB-2 trial I was able to count a total of 10; in the Scrima study 17; and in the Lammers study 7.

[Slide]

This is based on data provided by Orphan. As you can see, in the GHB-2 trial the Epworth Sleepiness Scale measure did reveal a fairly clear-but efficacy for GHB but only at the 9 g dose. The p value of 0.001 probably remains statistically significant even when adjustment is made for multiple comparisons.

On the other hand, the frequency of

daytime sleep attacks and duration of daytime sleep attacks should probably be considered negative evidence of efficacy if adjustment is made for multiple comparisons.

[Slide]

Again, in the Scrima study one primary efficacy measure was sleepiness index of the Multiple Sleep Latency Test. Here, the results must be considered negative whether adjusted for multiple comparisons or not.

[Slide]

The other measure was the frequency of daytime sleep attacks, again negative whether adjusted for multiple comparisons or not.

[Slide]

In the Lammers study the severity of daytime sleepiness was 1 of 7 secondary efficacy measures which is probably negative when adjusted for multiple comparisons. On the other hand, the frequency of daytime sleep attacks was positive, but using an ANCOVA which was not a protocol specified analysis.

[Slide]

So, here are the problems as we see them with the proposed claim for excessive daytime

sleepiness. Most measures were secondary. The only measure that was primary was negative. The majority of measures were negative after adjustment of the Type 1 error for multiple comparisons. The effects were inconsistent across studies, and the clearly positive results on the GHB-2 trial on the Epworth Sleepiness Scale were not replicated. As mentioned, the approval of modafinil for the treatment of excessive daytime sleepiness was based on replicated results in 2 efficacy studies. And a minor point, the results on the GHB-2 study were, to some extent, confounded by concurrent stimulant use, raising the question, among other questions, of whether Xyrem is effective as monotherapy for the treatment of excessive daytime sleepiness.

[Slide]

The second issue that I want to address briefly is that of sleepwalking. As you can see, I have put it in quotes. As Bill Houghton has already emphasized, we do not know what these episodes represent. They have not been clinically characterized.

[Slide]

The term sleepwalking does not correspond to the medical entity of somnambulism. The term is

based entirely on patient diary entries, and there has been no attempt to characterize the episodes further and define what clinical entity they correspond to.

The incidence of these episodes, whatever they may represent, was approximately 32 percent. The majority of patients did list as having more than one episode. A single patient had a total of 346 episodes over a 5-year period. As already said, an adequate clinical description is lacking, and the episodes cannot be said to be completely benign.

There was one patient who is reported to have overdosed twice during two consecutive episodes of sleepwalking. During one episode the patient became comatose and needed to be hospitalized, needed to be on a ventilator for some hours but completely recovered. A second pat had multiple episodes of sleepwalking. She was found by her husband to be smoking, apparently inadvertently. During one such episode her clothes were set on fire. The fire was put out. She was taken off GHB and did not have any further such episodes. A third patient is reported to have swallowed nail polish remover during an episode,

without any serious consequences.

I would also like to add one minor point in response to Dr. Houghton's presentation. That is, I believe that in the Scharf study there was one patient who was withdrawn from the study because he felt that he had benefitted from Xyrem and decided that these benefits could be extended to a circle of friends who also received part of his own supply, again apparently without serious consequences. Thank you. That is really all I have to say.

DR. KAWAS: Thank you, Dr. Mani. Does the committee have any questions they would like to ask before the break? If not, we will reconvene this meeting at 10:30 sharp.

[Brief recess]

Committee Discussion

DR. KAWAS: Will you please have a seat so we can reconvene this session? This meeting of the Peripheral and Central Nervous System Advisory Committee is now reconvened. We appreciate the presentations from the sponsor and the FDA, and the floor is open for questions. The first question is going to come from someone who has been patiently sitting on the phone. Dr. Chervin, can you hear

me?

DR. CHERVIN: Yes, thank you.

DR. KAWAS: Dr. Chervin, we can't year you yet, if you will give us a moment to do whatever it is we have to do?

DR. CHERVIN: Can you hear me now?

DR. KAWAS: Give it a shot.

DR. CHERVIN: I have a question perhaps for Dr. Houghton. In regard to the safety experience with the 1328 patient years, were there any reports that alcohol was taken in the evening in combination with GHB? If so, what was the outcome?

DR. HOUGHTON: It was certainly recommended as a contraindication in our protocols. The advice to the patient was that they not consume alcohol during the studies. I can't vouch for the fact that it was entirely complied with, but we don't have protocol or database record of consumption of alcohol during the trials. There certainly is record of patients having imbibed during the Scharf study and I am not in a position to clarify that.

DR. GUILLEMINAULT: This is Dr. Guilleminault. I have also a question, and it is

for Dr. Mani, about the sleepiness data. Was there the slow wave sleep information looked at for sleepiness? As you know, delta power greatly improves alertness and there are many studies, sleep deprivation studies and investigation into sleep disorders such as obstructive sleep apnea, where it is very clear that decrease in delta power and in slow wave sleep has a big impact on the alertness, and the more delta power you have and the more slow wave sleep you have, the better alertness the next day.

So, one of my understandings is that this drug has an impact on slow wave sleep and delta power. Was there any analysis of that in data looking at alertness?

DR. MANI: To the best of my knowledge, it was not listed as an efficacy measure in any of the controlled studies that I looked at.

DR. GUILLEMINAULT: Okay. The second question is maybe a question about my ignorance. I did not understand exactly the statistic about the ESS because in the investigation of the results of the ESS there was an investigation with negative studies. All the results, when you look at everything there, was there a positive p value?

Was there a statistical difference? Because I don't understand the manipulation which was done. Maybe through poor knowledge, I have never seen this type of manipulation.

DR. REARDAN: Dr. Guilleminault, which study are you referring to when you ask about the Epworth Sleepiness score?

DR. GUILLEMINAULT: I think OMS-2.

DR. REARDAN: Is that for Dr. Mani, or do you want to pose that to the company?

DR. GUILLEMINAULT: No, I was asking that because Dr. Mani reported that he looked at that study and classified the results, and my understanding, and it may be a wrong understanding, is that he made a subdivision in looking at the results and I did not see completely the statistical rationale for that approach.

DR. MANI: Are you referring to the statistical adjustments for multiple comparisons? Is that what you mean?

DR. GUILLEMINAULT: No, the Epworth Sleepiness Scale study in GHB-2, secondary efficacy daytime sleepiness on your slide, and I did not understand exactly how that was analyzed, the type of analysis that was done or redone.

DR. MANI: Perhaps I should ask the Orphan statisticians to explain that in greater detail, but the analysis was an ANCOVA.

DR. GUILLEMINAULT: The microphone must be poorly placed because we cannot hear the response.

DR. MANI: Can you hear me now?

DR. GUILLEMINAULT: Yes.

DR. MANI: The analysis was an ANCOVA. I mean, perhaps I should get the Orphan study statistician to explain the analysis to you in greater detail.

DR. REARDAN: I am just asking Dr. Richard Trout, the statistician, to comment on how the Epworth Sleepiness score was statistically analyzed.

DR. TROUT: Hi. My name is Dick Trout. First of all, the analysis was just as you described, that is to say it was an analysis of covariance which was preplanned. I think the concern that you expressed was the fact that it was listed as a secondary efficacy measure --

DR. GUILLEMINAULT: Right.

DR. TROUT: -- as compared to a primary, and there was a number of secondary efficacy measures, but even if one adjusted for the multiple

testing which I think you were concerned about, the 9 g separation from the placebo group would still be significant. We already adjusted for the multiple testing with regard to the dosing issue, using Dunnett's test, but your concern was with regard to the fact that there were a number of secondary efficacy measures which would then diminish the effect.

DR. GUILLEMINAULT: Okay, thank you.

DR. PENN: I can see that the claim for helping daytime sleepiness is going to be one that we will want to look into very carefully, and I want to ask our FDA statistician a question about that in a general sort of way. If you were a gambling person, which I assume a statistician would not be --

[Laughter]

-- from the data that you have looked at for 9 g, would you say that in a good controlled trial you would bet on it working to decrease daytime sleepiness? It looks like the strongest data is at 9 g and that is what the company is suggesting. I am going to ask you to bet on that, and then I am going to make a point.

DR. MANI: You addressed the question to a

statistician; I am not a statistician.

DR. PENN: Oh, I am sorry. Anybody else want to gamble with this?

DR. REARDAN: Coming up to the podium is Dr. Sharon Yan, who is the FDA statistician that has been working on the Xyrem program.

DR. YAN: Basically we rely on the results that were prespecified, and a lot of results that we looked at -- and you want me to bet -- after looking at those results, most people would bet that the data shown, for example, the 9 g it seems that it is highly positive; it is highly significant, but we rely on the analysis which is prespecified. Without that, the data information -- it is hard to bet on anything.

DR. PENN: But I am asking you how you would bet on that if you had to make a bet now in Las Vegas, and the point I am trying to make is that it seems to me a reasonable bet that it does help daytime sleepiness but that they haven't presented two clean studies that show at 9 g that that is the case. And, is there going to be some middle ground to this where that claim can be put in language that would be acceptable later on? So, I wanted to see if you agree that that analysis

then presenting of the problem is the correct one, that is, that there is very strong suggestive evidence, not as strong as we often want for a claim, that it helps daytime sleepiness. When you sit back and you look at all the data, would you bet on that helping daytime sleepiness?

DR. KAWAS: Perhaps Dr. Katz could help with this response.

DR. KATZ: Yes, again, I will just sort of reiterate something that Dr. Yan has already said, which is that whether or not we personally believe something is true or what we would bet on is not really the standard. The standard which we apply is what the law requires, which is substantial evidence of effectiveness, ordinarily defined, unless there is some compelling reason to do otherwise, as data from at least two adequate and well-controlled trials demonstrating effect. We have adopted by tradition a usual sort of statistical rule by which we decide whether or not a study is "positive" for a particular indication. So, I think that is the standard. Unless there is some, as I say, very compelling reason to apply some different standard, like what would I bet on or what my personal belief is, that is the standard

we need to apply. Again, unless there is a view that there is some compelling reason to apply some different standard, we would ask you as a committee whether you think that the evidence for that particular claim meets that standard.

DR. PENN: So, once again the question should go then to Orphan, whether or not they feel they have met that standard on two separate occasions using their 9 g amount, and I haven't gotten a clear-cut idea in my mind whether they are really claiming that or just showing us data that would be for a good bet.

DR. YAN: May I clarify one thing? For the analysis for daytime sleepiness for GHB-2 the sponsor showed it was highly significant, with a p value of 0.001, and I analyzed the data with the original scale and, as I analyzed it, it shows that the normal assumption was validated and then the log transformation to then improve the data, and I used nonparametric analysis to analyze the p value, and it is not that small. As I remember, the p value is 0.03 or something.

DR. REARDAN: I can comment on the trials. We have GHB-2, obviously, where the trial was very effective. I don't think there is a dispute with

FDA on that. The question is do we meet the standard of two well-controlled trials for that indication. The data in support of that comes from the Lammers study. The sleepiness scale used there was something he developed, not a validated scale but it was statistically significant for daytime sleepiness, albeit in a very small, 24-patient crossover trial.

So, we have a small supportive study. We have the large controlled study, GHB-2. That is the evidence basically. Bill, do you want to comment?

DR. HOUGHTON: Yes. We are not trying to make this something that it is not in any way, and if you apply the absolute, most rigorous standards of normal drug development to our database, we have a small database. We did have the two components that were statistically significant. This was supported by the reduction in daytime sleep attacks which are very clinically significant to the patient, and we had two components of statistical significance there.

The other issue, and I know that this from a pure mathematical sense is problematic, is the evidence of long-term support in daytime sleepiness

claim with the GHB-3 protocol, which showed the Epworth Sleepiness Scale and the daytime sleepiness reduced and maintained over the long period of time. The fact then that the objective data in SXB-20 was so strongly supportive and the change in Maintenance of Wakefulness Test is an objective measure and was clearly positive was very important.

The part that concerns me from a clinical point of view is if you look at the patient profiles as they enter the studies, they are on stable doses of stimulants and, yet, their ratings are very low. The real issue is that daytime sleepiness with current medications isn't well addressed. So, the question is not only have we shown absolute irrevocable evidence of long-term efficacy for daytime sleepiness with the existence of the present treatments for long-term effectiveness, what we didn't do is ask for a claim in daytime sleepiness.

[Slide]

Our proposed indication was to improve the symptom. We didn't attempt to do studies that displaced the stimulant therapies. What we are really looking at is a hand-in-glove approach that

actually makes patients better as an incremental change, and all therapies up to now have been very separate. The symptoms of daytime sleepiness and those of the associated REM phenomena have been treated by entirely separate medications. If there is a component of Xyrem that assists in daytime sleepiness as an incremental change, we think it is very clinically important and that is what we sought to present today. I want to stress very clearly that we are not looking for the claim of daytime sleepiness; we are looking at an improvement in the symptom thereof.

DR. KAWAS: Dr. Houghton, can I ask you then, to my reading, that indication is actually two indications, I mean, cataplexy and sleepiness being a separate one. When I was reading the materials that you very carefully provided us, obviously for cataplexy the GHB-2 and the SXB-21 study speak to that issue as pivotal trials. I was going to ask you which were the two that speak to the issue of daytime sleepiness. Now I understand them to be the GHB-2 and the Lammers small trial with the questionnaire that was developed there. In both of those cases, however, we are talking about subjective sleepiness from the Epworth scale

and the other question. Since there are factors that can influence someone's subjective feelings of sleepiness, do you have any objective measures that support the indication of daytime sleepiness? Specifically, the one trial that I am aware of that had an MSLT and did daytime sleepiness as a primary outcome measure, in fact, appears to be not supportive of the indication.

DR. HOUGHTON: Yes, in the Scrima trial he used the MSLT measure and that was not statistically significant, as shown. The objective data that we propose supports very strongly the effect of adequate dosing of GHB was the SXB-20 trial that Dr. Black discussed. That is not only a profound improvement in the MWT at the 9 g dose but a defined dose response across all doses. That is very positive data.

DR. KAWAS: In ten patients, it appears.

DR. HOUGHTON: Twenty-one.

DR. MANI: May I also add that that was an open-label, non-randomized study?

DR. HOUGHTON: Sure, but using an objective measure.

DR. RISTANOVIC: I am I am Ruzica Ristanovic, medical director of Sleep Disorders

Center, in Evanston, Illinois. I would like to comment on add-on Xyrem in the presence of other stimulants. Other studies attempt to try to document the effectiveness of other stimulants in narcolepsy-related sleepiness documents, including the most rigorous trial of modafinil in double-blind, placebo-controlled studies. They document that these drugs improve sleepiness but very seldom outside of the range of pathological sleepiness as measured by Multiple Sleep Latency Test and Maintenance Wakefulness Test. So, the patients remain sleepy. That is the message. Add-on treatments are approved for other indications in other neurological diseases, such as epilepsy. So, I assume that this application for that particular indication is not for monotherapy but as an add-on to concurrent use of stimulants. I would like to bring this to your attention. So, patients do remain sleepy on stimulants and they need additional treatments.

DR. KAWAS: Dr. Temple?

DR. TEMPLE: Dr. Houghton also seemed to be distinguishing between monotherapy and add-on therapy. That is not the problem. The problem is whether there is adequate support for use as an

addition for whatever else the patient is on, and whether there are well-controlled studies that support that. So, add-on would be perfectly fine. That is usually true in a lot of conditions, not just neurological ones, where you continue to give standard therapy and try to improve it.

I just want to make one observation about the evidence. We do expect to see replicated or reproduced findings. Some of the issues here are whether the fact that the endpoints are secondary and need some correction means that there isn't adequate support. A lot of these things are matters of judgment that the committee can weigh in on. Not everything is, you know, a yes/no. Some of the things are moderately subtle and that is why this is being brought to you for judgment. There is one study that is obviously stronger than the rest but the others can be considered, and you sort of have to think about how many real endpoints there really are; how much of a correction is needed. Those are difficult discussions but worth considering.

DR. KAWAS: Dr. Katz?

DR. KATZ: I agree, but I think we would still have to have the application meet the

standard of independent replication, in other words two trials. You can decide that one of the other trials actually does meet the usual standard, again, taking into consideration the multiplicity and that sort of thing. All I am saying is that I don't think we can say we have one study that looks good. If you believe that GHB looks good and the others sort of contribute to a feeling that it probably is okay, I mean, we really need two independent sources that you believe demonstrate the effectiveness.

The only other point I wanted to add is to something, Claudia, you said which has to do with Dr. Houghton's view that they are not going for a claim of daytime sleepiness; they just want, I guess, to have language in the labeling that says that it improves that symptom. Most of the drugs we approve are for symptomatic claims, so there is no question that the inclusion of this language in the indication is a claim as we always understand that term.

DR. KAWAS: Dr. Guilleminault, followed by Dr. Wolinsky, please.

DR. GUILLEMINAULT: If you look at all the published data on modafinil, on amphetamine, on

methylphenidate, none of these drugs ever normalized all the objective tests on alertness and daytime sleepiness. None of them, including the modafinil data which were approved by the FDA. The MSLT and MWT for all these drugs are pitiful. The only data which shows significance was the Epworth Sleepiness Scale, which is a subjective scale, in all these trials. So, we cannot expect to have any positive result with subjective tests in any of these drugs. We will always have to rely on subjective tests even if the subjective test is not great. Everybody in the field agrees that the Epworth Sleepiness Scale is the most used scale despite the fact that it has a lot of downfall, and we have to remember that when we look at what has been approved and what is being used.

DR. KAWAS: Thank you, Dr. Guilleminault. I think that many people would agree with those comments, but my question to you would be not whether or not the Epworth Scale subjective measurements are good but do we have two randomized, controlled trials that show an improvement in subjective sleepiness.

DR. GUILLEMINAULT: That was my initial question because my understanding is, when the

statistician from the FDA responded, she said that when she did a nonparametric analysis she found out that she had a p value of 0.03. So, my understanding is that she had a significant finding even when she did the reanalysis. That was my understanding of her response.

DR. KAWAS: Would you like to comment, Dr. Yan?

DR. YAN: I am sorry, the previous number is not right. I checked. The number for the nonparametric analysis, the p value was 0.0109.

DR. WOLINSKY: I have a couple of questions first for some information before I ask the real question. For the informational questions perhaps Dr. Mignot could help with. So, the first question I have is if you could enlighten us or re-enlighten us about how many patients that have narcolepsy have had cataplexy as a component symptom. What proportion?

DR. MIGNOT: In most case series it is about 70 percent.

DR. WOLINSKY: The second question is that at least for most of these studies which were done and presented to us since cataplexy was being measured, as is appropriate, the number of

cataplectic attacks was relatively high. I think in these studies it was around 20 cataplectic attacks per week. So, how many of the 70, 75 percent of patients with narcolepsy who have cataplexy have cataplectic attacks at that level?

DR. MIGNOT: I would guess 20 percent.

DR. WOLINSKY: Thank you very much.

DR. MIGNOT: Yes, roughly.

DR. WOLINSKY: And then they would fall down below that level for the remainder of the 55 percent of narcoleptics with cataplectic attacks.

DR. MIGNOT: If you analyze the spread of the number of cataplexy episodes per week, but you have to balance that also with the efficacy of current treatments. A lot of people that currently have cataplexy that is relatively mild just don't want to take the antidepressants because they have so many side effects, especially sexual side effects, dry mouth, all these problems --

DR. WOLINSKY: This is not the question though. So, now the question to Orphan which has really, truly become an orphan drug question, is since all of the studies that have been done have enriched for cataplexy, do we have any data that would suggest that if cataplexy is adequately

controlled or if there is no cataplexy so we don't have to worry about the control of cataplexy there would be any effect of the drug on daytime sleepiness in non-cataplectic narcoleptics?

DR. REARDAN: I think Jed Black wants to make a comment on that.

DR. BLACK: Just a comment on the prevalence of cataplexy in the 70-75 percent of folks with narcolepsy that had cataplexy, the frequency of events -- this is something that Dr. Mignot is not aware of, the cataplexy was subdivided into major events and minor events. About 20 percent or so would have the major events to that level, but when we look at the minor events a far greater percentage of that 70 percent, which may be up to 80, 90 percent of that 70 percent, will have that number of minor effects. Those are not complete attacks where they fall down. In fact, with most narcoleptic patients, they distinguish between the two and they will often only report to the physician the major events. But in the diaries that Orphan had set up all the events are characterized.

DR. WOLINSKY: So, the second question --

DR. BLACK: We have no idea. That is an

excellent question that I think needs to be determined, but in the studies that have been completed that question cannot be answered.

DR. REARDAN: Jed, the only study I can think of maybe is SXB-20 where cataplexy was not an entry criterion and I don't know what the cataplexy incidence in that trial was. Bill is shaking his head -- we didn't record it and we didn't quantitate it.

DR. BLACK: We can't comment on that.

DR. REARDAN: It is true that in most of our studies patients were selected because at entry criteria they had to have a baseline cataplexy.

DR. KAWAS: Dr. Penix?

DR. PENIX: Before we address the two separate indications issue -- and I guess, Dr. Black, I could direct this question to you -- in the GHB-2 study you did look at all cataplexy events, I guess, and then total and partial cataplexy. In the background material, in the separation of the two it appeared that there was no significant difference in any of the three doses of GHB on total or complete cataplexy but your effect was primarily in partial cataplexy. Is that correct?

[No verbal response]

So, my question in that regard is what is the clinical significance of partial cataplexy, and you mentioned that patients frequently do not want treatment for partial cataplexy. So, is this a big problem? I presume that the patients that would perceive a problem would be the ones with the complete cataplexy but there we see no significant difference. So, is there a problem there with that?

DR. BLACK: I think this is a good point, and the difficulty comes in trying to separate the two because it is not sort of a box of partial and a box of complete; it is a gradation, you know, ranging from small partials to large partials and the completes. So, I think this analysis is difficult to perform. Clinically the degree of improvement with traditional anticataplectic medications that we use is similar. So, the reduction in partial -- if that is all that is being seen here and I am not convinced that clinically that is the case -- while the statistical analysis didn't demonstrate a significant difference in the complete cataplexy attacks, clinically there is an improvement in all

the different categories, and it is very substantial in traditional anticataplectic medications as well as with GHB.

DR. PENIX: Could Dr. Mignot comment on the clinical significance of partial cataplexy? Is it a big problem?

DR. MIGNOT: Yes, it is a big problem. In fact, the problem is especially the social aspect of cataplexy, when you have to realize that you are just in the middle of a crowd and are meeting some friends, and you can never tell when it is going to happen. It may happen in very odd circumstances. So, often even the doctors don't know what it is and they just look at it and they wonder why this person is kind of losing slight control and has to sit down. There is also almost a social aspect with fear of cataplexy that can occur at any time, any moment and, yes, it is a very significant problem.

Again, it is a balancing act because the drugs that we use are somewhat effective but they have all these side effects and you just have to choose between two evils. I am pretty sure that, for example, GHB, based on my relatively limited experience, has less side effects than

anticataplectic classical tricyclic antidepressants, and that a lot of patients would prefer to take GHB even for partial cataplexy.

DR. PENIX: The case that you showed of the nine-year child I assume is complete cataplexy --

DR. MIGNOT: Yes.

DR. PENIX: -- but you are also saying that patients with partial cataplexy have a significant impairment of their life.

DR. MIGNOT: Absolutely. But, as Dr. Black mentioned, it is not an "all or none." I mean, most patients, the ones that are complete, have a lot of partial cataplexy. You never know how bad it is going to be. Most of them are small, little attacks, and sometimes they may even be perceived only by the patient. Sometimes the face may melt; the head drops. Sometimes they just have to sit down; sometimes they don't have to sit down. I showed a young kid because it is more dramatic, but you would see the same thing in some of the patients with partial cataplexy occasionally.

DR. BLACK: I am realizing that a definition may be useful here. In general when we were describing patients who documented the partial

versus complete, we told them to think about complete as an episode where they fall to the ground with complete paralysis or where, if they weren't sitting, they would have fallen to the ground with complete paralysis. Otherwise, anything else is partial -- so, slurred speech, head drops, dropping things are the partials, and those become very important for quality of life and daytime performance. Driving, those kinds of things can become a very significant event for partials.

DR. MIGNOT: Yes, one thing I should also emphasize is that in a very large number of series that, for example, have analyzed several hundred patients with narcolepsy and cataplexy, as a mean the large majority of patients have several attacks per day, several attacks per week. Between several attacks per day and several attacks per week, that is generally partial or complete attacks and it is not something that appears just once, you know, every ten years. It is really something that occurs regularly and sometimes totally unexpectedly.

DR. KAWAS: Dr. Falkowski?

DR. FALKOWSKI: That leads me to a

question just for clarification. For the purposes of these clinical trials, were the cataplectic events something that was just perceived by the patient and recorded in a diary, or were they verified by some third party?

DR. REARDAN: These were taken from patient diaries. So, it is patient recorded episodes.

DR. HAGAMAN: I am Dr. Hagaman and I just wanted to address the partial versus the complete cataplectic events. I think that you have to take it on an individual basis. We have patients that come in that are teenagers that have tests in front of them and they have a partial cataplectic event and they drop their pencil; people that cut hair that have scissors in their hands and they drop their scissors. So, even though they have not had a complete event, this has been a very debilitating event in their lives. So, it is a continuum and I think you just have to really look at each person as an individual and what they are doing.

DR. KAWAS: Dr. Dyer?

DR. DYER: How variable in the same patients are the number of cataplectic attacks per week? What is the variance in that?

DR. MIGNOT: We have looked at that quite a bit.

Actually, I did some diaries in a large number of patients with cataplexy. It is really totally unpredictable and that is one of the most scary parts about cataplexy when you have narcolepsy. Of course, if something emotional is going to happen, say a patient is going to go to a wedding, often they will kind of fear that event much more because they think it is very likely that they are going to have cataplexy in front of everyone and, indeed, they may actually have a lot more cataplexy because it is an emotional event.

Still, I have followed, for example, patients and sometimes they may have like 80 for one week and then the following week they may have only three or four. I mean, it can really vary quite a bit. And, one of the main reasons is really that emotion is something that is very variable. In fact, someone mentioned how easy it is to observe cataplexy. It is very difficult to get it on tape because typically the patient come to your office; he really wants to show you what it is but, you know, he is tense and it just will not occur but as soon as he leaves the office and

something happens -- boom, he is going to collapse. So, it is very difficult to predict and it is quite variable.

DR. ROMAN: For Dr. Mignot also, you mentioned that cataplexy probably is the result of what you called dissociated REM. However, if I recall correctly, the polysomnographic analysis has shown that Xyrem actually decreases the amount of REM sleep and increases delta sleep. Would you like to speculate on what could be the mechanism of action to improve the cataleptic component?

DR. MIGNOT: That is a very, very difficult question. One of the difficult questions, of course, is the mode of action of GHB. I have looked into it myself for quite a while because I was trained as a pharmacologist, and it is not clear. There are two camps. Some people think it acts on GHB receptors, specific receptors; others think that it acts through the GABA-B receptors. We know that it has some strong effect on dopamine transmission. If you inject GHB in animals the rate of activity of dopaminergic cells shuts down and dopamine can increase in the brain proportionally to the dose. We have done quite a bit of studies that have shown that the

dopaminergic system is very important to regulate both wakefulness and also cataplexy and the regulation of emotion. I believe it is by changing the balance of the dopaminergic system, that improves cataplexy the following day maybe by increasing dopamine in the brain during the night, but this is highly speculative and a lot more research needs to be done.

The fact that it does not increase REM -- first, it is quite variable because some studies have shown that it does increase REM and this contrasts dramatically with what all hypnotics do. If you take MVN or all the other benzodiazepine-like hypnotics, what they do is actually, rather, reduce slow wave sleep and reduce REM sleep. Xyrem doesn't do that. It actually promotes slow wave sleep and, if anything, would promote REM sleep or doesn't change it. That is still, you know, much more in the right direction of promoting normal sleep, including REM sleep.

The last comment I want to mention is that it is not sufficient -- if you know a lot about narcolepsy, it is not sufficient to just explain narcolepsy as a disorder of REM sleep. Indeed, they have all this transition to REM sleep but they

also have impaired wakefulness per se. For example, if you do MSLTs they don't always go into REM. They will often just fall asleep into normal sleep. So, it is not only REM sleep that is disregulated in narcolepsy, it is also wakefulness and by improving slow wave sleep you presumably also can improve the wake aspect of narcolepsy. My answer may be a little complicated but I would be happy to discuss it in more detail.

DR. KAWAS: Dr. Van Belle?

DR. BLACK: Just another comment on that, the Broughton study showed an increase in REM at a lower dose. The first dose of the SXB-20 that I participated in showed at 4.5 g the first night an increase in REM, which was then followed by a dose-related decrease in REM over time, which is very different from REM suppressant agents where there is a robust, or in fact the largest effect that can often be seen on the first night of administration.

So, we don't know exactly why it is that over time the REM with higher doses is reduced, and why with the first dose, and with the lower doses, as has been demonstrated here with Roger Broughton's work, why the REM is increased. There

has been established sort of a competitive reaction between slow wave sleep and REM sleep. It appears that there may be factors that regulate slow wave sleep that also are important in regulating the appearance, or lack thereof, of REM sleep. It may be that gama hydroxybutyrate is sort of normalizing slow wave activity which then results in a more normal control or regulation of the REM or REM-related events.

DR. KAWAS: Can I ask for my clarification, what dose the company is proposing?

DR. REARDAN: Bill, can you take that question?

DR. HOUGHTON: Yes, the dosage regimen that we are proposing is that patients be started at 4.5 g and then titrated between the range of 3-9 g to clinical efficacy. Although in the strictest mathematical sense the only statistical efficacy in the GHB-2 study was clearly defined at 9 g, that may well represent that the study was too short because in the open-label study that followed, as I showed, the maximum nadir occurred at 8 weeks, and when those patients were followed over the course of 12 months they maintained efficacy across the dose range. Certainly, there is an advantage in

terms of the important side effects to dose titration. In all of the treatment IND protocols and the safety studies the data was generated at between 3-9 g. Now, 80 percent of the patients were maintained between 6 g and 9 g, but there was certainly facility for down-titration from the 4.5 or maintenance there as well.

DR. KAWAS: Thank you. Dr. Van Belle?

DR. VAN BELLE: It seems to me that there is reasonable agreement with respect to efficacy for cataplexy at least between the FDA and the sponsor. So, I would like to get back to the secondary endpoints. I would like to ask a question to the sponsor's statistician, Dr. Trout, as to whether he thinks that multiple comparisons is a problem. Secondly, if multiple comparisons are a problem, how he would adjust.

DR. REARDAN: Do you want to put this in relation to a specific trial or all the trials in general?

DR. VAN BELLE: Well, I bring it up in connection with the analysis of Dr. Mani where he clearly comes to conclusions that differ from yours with respect to the efficacy of some of these secondary endpoints.

DR. TROUT: You know, it is hard to answer that question. I think the way I would answer that is as follows: The GHB-2 analysis, the results that we found and also that were expressed earlier were very strong. So, even with the fact that there is some multiplicity, we also have, remember, some other outcome measures which were related to this particular general area in terms of daytime sleep attacks. So, there were at least two measures that suggested improvement with respect to that particular outcome.

The other second study that has been discussed is the Lammers study, and that study is obviously much smaller. It is obviously a weaker study, and there is some issue with regard to whether the appropriate method of analysis was there. So, I think that is a harder one to address.

Now, there are two kinds of multiplicity going on here, which you are well aware of. One is the multiplicity with regard to the multiple dosing levels and that was accounted for in our analyses. The question that was brought up by Dr. Mani with regard to the multiplicity of secondary endpoints, and I am not a betting man but I think there is

certainly evidence to suggest that daytime sleepiness is being affected possibly. But I don't go to Las Vegas nor Atlantic City.

DR. KAWAS: Actually, while we have Dr. Trout up, I would ask him with regard to excessive sleepiness on the Epworth Scale in the GHB-2 study, while there certainly was a difference in the two groups, there were also major baseline differences in sleepiness for the responders and the non-responders. In fact, those that appeared to respond had a baseline that was better than the improvement in the other group. There was a significant difference. Are you concerned about these and how these might affect the results?

DR. TROUT: There is always concern about baseline differences, and that was attempted to be accounted for in two mechanisms, one, we looked at change from baseline and we also did a covariate adjustment to try to account for that.

DR. KAWAS: Dr. Katz?

DR. KATZ: I would like to ask Dr. Trout a question also. Dr. Yan mentioned that we didn't believe that the data were normally distributed, and when you transformed the data it didn't really help very much. I don't want to get bogged down in

a hyper-arcane discussion about normally distributed data, but when we did that we got a p value for that comparison -- I guess it was the Epworth, of about 0.01 --

DR. MANI: I am sorry, it wasn't the Epworth. You are talking about the Lammers study where you are talking about the frequency --

DR. KATZ: I thought we were talking about GHB-2.

DR. MANI: Oh, sorry, fine.

DR. KATZ: So, if we are right, it takes the p value which was 0.0001 or something like that to 0.01, and then when you get to the multiple comparisons issue it makes it less weak. I agree if you take a p value of 0.001 or 0.0001, no matter what you do to it as far as a multiple comparison, it is still going to be significant. But if it is 0.01 it is a little different story. So, I am just wondering, again without getting into excruciating details, what about this question of the data being normally distributed and not necessarily being improved very much by transforming it? Is there common agreement about that or not?

DR. TROUT: My recollection, and it has been sometime since I have seen the results of the

analysis, is that it suggested that we didn't see a particular problem with the normal distribution as, for example, was the case with cataplexy which was clear. I am not sure if Dr. Yan did a nonparametric covariance analysis or not. I haven't seen those analyses. And, I think the point was made earlier that that would be, I think, an appropriate thing to do in order to account for some potential baseline differences. If she did, then whether it is a reflection of a decreased sensitivity of a nonparametric analysis or whether it is a normal distribution -- I can't answer that without seeing the data. Maybe it was just a standard, nonparametric analysis which might help account for the difference.

[Comment away from microphone; inaudible]

DR. TROUT: No, I know that but Dr. Yan did a nonparametric analysis because she was concerned about the normality, and did look at the log transformation and it didn't have any impact on that, which doesn't surprise me at all.

DR. KAWAS: I would like to ask the sponsor, I mean, there clearly was a dose relationship in terms of the adverse events. Were any other factors looked at that may be related to

the adverse event profile, things like age, even previous psychiatric history, other medications? Whether or not they drank alcohol? Anything?

DR. HOUGHTON: No, we didn't go as far as an alcohol history. Certainly for the major psychiatric, a preexisting history of major psychiatric disease emerged. Major psychiatric disease was actually a protocol exclusionary criterion, but in those that, for instance attempted suicide, post-study it was discovered that they had a previous psychiatric history and in actual fact in one of the patients a previous suicide attempt had been made. There was major depressive disease reported in those, but for those who developed psychosis there was definite recorded preexisting psychiatric history.

In terms of age, we haven't done a breakdown of the database, and in most instances there was not a dose relationship. There were just instances that were mentioned in the presentation. Confusion and sleepwalking suggested a dose relationship. In the GHB-2 protocol which was obviously blinded, there was the association with nausea, vomiting, confusion and enuresis that was definite, but that didn't extend across the whole

study database. So, the relationship with dose is not well defined.

DR. KAWAS: But how about relationship with anything else? For example, were the patients who had confusion more likely to be the elder patients? You might be able to tell I am in aging.

DR. HOUGHTON: I can identify well. Do we have a breakdown of confusion by age? A range would be still useful.

[Slide]

Here is a slide that shows that the distribution of age was between 25 and 73 years, with 67 percent over 50 years of age, but the range is still wide. There is the distribution across doses. Four events at 3 g, 10 at 4.5, 12 at 6 g, 8 events at 7.5, and 13 events at 9 g.

DR. KAWAS: Thank you. Do we have any other questions from the committee? If not, we will move on. Dr. Katz?

DR. KATZ: A quick question, if I heard you correctly, there were 14 events reported as convulsions, but when you went back and looked at that, 13 of them were actually cataplexy. So, presumably cataplexy was a verbatim term. How is it that cataplexy got coded as convulsions?

DR. REARDAN: The COSTART dictionary puts cataplexy in as a convulsion. It is a definition. Convulsion has ten different terminologies, verbatim events, and they all code up to convulsion.

DR. WOLINSKY: Along those lines, how come there were only that few number of convulsions when we were studying cataplexy in the trial? I mean, I don't know that it is easy to explain this in both sides of one's mouth.

DR. HOUGHTON: No, and we are not trying to. If there was a cataplexy event that occurred of a severity to be seen as unusual for that patient, and the patient volunteered it as an event, then it was recorded as an adverse event. Or, there may have been injury related to the cataplexy events. We do have representation in the database. I can recall absolutely a fractured ankle in the washout study. So, there were traumatic events associated with a major cataplexy event that would have been of sufficient impression on the patient to report as a separate event.

DR. WOLINSKY: But then the event would not have been withdrawal from the primary measure of efficacy even though it was also registered as

an adverse event?

DR. HOUGHTON: I am sorry?

DR. WOLINSKY: Was it still counted as an event in the measure of efficacy if it was also shifted to be counted as an adverse event?

DR. REARDAN: Yes, the patient diaries recorded cataplexy. If they record cataplexy as an event itself, that was part of the efficacy outcome. It wasn't necessarily an adverse event. If they had an adverse event -- fall and break an ankle, cataplexy is coded as part of that adverse event. It is the cause of the adverse event and so it shows up in the database.

DR. KAWAS: Dr. Simpson?

DR. SIMPSON: I have two questions. One really was just a clarification of this business about the sleepiness. I think we have all agreed that there has to be some adjustment for multiple comparisons on the sleepiness index, and the GHB-2 study, even if you make an adjustment, there are certainly some of the indices about sleepiness which seem to be significant. But coming back to the Lammers study, have we established whether or not, once we have made an adjustment, we have any significance there or not? Because that is the

pivotal trial, isn't it, because we need two?

DR. REARDAN: Remember that the Lammers study was a very small trial, 24 patients. Daytime sleepiness was a secondary endpoint in that study, and I forget the p value. Maybe Dr. Yan or Dr. Katz could comment. I don't think any formal study of multiple analysis was done, except maybe by Dr. Yan --

DR. YAN: No.

DR. REARDAN: -- and I think she needs to comment on that.

DR. YAN: For Lammers study there was no prespecified analysis, except the Wilcoxon assigned rank test. It was across the study and we considered it not very appropriate, and for a secondary analysis none of the statistical analyses were specified. The problem with this Lammers study is that if you use different statistical analyses which are considered appropriate, you get a very different result. Some could be less than 0.05 and some ranged to something like 0.2. So, the results are not consistent and we don't have a reliable method to see which one we could consider.

DR. REARDAN: We don't disagree with that. I mean, the problem with Lammers is that it was a

one-sentence statement about how he was going to analyze it, and it was an inappropriate statistical analysis for a crossover study. So, that creates issues about not having a prospective statistical plan appropriate for the study. But even in that initial Wilcoxon analysis the daytime sleepiness was statistically significant. It was not corrected for multiple analyses.

DR. KAWAS: Dr. Simpson?

DR. SIMPSON: I just have another question that I wondered if you could clarify. In a lot of these studies you talk about an intent-to-treat analysis, but when I read it I wasn't clear whether or not that meant the patients that were randomized were actually included always in the analysis or not.

DR. REARDAN: Yes, the intent-to-treat would include every patient who received drug. Is that correct?

DR. TROUT: Yes, every patient who received at least one dose.

DR. SIMPSON: So, how did you then deal with the patients who dropped out?

DR. TROUT: In the GHB-2 analysis we selected an endpoint. So, in order for the patient

to be included in that analysis there had to be at least one post-baseline measure of cataplexy or sleepiness, or whichever outcome you want. So, it was an endpoint analysis that was done in order to accommodate that.

DR. KAWAS: It looks like we are completely behind schedule and we will have a very late lunch, I will warn everyone. The FDA's invited speakers on risk management issues is the next component of this discussion. The first speaker is going to be Dr. Carol Falkowski, of the Hazelden Foundation, in Minnesota, who will be speaking on the epidemiology of GHB abuse issues.

FDA Invited Speakers on Risk Management Issues

Epidemiology of GHB Abuse Issues

DR. FALKOWSKI: Hello. Good morning, almost afternoon.

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This is the title of my talk, GHB Abuse in the United States. I am Director of Research Communications at the Hazelden Foundation. I have been a member of the National Institute on Drug Abuse's Community Epidemiology Work Group since 1986. I am author of a book, called, "Dangerous Drugs: An Easy-to-Use Reference for Parents and

Professionals." What is missing from this overhead is that I served on the Drug Abuse Advisory Committee for the FDA from 1995 through 1999.

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In the very short time that I have, I am going to try and just hit the big points about what we know about the abuse of GHB in the United States, starting off with measuring drug abuse. There are a number of things that are thought to bear when we talk about measuring something as complex and multi-dimensional as drug abuse. This includes population surveys. It includes hospital emergency room episodes; medical examiner data; addiction treatment data; law enforcement data, as well as ethnographic studies that look at specific populations of users that are more anthropological and ethnographic in nature.

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I also want to make the point that all data systems have limitations, and this is particularly true in the case of new drugs of abuse. For example, if we are talking about GHB and trying to measure the number of patients who have presented to addiction treatment centers across the country with GHB as their primary drug

of abuse, it is now the case that it is often grouped in a category of drugs called sedative hypnotics. It is not its own line item. So, in preparation for a meeting like this it is very hard to get an accurate count of the extent to which GHB itself is the presenting drug of abuse.

Similarly, surveys that are conducted -- we have not added GHB to the National Household Survey or the Monitoring the Future Survey, although to the Monitoring the Future Survey that looks at drug use among 8th, 10th and 12th graders ecstasy, another club drug, has been added.

Also, in terms of law enforcement indicators, there is no field test for GHB so it is hard to also get that indication of it as well.

In addition, new methods of abuse are hard to track. I recall, in 1986, when we started at the national level wanting to track crack cocaine, we knew about how to track cocaine but, all of a sudden, we were looking at it by a different route of administration. So, it was a challenge to all of us to start switching our data systems just to measure crack instead of cocaine, to make that distinction.

Existing data systems are slow to respond,

and there is a system-wide learning curve when a new drug of abuse appears on the scene. That means it is a learning curve in terms of emergency room personnel, treatment providers, law enforcement, as well as prevention agencies, and that is why we rely on a lot of the scientific literature put out, particularly in emergency medicine, to inform the field about emerging drugs of abuse and how people present with those problems.

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My background in this has been as part of the Community Epidemiology Work Group. This is a group of drug abuse researchers from twenty cities in the country that has been convened by the National Institute on Drug Abuse since 1976. This model of drug abuse epidemiology has also been adapted in different parts of the world. There is a similar group in Europe, in Canada, Mexico and Asian cities.

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The Community Epidemiology Work Group is an early warning epidemiological surveillance network that detects new drugs of abuse, patterns of use and populations at risk.

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It involves researchers looking at the same data from different geographic areas and in this case, as I mentioned, there are people like me in twenty cities in the country who write quantitative reports on drug abuse twice annually, and we are convened by the National Institute on Drug Abuse twice a year.

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Having done this and written over twenty reports on drug abuse trends in my city and met with my colleagues, it has given me a sort of broad-based perspective on how emerging drugs are measured and how we get a handle on them. But everyone looks at medical examiner data. We look at the data from the Drug Abuse Warning Network, which is data from a representative sample of nine federal short-stay hospitals with 24-hour emergency rooms, and that is conducted in 21 cities, as well as some other areas of the country.

We also look at treatment data, law enforcement data and price, purity, trafficking and the sale of drugs, as well as supplemental research data and information from multiple sources.

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I want to start my introduction to GHB by

telling you about the abuse of a group of drugs that are called club drugs. That is really the first time in a long time we have had a name like club drugs applied to drugs because they are used in a particular setting. That is why they came to be called club drugs. It is a mixed category of drugs. It includes stimulant drugs as well as depressant drugs that are used in nightclub settings. GHB is also known in these settings as liquid X, gamma, G, easy lay, Georgia Home Boy or great hormones at bedtime. MDMA or 3,4 methylene dioxide methamphetamine is ecstasy, e or x. Ketamine is known as special K. It is a veterinary anesthetic, a dissociative drug similar in effects to PCP. Flunitrazepam, Rohypnol is a long-acting benzodiazepine, which was dubbed the original date rape drug which is a drug not approved for medical use in this country; methamphetamine and LSD.

If there is one point to make about club drugs as a term, one thing that has emerged is the fact that clearly these drugs are not limited to club settings and I will be talking to that in a moment. It is not just clubs where they are used.

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To give you a little slice of the

progression of GHB and how it came on the CEWG radar screen, it was first mentioned in 1990 through a poison information center from my colleague in Miami. Then, from 1990 to 1994 it appeared in the Miami and the New York city reports. In 1996 it appeared in 6 other cities, and by the year 2000 most cities in this 21-city work group were reporting GHB. It reports 23 deaths in the 20 CEWG cities, and I refer you to a handout that I prepared that sort of gives the chronology of how my colleagues describe the growing abuse of GHB in their cities.

[Slide]

Now, in terms of user typologies, they tend to be young adolescents through adulthood. There is really no age group but when we look at population surveys in this country of who are drug abusers, by and large the biggest bulk of drug abusers are people who are under the age of 35.

The motive for use is multiple. It includes not only intoxication, but also people seeking intoxication effects in the absence of alcohol. I have had people describe it to me as it gives them the effects of alcohol without having to waste that time drinking alcohol. This is by young

people who haven't developed the taste.

It is also used by weight lifters and body builders for its alleged anabolic effects. It is also marketed in nutritional supplements to promote better sex, better sleep and some people take it to counter the effects of other club drugs. One of the characteristics of drug abuse in nightclubs that has come up over the past year is the fact that people seem to have the impression that if you take just a little bit of this and a little bit of that nothing can really hurt you in a club setting. So, you might take a little bit of ecstasy to get you going, with a little bit of cocaine to keep you there, and maybe a little bit of heroin to take the edge off. This sort of mixing and matching is also part of the user typology.

The settings it is used in are nightclubs, raves, parties, but also in homes, in health clubs, gyms and other settings. The sources of it come from health food stores, mail order kits, the Internet or at these clubs where it is being used by the capful. Sometimes at these clubs, because ecstasy dehydrates you, people have a lot of water bottles and it is not unusual to have a water bottle that may have GHB mixed in it, and for ten

bucks someone can get a swig of it. This makes it very imprecise dosing, as you can imagine.

[Slide]

In terms of deaths, in terms of the consequences of use -- there is a huge bullet missing from this slide, which I will get to. So, if everybody wants to find their slides and write a bullet in it, I would appreciate it. Deaths -- there have been 71 documented deaths, according to the Drug Enforcement Administration, through November of last year. Again, the problem is that because it is a new drug of abuse people don't know. You know, you have to know what you are looking for to be able to find something and this has clearly been the case in trying to document GHB deaths. It is a huge issue and I hope we get enlightened on that this afternoon.

Also, there have been adverse medical reactions, not only people who come into emergency rooms, but the countless people, which is quite hard to quantify, who have episodes but never get emergency room treatment for it. But there have been medical reactions, adverse ones.

Dependence -- there has been a reported increase in people presenting to addiction

treatment centers with GHB as their primary substance of abuse, and an increase in the reported addiction to GHB by those who may not make it to treatment programs.

I work at the Hazelden Foundation. We are based in Center City, Minnesota, with campuses in Chicago, New York City and West Palm Beach. There were 5 patients in 1999 who had a history of GHB abuse, and that had grown to 39 in the year 2000 and we are just one treatment center.

Finally, the missing bullet on here is drug rape. One thing we have seen in this country since the early 1990's is the use of drugs, this predatory use of drugs where you administer drugs to people without their knowledge for the purpose of disabling them to commit crime on them. The first drug that came to this sort of notoriety was Rohypnol, but now we are in a situation where GHB is often used in drug-induced rape. In fact, several years ago when President Clinton signed the federal date-rape law, the Samantha Reid and Hilary Farris Date Rape Act, that was in response to two cases of drug rape that were not related to Rohypnol but to GHB. So, that bullet should be up there, drug rape.

Also, another bullet would include the trafficking, sale and manufacture, the law enforcement consequences.

[Slide]

Let's look at hospital emergency room episodes of GHB. This looks at them from 1994 through 1999. You can see the increase in hospital emergency department mentions of GHB. Mentions is sort of unusual term for people who aren't familiar with the Drug Abuse Warning Network, and it quite literally means, in a retrospective review of patient records, that they find a mention of GHB. Sometimes it is the sole drug that precipitated the medical emergency and sometimes it is used in combination with other drugs. For every drug abuse episode in the Drug Abuse Warning Network there can be the mention of 4 drugs and alcohol, but when alcohol is used in combination with other drugs; it is not an alcohol tracking system.

[Slide]

So, this is what it looks like through 1999. This looks at it by half year increments. You can see this takes us into the year 2000 and we have the first half of the year 2000.

I want to go back to just my opening

remarks about club drug abuse. I think in the general population when we think of club drugs, you know, what we hear about, what everybody is talking about, what seems to be in U.S. News and World Report, in Newsweek and Time Magazine is ecstasy.

[Slide]

This is from exactly one year ago. This is Time Magazine from June 5, 2000. It talks about ecstasy. For many folks, club drugs -- you think ecstasy.

[Slide]

This was, I believe, from Time magazine as well. You see the water bottle there. If you didn't see Time magazine, you may have seen The New York Times Sunday magazine insert. This is from January of this year, talking again about ecstasy. This is from January 2001.

So, since it is in the same category of drug, I think it is relevant to look at how GHB emergency room episodes compare with those of ecstasy.

[Slide]

Ecstasy, or MDMA, is in the pink and GHB is in blue. You can see in the first half of the year 2000 that GHB hospital emergency episodes have

surpassed those of ecstasy.

[Slide]

Efforts to control GHB -- a number of states have done things to try to control GHB abuse in their states. This is sort of a listing of the scheduling of it in various different states. It was added, as you know from the materials the committee received, to the Federal Control Substance Act.

[Slide]

Finally in conclusion, GHB is a significant, growing drug of abuse. We have seen rapid growth in the adverse medical consequences related to GHB since 1999 and, in fact, hospital emergency mentions of GHB now surpass those of ecstasy or MDMA. We have seen rapid growth in adverse medical reactions despite not only federal scheduling but the scheduling in numerous states. We have multiple user typologies. This is not a substance that is sought after simply by people at parties and raves. These products that contain GHB as well as its precursor drugs, GBL and 1,4-BD, are sought after by people who believe the claims on these nutritional supplements and take them for promoting muscle growth, for sleep; and take them

for better sex, as well, and as I said, use it in sort of predatory way. Dependence is clearly possible.

So in closing, here we have a drug with an established widespread abuse record. With GHB we needn't talk about abuse potential. With GHB we have abuse reality. We have a decade of GHB abuse in this country; a decade of deaths and hospital emergency room episodes and dependence. We have escalating abuse of GHB in spite of recent efforts to control it and, yes, people acquire this drug and its precursors in many ways. But make no mistake, the effects being sought are the GHB effects. The chemical agent in the body that is producing these effects is GHB, and this undisputable fact is entirely relevant to our discussions today.

I have to take issue with the statement from the sponsor that says Xyrem is not the problem. If Xyrem equals GHB, then I believe it is a problem. This drug, if approved, will exist outside the confines of this room. Patients will use it outside the confines of clinical trials. In America, in 2001 we have a serious, significant and growing problem with GHB abuse in this country, and

it just so happens that this coincides with Orphan Medical seeking approval for this drug.

This drug already has avid followers, and there is no reason to assume that another source of GHB would not be sought after by these folks, and I think we need to bear that in mind throughout our discussions. Thank you.

DR. KAWAS: Dr. Falkowski, can I ask you one question? With regards to the emergency department data for GHB, I recognize the difficulties of all of this kind of data but, for example, MDMA is not infrequently the only drug and when they go to the emergency room that is clearly because of the MDMA. Can you give us any kind of quantification or semi-quantification? You mentioned that sometimes GHB is the only drug.

DR. FALKOWSKI: The question was how often is GHB used in combination, and let me find that.

DR. KAWAS: For the emergency room data.

DR. FALKOWSKI: Yes, that is what I am looking for. I have it right here. It is 70 percent of the time. Like many other drugs, GHB episodes involve drugs other than GHB as well.

I would also like to add that I believe these hospital emergency room episodes

underestimate GHB because drugs that are used in a predatory way, that are administered to people without their knowledge are not DAWN reportable. So, if someone comes to the emergency room and says I believe somebody gave me something and it is making me sick, that is not a DAWN reportable thing. That is being addressed by the Substance Abuse and Mental Health Services Administration. But what that means is that people who are drugged with any sort of drug are not picked up by this particular reporting system.

DR. KAWAS: And, what are the most common drugs or classes of drugs that go along with GHB when people take them in combination? What are the favorites?

DR. FALKOWSKI: It is probably ecstasy, MDMA, and to a lesser extent ketamine and also alcohol.

DR. SANNERUD: I have some data on the DAWN statistics too. When drugs are used in combination, 50 percent alcohol, 11 percent stimulants, 8 percent marijuana, poly drugs, hallucinogens and sedatives and all these are at least at 3 and 2 percent each.

DR. KAWAS: Dr. Dyer, I believe you are

our next speaker.

DR. KATZ: Claudia, if I could just ask a question, and I don't know who best to direct it, but you said 70 percent of the time the reports are of GHB in association with something else. So, presumably 30 percent of the time it is the sole drug. I have a sort of methadologic question. How reliable would you say that information is, just in general? What is sort of the nature of the information that is recorded and from whom that allows us to conclude that, in fact, GHB is the only drug that was taken? Who reports that, and how reliable are those reports, just as a general rule? Number one.

Number two, how many of the deaths and very serious adverse events were associated with GHB use alone?

DR. FALKOWSKI: I believe you could address the reliability of DAWN. You are a DAWN reporter. Again, regarding the deaths, you know, the Drug Abuse Warning Network also collects data from medical examiners, but the people in the 20-city work group of mine rely more often on getting data directly from the medical examiners, first because it is more timely and also because it

casts a better net. It captures situations that are not only due to drug-related toxicity but also ones where the use of drugs were considered by the medical examiner to be significant contributing factors to the death. So, that is what I can say about deaths.

Also, I have a table, if you are interested, that I could make available that shows exactly DAWN emergency room data for 1999 and what were the co-ingestants.

DR. KAWAS: Our next speaker is Dr. Jo Ellen Dyer, from the California Poison Control System at UCSF, speaking on adverse medical effects with GHB.

Adverse Medical Effects with GHB

DR. DYER: Thank you and good afternoon.

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In 1990 I identified and made the first reports on GHB abuse from over-the-counter sales of GHB. Over the next 11 years I have been following GHB. I have an interest in it and I have been reporting on the progress, the adverse effects and the trends in use.

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This is a description of the California

Poison Control System data of GHB reports to our center. We logged these reports over 10 years. The first years are when the San Francisco center stood alone so it is a population base of 7 or 8 million. We became a system in '97 so we have 4 years of data for the entire state.

We are a medical toxicology consult service, so we are not a required or mandatory reporting center. So, this reflects just the tip of the iceberg of use and abuse and adverse effects that are out there.

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In our experience GHB produces a profound coma. This has been known for over 40 years, starting out in surgical anesthetic studies where it was evaluated as an anesthetic and now through numerous occurrences of coma in users through this widespread public use, where accidental overdoses are occurring because of the narrow and variable therapeutic index for this drug.

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Looking at 5 studies, anesthetic studies that cover over 700 patients -- there are many other studies; I just picked a small set of them -- you see the effects of GHB in a controlled

situation. GHB causes unconsciousness and a profound coma. This is what is intended with an anesthetic. The respiratory effects that are seen are Cheyne-stokes respiration. There were aspirations. There was a case of unexplained pulmonary edema. In many of these cases the patients are intubated and the airway is attended to. If their airway was left to chance in these situations, it would be compromised. They lose their airway protective reflexes. They have no gag. So, with the high incidence of vomiting, about 30 percent in these studies, combined with the loss of gag, it is not difficult to see how aspiration is going to occur.

There are cardiovascular effects, like bradycardia, and then there are isolated incidences where blood pressure rose up to 30-60 mmHg for unexplained reasons really. There is myoclonus that we see. There is an emergence delirium, confusion. There are also secretions like salivation, vomiting, incontinence and diaphoresis.

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If I look at 16 reports that cover 175 cases of adverse events where GHB was in public use, you see these same physiologic responses to

GHB. You have profound coma. They develop a mild respiratory acidosis; bradycardia; myoclonus; confusion; emergence delirium; and then the secretions. This raises doubts for safety of use among a generalized public population.

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If we look at a closer group where we did a study in our emergency department, and this is the San Francisco County emergency room that sees over 200 patients a day -- we looked at GHB overdoses that we had over 3 years. This is just a retrospective descriptive study where we were trying to get a handle on what is going on. We found that of those cases, about 33 percent had no co-ingestion. This was documented by either toxicology or patient report. Those patients came in, a quarter of them, with Glasgow Coma Score of 3. So, they were profoundly comatose and 33 percent of them had coma scores between 4-8. The coma lasted 15 minutes to 6 hours.

Again, a third of the patients had these same symptoms, bradycardia, respiratory acidosis, hypothermia, vomiting. We saw hypotension in about 11 percent. Those cases were primarily cases where alcohol was co-ingested. Then, on emergence these

patients are difficult to manage. They can have an emergence delirium which includes combative, agitated behavior.

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Because of that evidence and wanting to focus in closer and get some GHB levels to find out if that is truly what we were looking at, we did a prospective study over 6 months, looking at 15 cases of GHB overdose, and 73 percent of those came in with a Glasgow Coma Score of 3. Our intent was to document the presence of GHB, to detect the co-ingestants and what they were or if there were none, and then to verify that our ability to predict an overdose is truly GHB by the toxidrome that we are using, whether or not that was effective.

So, all of these 15 cases did have GHB that was measurable. They were young, ages 20-39; 73 percent were male. The study inclusion criteria were patients presenting with Glasgow Coma Scores less than 8 and 73 percent of these patients had a Glasgow Coma Score less than 3.

In 5 of the cases there were no other drugs or alcohol detected. The GCS was 3 in 80 percent of those cases. So, profound coma from

accidental overdose; no other obvious cause.

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It is clear to us that there is really substantial evidence that GHB causes coma. Coma is life-threatening, and these deaths are occurring from accident or injury and from respiratory compromise. We are seeing that through aspiration; through apnea; through positional asphyxia -- these are profoundly comatose people, they can't even move to open their airway -- and through pulmonary edema.

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So, I have reviewed 20 GHB related fatalities where I had autopsy reports. I just sent letters to medical examiners asking for their reports. In these cases, the ages ranged from 15 to 46 years. Three-quarters of them were male; 20 percent of them had no concurrent ingestions. If we look at those that had co-ingestants, the 80 percent. We will see that many of these substances are legal commonly ingested things. Tylenol was one of them; caffeine; alcohol. The levels of alcohol went up to 0.17 percent. The legal limit for driving ranges from 0.08 to 0.1. So, most of these cases were in the lower range, right around

the legal limit of driving, saying that they had maybe one or two drinks and none of these would reach an alcohol level that would cause coma.

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The societal costs that were seen from GHB abuse, there are many driving under the influence arrests that have occurred with GHB. There were a whole lot that were not recognized until GHB testing became available and now they are being recognized. I don't go out really and collect this data but there are two vehicular manslaughter, I guess they would call it, cases where a person driving under the influence of GHB has hit and killed another individual. One of those was in '96 and one was in 2000.

Another societal cost is the assaults where the victim is under the influence of GHB given to them or slipped to them by the assailant. It is common enough that they have a term for it. It is called being "scooped" by GHB. The assailant then attacks the victim while they are unconscious or amnestic to the effects of the drug, making prosecution and even reporting of these very, very difficult.

These are 4 cases. There are others. But

in these GHB was clearly documented as the cause. The first was a woman who was drugged and assaulted by her boss as they went out with a group of colleagues after work. She had GHB in her urine. There were 10 victims of some DJs in Los Angeles that were slipping GHB into drinks and then assaulting them. There was a 24-year old that was eventually prosecuted more for trafficking drugs after a woman had reported an assault to them and, in kind of the bargaining, he admitted, yes, he had drugged her twice with GHB and she has no memory of the first event at all. Nothing. The last is two 15-year old females who were unconscious at a party. One was hospitalized and one of these girls died.

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We also see addiction as another burden from GHB abuse. We are currently seeing one to two cases a month at our poison center, and this is eight cases that I collected. The age range is young, 22-38, again three-quarters male. The pattern just continues through all these of the demographics of who is using. Of these, 63 percent started taking GHB for body building. They had what they thought was kind of a legitimate use of

this dietary supplement. In this group, 88 percent of them were employed or students. These were functional members of society that have had trouble now because of this drug. These are not people that really had drug-seeking behavior. The onset of symptoms we see within 1-6 hours. It progresses over a couple of days. The duration is 5-15 days.

Now, these are often unrecognized by healthcare professionals when they present for treatment. GHB abuse addiction is not really very well known out there. These are severe neuropsychiatric symptoms with autonomic instability that we see. I have had physicians who have treated many, many cases of severe alcohol withdrawal that have called me up and said, my gosh, I am impressed; I am so impressed by this withdrawal symptom. The patients become agitated, combative, delirious. They are hallucinating. They require sedation, a milligram a minute of IV Ativan has been used over a few hours to gain control. They require four-point leather restraints and intensive care. One of the patients in this series died while being hospitalized for GHB withdrawal.

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Substantial and compelling evidence from case reports of accidental poisoning and from toxicology supported adverse events really shows us that these effects are due to GHB. It is not some contaminant or something else that is causing these. And, there is an insufficient or no safety margin between the effective level of the therapeutic dose of these drugs that these people are taking and the dose that causes these effects. As you can see from the sponsor's study, the adverse effects that they are reporting are very similar. The confusion, the nausea, the vomiting are very similar to the things that we are seeing.

One physician, Dr. Gallamberti from Italy, who is doing therapeutic use of GHB withdrawal states talks about a 15 percent problematic GHB use among his population. This can be dose escalation. This can be GHB overdoses up to 10 times a year, or GHB dependence.

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This slide just looks at the kinetics to illustrate that there is really a very narrow therapeutic index with this drug and there is a lot of variability. The pharmacokinetics of GHB are capacity-limited absorption, capacity-limited

elimination. The coefficient of variation of some of these parameters is 50 percent. There is a lot of variation and we don't really know what the consequence in different populations and different people of these really variable kinetics is going to be, or why they are so variable. You are used to using phenytoin. It has capacity-limited elimination. We know that when you are bumping the dose of a patient on phenytoin you have to be really careful because they can exponentially increase their level. Well, the same thing happens with GHB and we don't know where that is yet. There is not enough experience. And, with phenytoin the absorption is pretty good. We know the bioavailability of IV phenytoin and oral phenytoin. Here, I don't think it is so constant. It really changes with food and there is a capacity-limited absorption that is going to vary between patients. So, this is a really difficult drug to control, particularly orally on an outpatient basis.

[Slide]

So, what is the current level of GHB abuse that is out there? We really don't know. If we wanted to project from one survey that was done,

Dr. Miotto, a UCLA physician that works addiction medicine did a 45-minute structured interview with 42 GHB users. Among that group, 69 percent had admitted that they had lost consciousness, had periods of consciousness laps from minutes to hours. There was variability in the amnesia dependent upon how often people used. Twenty-eight percent admitted having an overdose; 9 percent had been to the emergency department for an overdose.

Now, there is an interesting misconception here where they don't consider the loss of consciousness to be an overdose, and people overdose and when they are in a profound coma are not taken to the emergency department. So, there are really some problems there, and this gives us an example of the kind of under-reporting that is out there.

If we try and extrapolate from the amount of drug that we are seeing marketed illicitly, this is just one arrest in Marin County, a small county north of San Francisco, where they had 207 L of butanediol. The average street dose varies around 2 g. If you look at that, that is 103,500 doses in one capture at one house, and there are many, many of these. There are lists of different amounts

that have been busted all over.

Then there is the problem that Carol has already talked about, surveying and policing the issues of this type of new drug abuse. There is no systematic method in place for data collection on this.

There is rapid metabolism of the drug. It clears from the blood in within about 6 hours; it clears from the urine within about 12 hours. We can't test these people and find it. When we are trying to get evidence in a drug assault case, it is gone. It is really difficult to detect. And, should we increase our level of detection to the very, very minute nanogram kind of range, then we are going to start running into the biological background so we aren't even going to be able to do that if we increase our ability to detect. There are also very poor assays currently out there. None of the hospitals have an assay for this, and none of the law enforcement has a field kit for it. So, it has to be taken into a lab and specifically run through a complicated GC mass spec procedure to get a level out, which is expensive.

The current documentation clearly grossly underestimates the amount of use that is out there.

And, it is very clear that there is a little, if any, safety margin with GHB use in the therapeutic doses that are proposed. GHB is a very potent new drug of abuse. It has been around 10 years. We thought it was going to come and go as a fad, it hasn't and it is not going to. The use is still increasing.

There is a very high acute toxicity in accidental overdose -- coma, bradycardia, myoclonus, vomiting, aspiration -- we are seeing a lot of it, and it has very high abuse and addiction potential. So, I think that we have to be very careful and it is very difficult to try and minimize these potential risks, the risks of having it get out into the drug abusing population but also among patients that we are going to be giving this drug to take at home. At the poison center, every night at bedtime, 9 to 11 o'clock I am called by people that say, oh, I'm sorry, I accidentally took a double dose of my medication. What should I do? In this case, they are all going to go to the emergency room. There is really not a margin of safety with this drug. Thanks.

DR. KAWAS: Thank you, Dr. Dyer. The next presentation is from the sponsor, presentation on

risk management and abuse liability, Dr. Bob Balster, from the Medical College of Virginia.

DR. REARDAN: Yes, I would like to now introduce Dr. Balster who will present his views with respect to abuse liability of Xyrem and GHB. Dr. Balster is a previous chair of the FDA Drug Abuse Advisory Committee and a widely published abuse pharmacologist from the Medical College of Virginia. He is editor and chief of a leading addiction journal, Drug and Alcohol Dependence, and a past president of the College on Problems of Drug Abuse.

Sponsor Presentation on Risk Management and Abuse Liability

DR. BALSTER: Thank you very much, Dayton. Good morning or good afternoon, I guess it is now.

[Slide]

Well, as you have just heard, the development of Xyrem as a medication has taken place in a context of a national epidemic of the abuse of its constituent GHB, and also the abuse of a number of GHB-related drugs that I will tell you about.

As Dr. Houghton told you, Orphan is very well aware of this problem and has consulted many

drug abuse experts to try to understand the problem better. My own analysis of this situation is that Xyrem has certainly not contributed to the problem that exists today with the abuse of this class of compounds. I guess where I may disagree a bit is that I am pretty convinced that Xyrem is not going to be a player in this over the long term.

I think in order to understand and make an appropriate public health response to this situation, you need to know a little bit about what some of the causes are of this GHB abuse problem.

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So, I hope to make two points in this presentation. The first point is that I believe that the recent abuse of GHB-like substances probably reflects a ready availability more than their inherent pharmacological propensity for abuse.

I think I will make this point by first off reviewing for you the incredible availability of these compounds, and then also review very quickly scientific studies that have been done on the abuse liability of GHB as it is compared to other drugs of abuse you might be familiar with. Secondly, I believe that Xyrem, if approved for

medical use, will not contribute to the public health problem of the abuse of these GHB-like substances in any significant way.

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Before we continue, it is very important to know the cast of characters here. I think next to the federal government, the next worst developer of abbreviations is a drug abuse research community, with MDMA, and PCP, and GHB, and BD -- it must be hard to kind of keep track of the players but, of course, the drug we are talking about here is GHB, gamma hydroxybutyrate. But there are a bunch of other drugs that are basically part of this national drug abuse problem.

You have heard a little bit about them, but these precursors, gamma butyrolactone or GBL, 1,4 butanediol or 1,4-BD are precursor compounds that, if obtained, can be easily and readily converted into GHB. They also can be consumed directly because they are metabolized by the body into GHB. So, they themselves are drugs of abuse like GHB. Then there are others that are also available.

Now, of all these chemicals only GHB is actually a scheduled drug. It is Schedule I under

the Controlled Substances Act for the abusable versions, GHB; Schedule III for an approved medical product. So, only GHB is scheduled. Now, GBL is what is called listed so its availability is diminished. These others are still freely available without any drug abuse controls.

[Slide]

You have heard a lot about GHB abuse but I am pretty convinced that what we are seeing here is something that has resulted from an amazing situation of the availability of these compounds. To remind you, GHB was available legally and legitimately through health food stores up through 1990 when you could buy it anywhere, and the abuse problem with this drug began during that period of time.

Then through that time and afterwards GHB could be obtained through the Internet. There was an amazing number of sites set up to sell GHB. Then, as GHB became less easy to get because Internet sources dried up, the Internet sources were selling the precursors, etc., etc. I will show you some data a little bit more, but these precursors are not going to disappear any time soon from public availability. Now that the

availability of GHB has been restricted by the federal scheduling actions and actions by the FDA, people can now purchase the precursors and make their own GHB. Essentially anyone can do that. It is a very simple thing and the recipes are right there on the web. As I said before, they themselves are widely abused. So, we have a class of chemicals here that are really basically part of what has been referred to as a GHB abuse problem, but it is really an abuse of a class of drugs, and you saw some evidence on that.

[Slide]

At this point I want to review the scientific literature on the laboratory studies of the abuse potential of GHB. You may wonder why I would want to do that, I mean, why would I want to review literature on abuse potential when the reality of GHB abuse is clear to us from epidemiological data that Dr. Falkowski mentioned and clinical data. The reason to do this is to try to understand what the basis for this is, and to know whether or not this wide abuse is due to some features of this incredible availability, or whether the drug has sort of the inherent pharmacological desirability that you would

associate with a really dangerous drug like cocaine or heroin where, no matter how many billions of dollar we throw at the problem, we are getting nowhere with it, or does GHB represent a drug which is less desirable or has less propensity for use.

[Slide]

Just to remind you, there is a well-established science of abuse liability evaluation, and it is used in evaluating new compounds that are under development. It is useful in making decisions about drug abuse control, and data such as these are used widely by the FDA for making regulatory decisions. All of these data are reviewed in your packages, but just to quickly tell you, first off, GHB is a unique drug. It is not just another depressant drug like barbiturates or even benzodiazepines that have its own receptor and its own characteristics.

In studies which are called drug discrimination studies, which allow you in a way to compare unknown drugs to known drugs of abuse, again, GHB lacks equivalence to these classical depressants like barbiturates or any other classes of drugs to which it has been directly compared.

In self-administration studies -- these

are laboratory studies where you can actually measure what we call the reinforcing effects of the euphorigenic potential of these drugs -- actually in this particular class of studies GHB has very weak reinforcing effects. It is difficult to obtain them in laboratory studies and there have been a number of those. We did one of these ourselves in our laboratory and we essentially found no evidence of GHB self-administration under conditions where we reliably get self-administration of cocaine, heroin, barbiturates, etc., etc.

The case of physical dependence is a little bit more complicated. You heard from Dr. Dyer about the fact that abusers can develop dependence and show withdrawal signs, and there is no question about that. These people are taking maybe 10 or more times the therapeutic dose. We are talking about 70, 80, 100 grams a day, and they take them every 3 hours or so because they have to maintain the blood level. Yes, in those cases you get dependence, but in patients receiving Xyrem, where they are getting it in lower doses and they are taking it only in the evening, as you have heard from the reports, there have not been

significant problems of dependence. So, yes, it can occur in abusers but it isn't really an issue in patients. Importantly, animal studies, for example, where you try to show the dependence of GHB and compare it, for example, to barbiturates, it is not easy to develop a model for GHB dependence in animal studies because it has less inherent dependence producing properties than these other drugs.

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So, my conclusion when I reviewed the literature on the scientific studies of GHB, when I was asked to do that, I basically thought it looked a lot like what I would say is a Schedule IV drug. Schedule IV drugs, you remember, are benzodiazepines and chloral hydrate and drugs of this type, and that is sort where it fit. It isn't like cocaine. It isn't like heroin. In fact, that analysis of looking at the data has been made by others with very much the same recommendation as mine, that is, it sort of fits pharmacologically with Schedule IV.

For example, the WHO expert committee which met not too long ago to make a recommendation to the UN Commission, the WHO expert committee

recommended Schedule IV and, in fact, the UN Commission ultimately placed GHB in Schedule IV. Schedule IV, under the Psychotropic Convention is very analogous really to our Schedule IV that you are familiar with under the Controlled Substances Act.

[Slide]

We are not here to talk about GHB abuse which we know is a significant problem. We are here to talk about Xyrem and what its role may be in the drug abuse problem in the United States. There are two issues we are really worried about here. Number one, we are worried about the possibility that patients legitimately prescribed Xyrem will abuse it in some way, or misuse it or escalate and then, secondly, we are worried about whether or not it might be diverted into sort of illicit channels and become part of a problem in that way.

[Slide]

Turning first to the issue of patients, first off, I think most of you know, and it is important to always know this, that the development of abuse among patients receiving therapeutic doses of abuse drugs is a much smaller problem than some

people realize. It is actually fairly unlikely to occur in a general sense. Of course, in the trials with Xyrem there weren't problems of abuse; there wasn't evidence that people were escalating their dose or complaining and asking for more, and that sort of thing.

It is important also to recognize that narcolepsy patients are patients that are receiving controlled substances all the time. The stimulant class of drugs, all those drugs that Dr. Mignot spoke about are all scheduled compounds. In fact, many of them are Schedule II where they can't even get them half the time because the production controls on Schedule II reduce their availability.

Then the issue about their dependence, if you understand, for example, that with benzodiazepines, when you discontinue benzodiazepine administration you will often see a withdrawal syndrome, well, that is because benzodiazepines have this incredibly long duration of action with active metabolites that accumulate so that the body continually maintains levels of benzodiazepines. So, when you quit using them there is a withdrawal syndrome. With GHB, as you saw from Dr. Houghton's presentation, the duration

of action is just a couple of hours. It would take many, many, many multiple daily uses, way more than the patients are going to get, to maintain the kind of levels of GHB that would be expected to produce dependence. So, yes, in abuse cases where people are just going all day and all night but not with patients.

[Slide]

Turning now to illicit diversion of Xyrem, first off, that hasn't happened yet. So, we are not aware of any diversion of any Xyrem through any of the products. This is, of course, only in clinical development but I think it is important to know. Most importantly, the company has been very much worried about this issue and has developed a distribution system that you are going to hear about, called the Success Program, which I personally believe is going to substantially prevent any opportunities for diversion. Lastly, Xyrem, whether you approve it or not -- it is going to make very little difference in the overall availability of this whole class of chemicals in the national scene.

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To illustrate that, this slide shows you

the product amounts anticipated, annual production amounts for this class of chemicals I mentioned to you. So, if Xyrem is approved the anticipated first year production amounts of gamma hydroxybutyrate are about 82,000 kg. GBL, gamma butyrolactone, the precursor that can be made into GHB easily and consumed itself, is 83 million kg, a thousand times more. 1,4-BD which is not a controlled substance and has no drug abuse control under it whatsoever right now, is widely available through all sources in large amounts, and is made in the neighborhood of 377 million kg. For those of you who don't do the metric system, that is 400,000 tons of 1,4-BD. And, all of these drugs are basically substituting for one another. So, whether you take Xyrem in or out of that graph, it is not going to make a difference.

[Slide]

In conclusion, I believe that the epidemic of abuse of GHB-like drugs has resulted really primarily from its extraordinary availability. In fact, when GHB was controlled -- it is hard now to get GHB. It is hard even for me to get GHB as a research scientist. So, the problem has now switched to these precursors that are available.

Secondly, the scientific studies of GHB show that you are not talking here about cocaine or heroin. It is a weak depressant of maybe the benzodiazepine, chloral hydrate type. Thirdly, I believe that Xyrem abuse is very unlikely among patients for the reasons I said. Lastly, the contribution of Xyrem to the public health problem, which is the matter of concern, is essentially not significant. So, you know, have your way with the drug in terms of efficacy and safety but I don't think you need to be worried that this drug is going to be a major factor in the drug abuse problem with this class of drugs. Thank you.

DR. KAWAS: Yes, a quick question, Dr. Leiderman.

DR. LEIDERMAN: Yes, I would like to ask Dr. Balster two questions. I would like you to comment on the species of animal that you are addressing when you talk about self-administration in drug discrimination studies. Two, I would like you to comment on the data that those models show with other classes of drugs.

DR. BALSTER: All the studies are reviewed on that slide on abuse potential with laboratory animal studies, using fairly well developed

methodologies. The self-administration studies that Dr. Leiderman referred to were studies that were done in monkeys in sort of a standardized method that is done through a program directed by the College on Drug Dependence. Those are the models, and I can show you data if you give me the time to do it. Maybe later, if the committee is interested, I can show you data. But these are models in which basically it is extremely easy to get animals to actually literally self-inject most of the drugs of abuse -- cocaine, amphetamines, opiates of all types, barbiturates, depressants, benzodiazepines -- benzodiazepines are a little harder but in the model that was used that I showed the negative results from, benzodiazepines were the positive control. So, basically the only area where that model has been not very successful and underestimates abuse potential is with hallucinogenic drugs and marijuana type drugs.

DR. LEIDERMAN: Yes, many of the Schedule I drugs. DR. REARDAN: We just have about another ten minutes. If we can prevail on the committee, we have one last speaker, and that will be Patti Engel, who is going to describe for you the risk management system that the company

has developed to help control diversion. Patti?

Risk Management

MS. ENGEL: Good afternoon. My name is Patti Engel, and I am here today to talk to you about the risk management program for Xyrem, which we call the Xyrem Success Program.

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This program will ensure the responsible distribution of Xyrem, namely, to meet two goals. First, to ensure that patients who desperately need the medicine can get it. Secondly, to keep this out of the hands of those people who might abuse it.

[Slide]

To develop this program we consulted broadly with a number of people interested in the issues not only germane to patients but also that of drug abuse. As you can see, we spoke with drug diversion investigators, field law enforcement, forensics experts, toxicologists, pharmaceutical distribution experts, drug abuse trend experts.

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Through those discussions we followed FDA's proposed risk management guideline, which is risk management through risk confrontation, in

essence egging the partners and the shareholders to not only identify the issues but also assess the risks, identify the options and select a strategy. The program that I am going to be sharing with you today is certainly a draft program that the company has designed after discussions with these numerous stakeholders.

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This slide I show to you really to point out the standard route of distribution of a pharmaceutical product in our country today. This includes not only commonly used medications like products for blood pressure control or products for arthritis, but also products under Schedule II, including such agents as amphetamines. Typically, a product is manufactured and goes to a number of national, regional and local wholesalers, eventually getting to 63,000 retail drugstores around the country. One can only imagine the number of loading docks, transport vehicles and hands that touch a pharmaceutical product in this traditional distribution system.

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As we contemplated the distribution of Xyrem and how to do this responsibly to meet the

prior stated goals, we determined that a closed distribution system would best fit everyone's needs for this product. The product is manufactured at one single manufacturing facility. It is sent to one single national specialty pharmacy. Eventually it goes by courier to patients with narcolepsy.

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The benefits of this program are that not only is the product distributed from a central location, but all the controls and all the records are in one place.

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So, how will this work? Because a number of doctors prescribe medicines for narcolepsy, we will focus our promotional effects on those physicians. They include such specialists as neurologists, pulmonologists, psychiatrists, internal medicine physicians and several primary specialties who practice sleep medicine.

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Our small sales force will call on these physicians, communicating the clinical benefits of Xyrem in narcolepsy. At those calls, the sales representatives will also review with each physician something that we call the physician

Success Program. I will go into the details of this program in a more in depth fashion in just a moment. But it is important to know that each physician will sign that they have reviewed this program with the sales representative and understand the program. I should also note that at no time will we embark upon physician sampling.

[Slide]

I promised to come back to the components of the physician Success Program. I know that many of you received copies of this but I would like to highlight some of the main points. First, because we know individuals all learn differently -- some by hearing, some by reading, other methods -- we have made this a multi-faceted program which includes videos, brochures, pamphlets that describe four main areas.

The first is to highlight to physicians that the distribution process for Xyrem is different, that their patients won't be able to get this at the corner drugstore. The second important issue that this binder points out to physicians is the dosing and administration of Xyrem. The next important issue is that of home storage and secure handling. The fourth is an important module that

we call "doctor be wary" which is an educational module that educates doctors about the ways that drugs are commonly diverted in this country so they can be aware of patients who are attempting to illegitimately get a prescription from them for this product. Each of the kits will also contain a number of unique prescribing forms for Xyrem which will be necessary in order for the prescription to be filled. This is, in essence, a special prescription form. As well, contact information will be provided should the doctor have any questions at all about the program.

[Slide]

Once the physician decides to prescribe Xyrem the physician faxes this special prescription to the specialty pharmacy. Now, I am going to come back to how this prescription is verified. So, I will ask you to hold on that point for just one moment. But, based on that prescription and based on the patient's geographic location, the pharmacy assigns that patient to a dedicated pharmacy team. So, each time that the patient deals with the system they are talking with the same pharmacist and the same reimbursement specialist.

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I mentioned that as the prescription comes to the specialty pharmacy there will be a number of checks to determine if the physician is, in fact, eligible to prescribe Xyrem. We will be utilizing DEA's NTIS or National Technical Information Services database to ensure that each physician has an active valid medical license, and also to ensure that that physician has current prescribing privileges which allow him or her to prescribe Schedule III medications in this country. As a backup check, the specialty pharmacy will also be checking with the appropriate state medical board to determine that there are no pending actions on the behalf of the state for that given physician.

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As a secondary step, the specialty pharmacy will also do a check on the patient in essence. What they will do is when that prescription comes in they will call the prescribing physician's office to determine that, in fact, that patient is real and a prescription has, in fact, been written for that patient.

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Once insurance reimbursement is obtained, the specialty pharmacy contacts the patient, first,

to determine the patient or the patient designee's location and availability for shipment, and also to describe to them the contents of the shipment. I will come back to the details of this in just a moment, but it is important that you know that each patient, when they get their first prescription of Xyrem will receive a multi-faceted educational program called the Xyrem patient Success Program, and I will come back to the details of that in just a moment.

In that same shipment they will also receive their Xyrem, and that will look something like this, with child resistant closure not only on the primary container but also on the dosing cups which are provided by the company.

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The shipment that goes to the patient is sent by a special system that has a special, unique tracking system called the Rapid Trac System. this system will allow detailed real-time tracking of that package which is delivered only by the authorized signature. If the patient or their designee is not available for receipt of the package at the time agreed upon with the specialty pharmacy, the package will be returned to the

specialty pharmacy after one delivery reattempt. So, a package will not sit on a delivery truck or in a hub for weeks at a time or anything like that. If the package is lost the system will allow an investigation to begin regarding the shipment's whereabouts at that point of loss.

[Slide]

I spoke a moment ago about the patient Success Program. Again, this is a multi-faceted program which includes video, brochures and pamphlets which deal with a number of important issues for patients. First addressed, of course, is the distribution process since it is so important that the patients understand that the only way they will get Xyrem is through the special pharmacy and not at their corner drugstore.

There is information about Xyrem's dosing and administration because we feel that that is an important message to be delivered in an understandable and a very consistent manner.

There is information on home storage and secure handling, and we also are very clear with patients about the criminal and civil penalties that the public law assigns to any illicit use of Xyrem. So, if I were, as a valid narcolepsy

patient, to take my Xyrem prescription and use it to conduct a rape or in an assault situation, or if I were to sell it to someone for illicit use I would be penalized, I would be subject to C-I penalties. The patient Success Program also includes contact information for the specialty pharmacy should the patient have any questions at all, and also reimbursement information.

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After the Rapid Trac System shows that the package has been received by the patient, the specialty pharmacist will call the patient within 24 hours not only to confirm receipt of that package but also to again reiterate certain important points with the patient. Those include the penalties for illicit use of Xyrem; Xyrem's dosing and administration; home storage and secure handling. The pharmacist will also take the opportunity to discuss with the patient the child-resistant features on the primary container as well as the child-resistant features on the dosing cups that are provided.

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The central data repository designed for Xyrem really allows for identification of a number

of unusual types of behavior, including any duplicate prescriptions, any attempts of over-prescribing, or any attempts at over-use by patients. The benefit here is that that information is available prior to filling the prescription so appropriate pharmacist intervention can occur.

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As you can see, the Xyrem Success Program is a comprehensive program which is designed to responsibly distribute this important medication in order that patients who need it have it available, and it is inaccessible for those who might abuse it. Thank you.

DR. REARDAN: Dr. Kawas, that completes our presentation and we will turn this back over to you.

DR. KAWAS: Thank you very much. I want to thank all of you for all of your nice presentations but, rest assured, you will have more questions in the afternoon. We are running quite late so we are going to cut lunch a little short and we will plan on reconvening at 1:30, at which time the public hearing component of this meeting will happen.

[Whereupon, at 12:50 p.m., the proceedings were recessed for lunch, to resume at 1:30 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. KAWAS: We will reconvene the meeting of the Peripheral and Central Nervous System Advisory Committee discussing Xyrem. We are now in the open public hearing portion of this meeting, and we have quite a few people that we will be hearing from and additional people who want to add to the list. I would like to ask all of the speakers to please do their best -- not their best, you must stay to five minutes. You will have a one-minute warning sign with your timer. If you go over, please don't take it personally but you might hear my voice ending your part for the meeting. This is in order to allow us to hear from everybody who wants to speak, as well as to get onto the deliberations of this committee. The first speaker in the public forum is Sharon Fitzgerald of Littleton, Colorado.

Open Public Hearing

MS. FITZGERALD: Good afternoon. I am Sharon Fitzgerald from Littleton, Colorado, and I am a narcoleptic. I am a volunteer member for the Orphan Medical Patient Council and the Narcolepsy Network is paying for my travel and my hotel to allow me the privilege of speaking with you today.

Five minutes isn't long enough. I have provided a longer version for you to read. Please, please read it. It explains my experiences with the five major symptoms of narcolepsy and how Xyrem gave back my American dream, the ability to pursue happiness without stumbling on the way when it gets tough, and without literally falling on my face when the goal of happiness is reached.

I have had daytime sleepiness since 1969. It threatened my ability to be a good mother and protect my children, and it trapped me in a series of entry level jobs. Not knowing it had a name, I tried to hide my problem from employers and I hid in restrooms for many years for 15-minute naps at unpredictable times lots of the time.

My symptoms dramatically increased and worsened in 1977 when I was in law school. I was raising school age kids on my own, being widowed at the age of 32. In daytime, against my will, I took naps in my classes, going instantly from consciousness to dream state sleep, the switch being so quick that I actually wrote words from my dreams in my class notes about things like my mother and helicopters, and wondered where they came from when I read them. These were usually

followed by a mark where I dropped my pen as I stopped writing, and that would startle me into wakefulness and I would stay awake for a while and take more notes.

Going to sleep nearly every night, my mind created vivid illusions of my very worst fears, often a murderous rapist breaking into my house from behind wherever I was sitting or lying. My knowledge of where I was, was accurate. I could not scream. I was paralyzed and I couldn't turn around to defend myself. These are called, as you know, hypnagogic hallucinations. I didn't know that at the time.

At the same time, the symptoms of nighttime wakefulness became more severe. I experienced long hours of anxiously lying awake, punctuated by times of intense dreaming so real and so vivid that in the daytime I couldn't remember whether events I remembered were real or dreamed. You may understand that I feared for my sanity, and this is when I sought medical help.

I was my doctor's first experience with narcolepsy. It took a very long time for him to find a diagnosis. When he did, it was because of my mild cataplexy and he found the diagnosis an

announced that was the good news because the bad news was there was no treatment. I self-medicated for years with Sudafed and coffee.

With determination -- if you knew me you would know about it -- and special accommodations from the university I actually finally managed to graduate from law school, but I turned down the dream job that was offered, clerking for a district court judge, because I feared I would fall asleep in front of the courtroom. He told me our first case would be about two nuns who had been brutally murdered and I feared I might experience cataplexy.

By this time my cataplexy had increased to the point that all my facial muscles would relax and my speech would become momentarily slurred. It passed so quickly that I couldn't hide it. I was a sole practitioner. I couldn't bill enough hours to earn a living. I took Ritalin; I took antidepressants unsuccessfully. I found a job with the State of Colorado. It didn't require my legal expertise but I got lucky, I found out about the trials. I had rebound cataplexy, like what they showed you in the pictures, and it was horrendous for several weeks, waiting to be on Xyrem and my secret was brought out at work. But they didn't

fire me because I told them I was going on Xyrem.

Its effects were immediate and dramatic. I have experienced no side effects. I get good restful sleep. I awaken refreshed. I stay reliably awake at work with fewer stimulants and I don't fall down. My supervisors noticed my increased wakefulness and rewarded it with committee chairmanships and memberships and, in 1999, a promotion. In 2000, January 1, I became an administrative law judge for the Division of Workers Compensation in the Colorado Department of Labor and Employment. It is responsible; it is emotional. I can do it. My colleagues know I have narcolepsy and they know that with Xyrem it doesn't interfere with my job performance. For years I was unable to safely carry my children or grandchildren. I carried my newborn to his first examination and that is just the beginning of my story.

DR. KAWAS: Thank you, Ms. Fitzgerald. Next is Richard Gelula, the executive director of the National Sleep Foundation.

MR. GELULA: Thank you. The National Sleep Foundation is an eleven-year old organization that was developed by the American Academy of Sleep

Medicine to educate the public about sleep and sleep disorders, and our leadership has always been drawn from the top tier of sleep experts, sleep scientists and sleep physicians. We are independent. We raise our money in a variety of ways including government grants, corporate grants, and many memberships, individual contributions that have played a major part, particularly from people and families affected by sleep disorders. Our funding from Orphan Medical for the last two years has been a total of 160,000 out of a two-year total of about 5 million. Our budget is about 2.5 million a year. And, their support has gone to broad activities -- sponsorship for National Sleep Awareness Week where they join in with other sponsors, and there is no name or brand specific recognition or benefit for them. So, I wanted to point that out.

The Foundation is qualified to address this and our interest is due to the fact that we have invested about a million dollars in narcolepsy research, including center grants for the genetic research done at Stanford. We presently have one of our postgraduate fellowships at UCLA studying the neurophysiology of cataplexy. We also have

established the National Narcolepsy Registry which has registered to serum DNA registry with about 700 patients and family members registered. That is managed at Montefiore Hospital in the Bronx, and it has been a resource for seven scientific investigations.

To summarize the position of the National Sleep Foundation on sodium oxybate, the National Sleep Foundation calls upon this panel to fully consider the safety and efficacy of sodium oxybate for the treatment of narcolepsy and cataplexy, and to do so in a comprehensive context that fully recognizes the extreme psychological, emotional, economic, social and health toll that this affliction exacts from people who suffer from it.

NSF does not presume to second-guess the evidence that has been submitted about the safety and efficacy of this drug, but it goes on record to say that such considerations should only pertain to affected patients and not other societal considerations. It is safe and effective for people with narcolepsy, like the speaker before me. Sodium oxybate should be made readily available to them. Any concern for illicit use should be addressed strongly through other channels, such as

law enforcement and professional licensing. The fact that narcolepsy is an orphan disease, for which only one medication is currently indicated, would be weighed as a factor in favor of approval of sodium oxybate because it is likely that availability of an approved drug will foster faster diagnosis and more appropriate treatment, and will also -- and we think this is very important -- stabilize patients who usually first experience the dreadful effects of narcolepsy and cataplexy during their developmental years, before the completion of their educations and initiations of a career.

I would like to summarize a few key background points. Narcolepsy and all of its primary characteristics, including cataplexy, are truly life-altering afflictions, a term that best connotes the life-diminishing and debilitating aspects of this disabling disease. Untreated, narcolepsy not only causes vivid nightmares and undermines the safe and secure feeling that most people get when they go to sleep, but it makes daily existence, both objectively and subjectively, frightening and strange, even alienating to the self and others. It makes the well-controlled process that routinely governs the existence for

almost all other humans, the alternating cycle of sleep and alertness, into something entirely different, an uncontrollable process where the maintenance of conscious attention becomes random and cannot be sustained or relied upon. Both the phenomenon of overwhelming sleep attacks and the muscular weakness and collapse that occur with cataplectic attacks undermine the sense of predictability and confidence required to fully develop and function in our contemporary world.

But a true understanding of narcolepsy goes beyond physiology. The cumulative effects of the distinctive daytime and nighttime characteristics of this disease are truly traumatic. They not only disrupt; they undermine and frighten and change the core experience of the individual, exacting a toll that ranges from difficulty coping and functioning to total disability.

I think some key characteristics that should be taken into consideration are that narcolepsy is not well understood or accepted. People who suffer from this suffer alone. They don't have generally the benefit of support groups, even though there is a fine support organization

out there, but the people are just spread out. There isn't enough concentration. Most people with narcolepsy do not have a relative with the disease such that it is even strange to them. People suffer a double blow because it is thought their sleepiness is volitional and a sign of laziness.

Thus, I think it should come as no surprise that people with narcolepsy suffer from a high rate of depression. It has been estimated from 30-70 percent in various studies. The good news is that in one study health quality of life was improved through effective administration and medical treatment, and I think that would pertain as well to sodium oxybate.

In sum, the National Sleep Foundation believes that narcolepsy exacts an unusual and cruel toll. We really call upon this panel to continue to do the professional job that brought you here today and fully consider the personal, psychological, emotional and human aspects of this disease and the great need for an effective medication. Thank you.

DR. KAWAS: Thank you, Mr. Gelula. The next speaker is Ms. Abbey Meyers, who is president of the National Organization for Rare Disorders,

Inc.

MS. MEYERS: The National Organization for Rare Disorders, which is known as NORD, came together initially because voluntary agencies for many rare diseases worked together to pass the Orphan Drug Act. So, we are the orphan drug folks who work to monitor the development of these drugs.

I have several conflicts of interest with this drug because for 20 years I begged practically every company I ever met to pick up this drug and to adopt it. It is a 20-year saga. And, I wrote something for you that you will be able to read about the history of development of the drug.

Also, about a year ago I bought some stock in this company. If I wanted to make money I would have put it in Merck, but the idea with the drugs that they are developing is I feel I have to make my own personal investment in the survival of the company.

For this drug FDA, rightfully, has asked for a risk management program, and there are several really good models to look at, most notably, I would like you to remember when you are discussing the risk management what happened with Clozaril because when Clozaril first got on the

market with the drug for schizophrenia, they had a very stringent distribution program, and they were sued by 30 states, attorneys general, because the laws in those states said that you could not restrict the distribution. In the settlement of that case, the federal court assigned us, NORD, with the task of distributing the drug to the people in this class action settlement.

So, I am very sensitive to what happens. FDA approved Clozaril's distribution program but then the law said that they couldn't do it. So, people really want the freedom to be able to get the drug when they want it, when their doctor prescribes it.

The other program you should look at is thalidomide because it is an extraordinarily important drug, again very orphan. Nobody wanted to go near it because of the liability problem. But they have a wonderful distribution program and I think it should be a good model for the field when there are drugs with specific dangers involved.

I also want to give you several cautions. Don't make the distribution too restrictive. For example, don't allow just certain specialists to

prescribe it because people with narcolepsy have a great deal of travel problems. Many of them don't have driver's licenses in many states. They may hold on to their driver's license but actually if it was ever reported to the state that they had narcolepsy they would lose it. It is just like epilepsy. So, you have to be sensitive to that.

There are many current problems with Ritalin and Dexedrine and the amphetamines that they are using because the government limits the amount of manufacture every year. So, at the end of the year they run out of drug and there are times when they just aren't able to fill their prescriptions and they can't order it by mail order because it is a controlled substance. So, these people have suffered so tremendously because of these distribution problems. With those drugs, pharmacies don't stock a sufficient amount and they will only dispense one month at a time.

Don't require a distribution program that is going to cause legal problems. So, ask yourself that, whether the program that has been designed by Orphan Medical could be loosened up a bit.

The other thing goes back to what you were talking about this morning, labeling. You know,

does this drug help with daytime sleepiness, etc.? I want to caution you that if you label this drug just for cataplexy with no effect on daytime sleepiness, there are a lot of insurance companies that are not going to reimburse for it. So, labeling on a drug is extraordinarily important to patients because of the managed care insurance system. So, try to be as liberal as you can on that, thinking about whether insurance companies are going to say no, except to just people with a particular type of narcolepsy.

Also, recognize that it is a unique disorder that is just as crippling as epilepsy, and that these people are already paying a very heavy price because of the problems they have with their current drugs.

Illegal use has to be handled, which I know that you are going to do, but you must pay attention to the valid use of this drug. Thank you.

DR. KAWAS: Thank you, Ms. Meyers. You are the first one who hasn't used all of your time and that is greatly appreciated. The next one is Robert L. Cloud, from the Narcolepsy Network.

MR. CLOUD: Good afternoon, and I wish to

thank the committee for the opportunity to address you on this issue. My name is Bob Cloud, and I would like to briefly talk to you, first about my own long, personal use of Xyrem, and I will call it Xyrem not GHB or sodium oxybate and, secondly, my very serious concerns as director of Narcolepsy Network, which is a national non-profit, primarily patient organization. In that capacity we have received funds, a minor amount of funds, perhaps ten percent of our revenues, from Orphan Medical over the last several years.

First, my personal experience with Xyrem as a narcolepsy patient with cataplexy. I am 57 years old, married, have two adult children, and I am an attorney in private practice, primarily family, probate and criminal law which sometimes can be intense and have a few emotions attached to it.

I believe I am the first American to have used Xyrem for narcolepsy, and I am probably the longest continuing user of Xyrem which now approaches 19 years every night without fail. My narcolepsy/cataplexy symptoms began in the mid-30's and by age 39 included severe and recurring cataplexy together with excessive daytime

sleepiness and sudden sleep attacks. My cataplexy caused numerous daily episodes of complete body collapse, such that I couldn't leave my office or home without risk of harm to myself or others. Feeling any emotion, humor, anger or mere enthusiasm, would result in sudden immediate collapse. I guess we are all ignorant of what diseases feel like that we don't have them, but my best description of the sudden collapse of cataplexy would be to imagine a puppet on strings and suddenly the strings, which are your muscle tone, are immediately let go and so you fall to the ground immediately, and your head comes down last and whips against whatever -- sidewalk or table corner or escalator or whatever might be there. I have been rescued by police and emergency squads and life guards and well-meaning strangers and friends.

Obviously no injury for me has been fatal because I am here, but unfortunately I do know others whose fall has occurred at the top of the stairs and they fell down backwards and killed themselves, and there are others that I don't know about.

In 1982 my treating physician sent me to

Sunnybrook Medical Center in Toronto, Canada to begin prescriptive use of Xyrem under the research being conducted by Dr. Mortimer Mamelak. After three weeks I returned home and continued using Xyrem, always prescribed by my local physician under his own individual investigational new drug application. My severe cataplexy symptoms disappeared almost overnight. I was immediately able to return to my full-time law practice and I have continued to this day to use Xyrem under that individual application and subsequently in the clinical trials under the Orphan Medical application. During these 19 years, I have never changed the dose. I have never experienced tolerance. I have never noted side effects. Simply stated, the drug is as safe and effective as it was on day one. It is hard to imagine a pharmaceutical product having such a quick, complete, safe and enduring benefit.

As director of Narcolepsy Network, I have said on a number of occasions that I think the greatest tragedy in the treatment of people with narcolepsy is that Xyrem or GHB has not been available so that other patients could benefit from it as I have. Hopefully, this committee will

remedy that.

We are sensitive to the reports of injuries and deaths and other victimizations from the abuse of GHB and, as an organization, we work with law enforcement and community drug agencies to partake in their activities to limit that and correct that. I think it is obvious that Orphan Medical is going above and beyond the call of duty to also contribute to restricting the unlawful use of GHB.

In closing, I submit that our concern for patients with narcolepsy should receive your highest considerations so that people can rediscover their economic and particularly their family lives and avoid disability. Thank you.

DR. KAWAS: Thank you, Mr. Cloud. The next speaker is Cindy Pekarick from Pennsylvania.

MS. PEKARICK: Hi. My name is Cindy Pekarick, and I am here today to tell you how GHB killed my daughter. In October of 1998, my daughter Nicole, a college student and gym enthusiast met a new boyfriend who introduced her to a product called Renewtrient. In November she researched the product over the Internet and received only positive information. She could take

it before bedtime and wake up in only four hours feeling refreshed, well-rested, and all her muscles would be completely recovered and ready for another workout.

In December I found out she was taking this supplement. I didn't believe the promises made by the advertisers. Arguments ensued and she promised she wouldn't drink it anymore. She was away at school from mid-January until April.

In April she returned home. She was behind in all her bills. She was black and blue on her arms and legs. She stopped attending classes, and she kept losing things. In May I discovered she had essentially dropped out of school.

In June I could see mild changes in her behavior. She began taking power naps, as she called them. She would sleep three hours in the middle of the day and get up at four o'clock and go to work. She continued losing things and having difficulty paying her bills. I searched her room and car but found no evidence of substance abuse.

By July, my younger daughter, Noelle, informed me that Nicole was having problems. She said, "mom, she isn't taking anything bad or illegal. She takes a muscle supplement that

doesn't agree with her. Sometimes she has bad reactions and she doesn't even know it. She embarrasses herself and me when she acts weird and then goes to sleep. When she awakes she never remembers anything that she did. She started taking it once in a while so she could go to sleep right away after work when she got home. Then she started using it more often. It disgusts me to see her out of control."

It was at this time I discovered Nicole had been taking GHB since November. I then began my own search over the Internet for more accurate information. In August, Nicole was found having a seizure in a public bathroom. She had urinated and defecated on herself while pulling at her clothes and hair and flailing her arms. She was rushed to the hospital where we arrived to find her unconscious, intubated, with her arms, legs and waist strapped to the bed. They claimed her seizure was violent. She barely had a pulse when they found her.

It was at this time I knew my daughter was addicted to whatever she was taking. There is absolutely no other reason why a young, bright, healthy woman would take a supplement that was

harmful. I begged the doctors to transfer her to a treatment center for chemical dependency, but they said they wouldn't do it without the patient's permission. She was clueless as to why she was hospitalized and she had no recall of anything that happened to her. She was discharged.

In September, Nicole, sweating profusely, with a red face and shaking hands while crying said, "mom, I have to talk to you. I'm really scared. I have a problem. I can't stop drinking it." I stood up, wrapped my arms around her and hugged her as hard as I could. I told her that she was on her way to getting better, that acknowledging that "g" had a hold on her was a step in healing.

On Monday morning, on her way to the treatment center, Nicole refused to go in. She claimed that "g" wasn't addictive; that she did the research and she was just having reactions to it. She said she was now in control of her life and future. She stayed in counseling and, by the end of September, Nicole had applied, transferred, and was accepted at the university. She was excited. Things seemed okay on the surface but she was hiding tremors, hallucinations and insomnia. She

went days without sleeping but never told me.

On October 3, 1999 at 2:00 p.m. she said she needed to take a nap before she went to work since she hadn't slept the night before. She set the alarm for 4:00 p.m. but she never heard it. She was in her final sleep. My firstborn child was found in bed, blue, at 6:00 p.m. We found a bottle of GHB in the trunk of her car. The autopsy revealed she had GHB and GBL in her system at the time of her death. No other chemicals were found.

Nicole was an honor student, captain of two varsity teams and graduated third in her class. For her undergraduate studies she majored in biology, with a plan to major in engineering for her master's degree. Her ultimate goal was to become a biomedical engineer. She wanted to be able to design body parts to help extend people's lives. She understood that to function well, one had to be healthy. She was a loving, sensitive, caring and intelligent woman. Her only fault was that she was naive. Thank you.

DR. KAWAS: Thank you, Mrs. Pekarick. The next speaker is Eric Strain. Doctor Strain is from the College on Problems of Drug Dependence.

DR. STRAIN: Thank you. I would like to

thank the FDA and the members of the Peripheral and Central Nervous System Drug Advisory Committee for providing me the opportunity to speak. My name is Eric Strain. I am a professor in the Department of Psychiatry at Johns Hopkins University School of Medicine. I am a board-certified psychiatrist with qualifications in addiction psychiatry, and I am here today representing the College on Problems of Drug Dependence, CPDD.

The College is the leading organization of drug abuse scientists in the United States. I am also the former chairman of the FDA's Drug Abuse Advisory Committee. I have sponsored my own travel to today's meeting, and I have no relationship with Orphan or other pharmaceutical companies that make narcolepsy products.

There are two point that I would like to make during these brief comments. The first is that the College on Problems of Drug Dependence would like to emphasize the importance of science-based assessments of new medications, especially as they relate to issues such as abuse liability evaluation and safety of abused products. The College wishes to stress the long history that has led to the establishment of reliable and valid

methods for determining abuse potential. This work includes both preclinical as well as clinical studies. Several academic medical centers contain rich experience in this area of research. Methods have been well tested, and outcomes from previous studies have helped inform and guide agencies such as the FDA in making determinations regarding abuse potential, therapeutic efficacy, and safety of new medications.

CPDD has played a key role in such matters, as its members are the primary group that have conducted such studies. The College wishes to strongly and forcefully advocate that decisions made by the FDA grow out of and be based upon well-conducted research, and whenever possible decisions should be derived from well-controlled studies and data driven. In order to achieve such goals, advice on substance abuse related matters should be solicited from experts in the field.

The second point I would like to make has to do with the Drug Abuse Advisory Committee. As the former, and the last chairman of this advisory committee of the FDA, I believe it is important for me to comment upon its termination. The Drug Abuse Advisory Committee has been dissolved by the FDA,

and in the process the FDA has lost an important resource that can inform decisions regarding substance abuse. To my knowledge, today's meeting is the first FDA advisory committee meeting since this termination where issues of drug abuse are an important element in your discussions.

I am pleased to see that there are several drug abuse experts represented here today, however, I am concerned that the numbers do not allow the breadth of expertise that would have been found on the DAAC. Such breadth is essential to fully consider all of the issues involved in advising the FDA on the abuse potential of new medications, the extent of the public health consequences of such abuse, additional data that the FDA should require companies provide, and recommendations regarding post-marketing surveillance.

The College is particularly concerned that comparable experience and knowledge brought to the Drug Abuse Advisory Committee by experts in the drug abuse field is no longer readily available to the FDA. In my experience as chairman of the committee, I was able to witness firsthand on repeated occasions the value of having a group of scientists and clinicians who could provide

informed knowledge and experience to the FDA on matters such as those that appear to be on today's agenda.

The loss of the DACC to the FDA is significant and substantial, and adequate representation of drug abuse issues on other advisory committees needs to be clearly demonstrated by the FDA. I speak on behalf of the College in expressing the College's continued concern regarding the dissolving of this advisory committee. Given the tragic consequences of drug abuse to our society, as exemplified by the previous speaker, its prevalence and the growing body of medications for the treatment of substance abuse disorders, it is particularly concerning that the FDA has decided to terminate this particular advisory committee.

Again, I wish to thank the FDA and this advisory committee for allowing me to make these comments today. The hope of the College is that these companies will spur tangible demonstration of FDA's commitment to having adequate outside input by experts in the drug abuse field in the advisory committee process either through the renewal of the Drug Abuse Advisory Committee or through adequate

and substantial representation by drug abuse experts on other advisory committees where issues of drug abuse may be of substantial importance. Thank you.

DR. KAWAS: Thank you, Dr. Strain. The next speaker is Deborah Zvorsec. Dr. Zvorsec is from Hennepin County Medical Center in Minnesota.

DR. ZVORSEC: Thank you very much. My research is in the area of gamma hydroxybutyrate abuse toxicity, addition and withdrawal. Dr. Steve Smith and I, with others, published a case series in Morbidity and Mortality Weekly Report in February of '99 that described adverse events due to ingestion of dietary supplements containing GBL, GHB precursor. I was the lead author of a case series of 1,4 butanediol toxicity that was published in The New England Journal of Medicine in January 2001. These toxicity episodes included two deaths that occurred with no co-intoxicants and no evidence of aspiration or asphyxiation or adulterants.

I will focus today on GHB addiction. In the course of our work, Dr. Smith's and my name were listed on the project GHB help site. We received calls from over 40 addicted patients from

25 states, and have treated an additional 5 cases of inpatient withdrawal at HCMC in Minneapolis.

The vast majority of these addicted people began using GHB to treat insomnia, anxiety, depression, chemical dependence or for body-building purposes, as recommended by marketers, websites and fringe pro-GHB physicians. Many, indeed, began with GHB, continued with GHB and never used any of the dietary supplement analogs. Our patients began with small doses, often only at night, and discovered that it made them feel good; increased dosing frequency and, as tolerance developed, needed more GHB in order to feel good. Within months, they were taking GHB every one to three hours around the clock to avoid withdrawal symptoms. By the time they realized that they might be physically dependent, attempts to abstain resulted in severe anxiety, insomnia, panic attacks and hallucinations.

Their addiction destroyed their lives. They lost their spouses. They lost access to their children, their jobs. They acquired tremendous debt to support their habit. They became comatose while driving and crashed their cars, frequently on multiple occasions. They called us in absolute

desperation. Their detox was frequently similar to the worst cases of delirium tremens, requiring large and often massive doses of sedatives, often with intubation.

Almost all patients suffered weeks or months of profound depression and anxiety after detox, and some also experienced muscle twitching and tremors. Of the over 40 patients we have worked with, only a scant handful have remained GHB-free, frequently despite CD treatment. Many have detox'd numerous times but continue to relapse, sometimes within hours of discharge from treatment. Unfortunately, many never lost faith in GHB and continued to be convinced that they could get back on it and use it responsibly. They continue to argue its health benefits.

One of our patients was a 50-year old businessman with his own business who began using GHB, not an analog, five years ago, initially for body-building purposes. Within months he had increased his dosing to around the clock. His life was entirely controlled by the need to have GHB with him at all times. He tried numerous times to quit. His wife was unaware of his addiction. She described witnessing frequent frightening hypnotic

states, punctuated with clonic movements. She believed that his frequent states of apparent somnambulism were due to a sleep disorder but despaired when a sleep specialist could not cure him. This woman is a very bright professional who was totally unaware of GHB, as is the case with many family members. It was only on the morning of his admission that she learned the truth. After six days of detox he was through the worse and appeared to be on the road to recovery. Psychiatrists treated him with sleeping meds and antidepressants, but within three days he was using GHB again to control anxiety attacks and depression.

GHB is perhaps the most addictive drug ever abused. Experienced drug users describe a euphoria that surpasses that of any other drug. Availability of off-label prescription presents profound personal and public health risks. The fringe physicians who now promote GHB will be joined by thousands of mainstream physicians with the approval of the FDA. The majority of physicians are ignorant of the diverse health risks of GHB, as are toxicologists and law enforcement officials. Users will seek Xyrem from physicians

who don't recognize sodium oxybate as GHB and are unfamiliar with the health risks. Patients will obtain prescriptions for sleep disorders, also for insomnia, depression, anxiety, treatment of alcohol and drug dependence and other conditions for which it has been touted.

We know that addicts often use GHB and its analogs interchangeably. Their compound of choice is dependent on access, determined by cost, perceived quality, ease of procurement. Clinical literature reports one user who spent $200 per day. That comes to $70,000 per year. Our patients report ingestion of up to a bottle every one to two days, coming to $11,000 to $36,000 per year. A Xyrem prescription will be a bargain for such users, who will then avoid the high prices, erratic availability and risks of supplement and solvent purchase. We know that many people are afraid to buy or make their own GHB due to risks of contamination or errors of production. Xyrem, a pharmaceutical product of controlled quality, available by legal prescription, and with very little risk if found in their possession, will be very attractive. We know that users are watching for the release of Xyrem. Recreational drug sites

post links to narcolepsy sites and publications about Xyrem. One hotyellow98.com, for example, instructs users "click here to find out when GHB will be released under the trade name of Xyrem."

DR. KAWAS: Your time is up, Dr. Zvorsec. Please finish. Thank you very much, Dr. Zvorsec. Our nest speaker is Trinka Porrata of California.

MS. PORRATA: I wish I had time to tell you the stories of 200 dead people that I know of, hundreds of rape victims and thousands of GHB overdoses, and About Caleb Shortridge, to whom our website www.projectghb.org is dedicated, about Matthew Coda and Joshua Parks to whom our GHB addiction hotline is dedicated. I wish I could tell you about Ben Croman, Mike Fox, Tyler Johnson and other young men from New Zealand to Sweden who either have or are right now considering suicide because of the withdrawal from this drug; about more than 300 people I personally know about who are horribly addicted to GHB, and who could each name at least one dozen people more just like them.

I have lived and breathed GHB since June of 1996 when I was first assigned to handle it for the LAPD. Four young men collapsed. Two literally died and were brought back to life by the

paramedics. One thing was clear, people were dying from GHB and it was being missed. It has been a heartbreaking five years, mixed with the privilege of learning more and teaching others to recognize the rape, overdose and deaths and getting rape victims into treatment and addicts help. It has been very lonely at times when the agencies who should care haven't.

DEA has reviewed and documented 71 deaths related to GHB but, basically, stopped counting once the drug was controlled, for obvious reasons. No one at FDA has ever expressed interest in these cases. My database now includes over 200 GHB-related deaths. In fact, Robert McCormick, of the FDA's Orphan Drug Unit, told me emphatically he did not care how many people had died nor were addicted to it because he intended to approve it anyway. Something is wrong with this picture. This is the most horrid drug I have encountered in 25 years as a police officer.

Much new has come to light during the past two years, none of it good. Around the world countries are just now awakening to their problems with GHB. Schedule IV by WHO is simply an awakening to the problem. As we speak, countries

are restricting it. France is backing away. England is struggling with it. Sweden has an unrecognized addiction and suicide problem. New Zealand tried it as a prescription drug and now realizes they screwed up royally. NIDA is currently releasing $2 million in research on this drug. This is not a time to be pushing it forward on an unsuspecting American citizenry.

You are here today to approve GHB, disguised as sodium oxybate, for use with narcolepsy/cataplexy. Orphan's investors have been assured that you will do so. When the last meeting was cancelled the stock dropped 30 percent in frustration over it. You have not seen my videotapes of the day-to-day struggle of GHB addicts showing that GHB clearly gives previously healthy people symptoms that can only be described as temporary narcolepsy/cataplexy, just like the nine-year old you saw in the tape. Their heads ricochet off board room tables around this country. They break mirrors. They are cut up. They crash cars. They die and kill others. It is destroying them. Their wives are terrified of their husbands and have no idea what is happening. They are locked in psychiatric wards because doctors and

emergency rooms do not recognize GHB psychotic episodes.

There are no answers for them. So, how can you approve this drug for use? My addicts suffer alone, much as narcoleptic/cataplectic patients do. Many do not have insurance or their insurance will not pay for this drug that is not recognized as an addictive drug.

I am deeply concerned about the off-label use policy, enabling any doctor ultimately to prescribe it for any condition as I have no faith that its use will be limited to narcolepsy/cataplexy. Look at the chatter around Orphan about fibromylagia, a condition with vague symptoms for which a drug seeker could easily get a prescription. I know the vast majority of doctors do not realize that sodium oxybate, Xyrem, is GHB. I see no significant talk on the legitimate narcolepsy websites about it, but the message boards where GHB addicts hand out are buzzing. In fact, the key figures in illegal GHB Internet sales were posting on the website www.xyrem.com.

There is very little drug diversion enforcement in the United States. Only a handful of agencies devote any time to this. It is a small

portion of DEA effort. States are not prepared. They are not able to handle it. Therefore, Orphan's proposed voluntary -- key word, voluntary -- promises of distribution are frightening.

More importantly, the issue goes beyond diversion of Orphan's product to use of Orphan as a shield for possession of GHB in general. It would be unrecognized by law enforcement. Once in possession of that prescription and a bottle of Xyrem, the addict will be home free. There is no field test kit. All investigations of GHB are difficult. Encountering a prescription, real or counterfeit, and a bottle of Xyrem, real or counterfeit, the officer would have zero ability to identify it -- none; zero; nada.

To those who claim real GHB is safe and only street stuff is dangerous, poppycock. My addicts have used everything from European pharmaceutical grade to bad stuff. The unprecedented split scheduling of GHB was unwise and unenforceable. We were forced to accept it. It was political, not science. The people in the clinical trials have reason to obey; people in the streets do not.

If I were to convey to you but one

thought, it would be that not enough information is known about GHB to approve it for any purpose at this time, and certainly not appropriate for off-label use. Any approval at this point will trigger an absolute further epidemic of general abuse because you will create an aura that it is safe. I ask you please table this issue until the NIDA research comes in. Please do not make this mistake.

DR. KAWAS: Thank you, Ms. Porrata. Our next speaker is Matt Speakman from West Virginia. While Mr. Speakman is coming up, I just want to remind everybody I am not trying to be mean; I am not trying to be difficult, but we are trying to keep the public hearing section of this meeting down to under two hours and that will only happen if everyone sticks to their five minutes. We would like to let the committee get a chance to have some more discussions for everyone. So, we greatly appreciate honoring the time constraints. Mr. Speakman?

MR. SPEAKMAN: Thanks. I just wanted to say thanks. This is kind of a unique experience addressing doctors. It is really cool.

My name is Matt Speakman and I have

narcolepsy. I will describe very briefly my experience. I have cataplexy also. My first experience was in chemistry class my junior year in high school. The professor pulled out the liquid nitrogen experiment and was freezing flowers and flicking them, making them shatter. I got very excited and he called us to the front of the room and, on my way up to the front of the room, I felt my legs start to buckle. This was the first time anything like this had happened. I had had trouble laughing a little bit because cataplexy sometimes has onset with laughter and emotion, but it wasn't very serious.

I eventually just realized that I was going to fall. So, I went back to my desk and collapsed on the desk with my face down in my arms, kind of draped over the thing. It was humiliating. I couldn't move. I was awake and aware and I could still hear the class kind of looking around and what-not.

This started to happen more regularly and I started to fall asleep during class. My grades started slipping. I had to stop swimming. I was on the swim team. Falling asleep in the pool is kind of dangerous. So, I quit doing that. Most of

my teachers suspected drug use and I don't blame them.

But I managed to get into the University of Kentucky and I went there for a year. I was unable to meet friends and my grades weren't very good because I spent most of my time in my dorm room. I didn't make it to class very often; very hard to wake up. It is very hard to keep consistent notes when you are falling asleep all the time.

My parents weren't happy so they found, you know, I needed some other treatment. So, I went to a doctor in Cincinnati who was part of the study for what is now Xyrem. That was four years ago, and I am taking it nightly unless I pull an all-night study session or something like that. I don't have any withdrawal symptoms when I don't take it. I don't have any side effects when I do take it. I sleep well. I have no cataplexy. I am here speaking to you right now and I certainly wouldn't be doing this without this treatment. I used to take stimulants and antidepressants to control the cataplexy, none of which worked; they just had nasty side effects. It wasn't very good.

Two weeks ago I graduated from West

Virginia University with honors. I am looking for a job --

[Laughter]

-- and I am thinking about going to grad school. That is definitely on the bill, but I am going to need some money first. So, first things first. Right?

I understand all the concerns about the illicit use and that definitely needs to be addressed, but this drug is working for narcoleptics and, you know, I have a girlfriend and I have a life, and I live normally. A couple of years ago I got a job as a full-time camp counselor in Maine; drove there myself; had no problems. I read the review they gave me after the summer was up and it said, this guy has the energy of a small power plant, which was nice to hear after suffering from narcolepsy for a couple of years. So, I am happy. I am working on success, and I just wanted to thank you for giving me the time to speak with you and I hope you can work all this thing out, but my main point was that the drug is working for narcoleptics and I want to thank the Narcolepsy Network for paying for my travel arrangements and my hotel. I am not in any way tied to Orphan

Medical. I don't care who makes it. I just want to let you guys know it is working. Thank you.

DR. KAWAS: Thank you, Mr. Speakman. The next speaker is Charles Cichon, president of the National Association of Drug Diversion Investigators.

MR. CICHON: Good afternoon and thank you. My name is Charlie Cichon.

DR. KAWAS: My apologies.

MR. CICHON: No apology. The nuns never got it in grade school; nobody has ever got it right. I go everywhere from Ceechon to Chicken.

[Laughter]

I have a 16-year background in law enforcement, but for the last 12 years I have worked in the health regulatory field with the Maryland Board of Physician Quality Assurance, the state medical board licensing and regulatory agency for Maryland. But I am here today as the president of the National Association of Drug Diversion Investigators.

Established in 1987, the National Association of Drug Diversion Investigators, NADDI, was formed in Maryland, in Annapolis by a sergeant in the Ann Arundel County police department. Our

organization is a unique organization whose members are responsible for investigating, prosecuting and preventing pharmaceutical drug diversion.

NADDI has proven to be a valuable asset to law enforcement, the pharmaceutical industry and health regulatory professionals. NADDI principal activities comprise cooperative education and training in the specifics of pharmaceutical drug diversion, investigation and prosecution; the sharing of investigated information and communication with a wide variety of interested parties with regard to the nature, scope and impact of pharmaceutical drug diversion; and the development of stronger effective measures to combat the problem of pharmaceutical drug diversion.

NADDI supports the safety and efficacy of the new drug application, NDA 21-196, Xyrem, proposed to reduce the incidence of cataplexy and to improve the symptoms of daytime sleepiness for persons with narcolepsy.

NADDI is aware that in many reported cases the use of GHB has changed from homemade GHB to ingesting of industrial chemicals that convert to GHB in the body. (My car got towed away yesterday;

I lost my other glasses. I noticed that when I was sitting in the back and I couldn't read my paper. So, I apologize.)

We are also aware that there are no known cases which involved Xyrem. Rather than consider the above issues as tangential, Orphan Medical has gotten involved, helping to educate and uncover solutions in conjunction with stakeholders such as NADDI. In fact, since November of 2000, an Orphan representative appeared at our national conference in Columbus, Ohio, and for the last several months has been involved in several states in multi-regional training with over 600 NADDI members.

Input has been sought regarding distribution systems that will minimize and identify potential diversion situations, allowing diversion investigators to more easily perform their jobs. It is the job of the pharmaceutical diversion professionals to investigate potential diversion, however, Orphan is willing to cooperate with the appropriate local, state and federal agencies. Thank you.

DR. KAWAS: Thank you. The next one is Debbie Alumbaugh from Florida.

MS. ALUMBAUGH: Good afternoon. My name is Debbie Alumbaugh, from Florida, and I am the surviving mother of Michael Tiedemann. He was 15 years old when he died. That was just over two years ago. The cause of Michael's death was aspiration vomitus and GHB toxicity.

Michael was a sophomore at a high school in Florida. He was a black belt in karate, and he was also an instructor. He had won several academic awards for reading, spelling, mathematics and music.

On October 1, 1998, Michael came home from school and asked if he could go to the show with his friends. It was unusual for a school night but we decided to let him go. We required Michael to bring home a progress report every week from school and he had brought one home and he was making A's and B's in all of his subjects. Before they left, one of Michael's best friends came into our home and they shot into Michael's bedroom. This boy was only in there for five minutes and when he left Michael was passing out within ten minutes of this young man leaving our home.

We found out 18 months after Michael died that when they left our home they drove three

blocks and started to play a game of basketball on the way to the show. Michael had the ball and was going for a lay-up, and when he came down he was unconscious. He lay there several minutes. His friends, not knowing what to do or recognizing the red flags, giggled and laughed. They scooped my son up and took him on to the movies. We understand Michael never saw the first five minutes of the movie. He passed out again.

When they brought our son home, my husband looked at him and he asked him, Michael, are you on something? Did you take something, son? He said, no, dad, nothing. Brad decided not to lecture Michael this late at night; he would talk to him tomorrow. Brad never got that chance. Michael died that night, alone in his bed.

The next morning, when Brad went to wake Michael for school he could hear Michael's alarm blaring. Michael had full intentions of getting up. When he opened our son's door he knew he was dead. The first thought that ran through his mind was to run, run out of the house and not look back. My son was on his bed, his eyes wide open, his mouth hanging open, his tongue swollen so much that my husband couldn't shut his mouth. He had dry

vomit running down his chin into a puddle on his collarbone. His hands were in a clawed position where he had tried to roll himself over but couldn't. GHB takes away the gag reflexes and it paralyzes you.

We didn't know why Michael had died. None of his friends would speak up. It took 12 weeks for us to find out that Michael had ingested GHB that evening. It was the first and only time that this had happened.

In the last three years, in Florida alone, we have lost 207 young lives to these drugs. From 1999 to 2000 our numbers have more than doubled in Florida alone.

After several months after Michael died, he came to his father in a dream and said, dad it is wrong to destroy the body the way I have done. I need you and mom to go out and tell my friends and my generation of people my story, our tragedy. This put a burden on our hearts and we seemed to stop healing until one day Michael's father gathered up enough courage and strength and he made the first phone call.

We now go to schools all over and share our story with students about GHB, and the tragedy

of our family. Friday, June 1 our son would have been 18 and he would have graduated on that day. When we went to his grave one Friday, his graduating class had left white roses and the mascot for the graduation cap. We missed prom; we missed graduation because of this drug. Our voices have to be heard. Please investigate this drug. It is not safe. It is killing our children and it is not the pushers that are dying; it is our good kids that we are losing. Thank you.

DR. KAWAS: Thank you, Ms. Alumbaugh. The next speaker is Brian Hunter, of the Young Adults with Narcolepsy.

MR. HUNTER: Good afternoon. My name is Brian Hunter. I am the founder of Young Adults with Narcolepsy or YAWN. I am also a medical student at the University of Minnesota and a person with narcolepsy and cataplexy.

I would like to preface my comments today by disclosing that Orphan Medical has provided my organization with a minor grant and it provided a general grant to the Narcolepsy Network who has paid for my travel and accommodations to attend this meeting.

YAWN is the first youth-focused online

narcolepsy support and advocacy organization. We work at the grass roots level to advance public awareness of narcolepsy on behalf of young adults and others whose lives are affected by this often debilitating sleep disorder.

As founder of YAWN, I believe I am in a unique position to comment on the issue currently under consideration by this committee. I do not, and have not used Xyrem for treatment of my cataplexy but as the representative of many young adults in need of an effective treatment for their narcolepsy, I am compelled to present my views on the risk management issues pertaining to the safety and efficacy of Xyrem.

Narcolepsy is most commonly diagnosed by the middle of the third decade of life, often 5-15 years after the onset of symptoms, the most dramatic of which is cataplexy. Excessive daytime sleepiness, combined with the impact of sudden attacks of cataplexy that may last from a few seconds to hours can be profoundly damaging to the interpersonal, educational and professional development of these young adults at an extremely critical point in their development. Although I am fortunate only to experience rare and mild attacks

of cataplexy, I know others who are completely incapacitated by cataplexy and have not, or would not been able to achieve their personal professional goals without a medication like Xyrem.

I submit that the risk for experiencing the negative impact of untreated cataplexy on the potential of so many young adults with narcolepsy is a serious issue that must be included in any discussion of risk management of Xyrem.

Xyrem offers a singularly important therapy for the 65-70 percent of young adults with narcolepsy who suffer with cataplexy. We must recognize the consequences of failing to approve Xyrem to treat the 1/1000 people suffering with narcolepsy. For example, after forming YAWN, I was contacted by the parents of a 16-year old boy, living in a small town not three hours away from the nearest city. This young man was bright. He did well in school, and was active in his community until his 12th birthday when he began experiencing severe episodes of cataplexy that lasted for hours.

When I first spoke to him on the phone he told me that his condition was so severe that he was forced to spend five days a week in a nursing home, and he is still there. What are the costs of

providing nursing home care in a public institution for a 16-year old boy for the next 60 to 70 years? By not adequately controlling his cataplexy, what are his chances for becoming a contributing member of our society? Unfortunately, this man's story is all too common. Unless something is done about the current environment of limited access to inadequate pharmaceutical therapies, the future of young adults suffering with cataplexy will remain bleak.

This, however, does not have to be the case. In fact, a brighter future has been achieved by the lucky few who have participated in Xyrem clinical trials. They have become success stories. To these young adults with narcolepsy Xyrem has meant the difference between a life within an institution and having the opportunity to achieve their goals, free from the physical constraints of their disease. Xyrem has enabled many young adults, my friends, to earn their Ph.D.'s or become lawyers, doctors or to simply be good parents.

These are people who took Xyrem and couldn't have succeeded otherwise. Yet, there continue to remain thousands of other talented and capable young adults who have not yet had a chance to fulfill their dreams. They are the reason I

formed YAWN and why I am here testifying before you today. We can no longer afford to neglect the potential of so many young adults by failing to provide them with the only medication known to be safe and effective. It is our responsibility to protect their right to pursue a happy and productive life by having access to medications like Xyrem that will effectively treat their disease.

Thank you for allowing me to present these remarks to you today. I urge you to approve the NDA for Xyrem. There really are lives at stake.

DR. KAWAS: Thank you, Mr. Hunter. The next one is Joe Spillane.

DR. SPILLANE: I would like to also say thank you for an opportunity to speak to the FDA and to this committee on this important issue.

I work at Broward General Medical Center which is a community hospital in south Florida. My experience with GHB is as a pharmacist and in clinical toxicology. I also teach as an associate professor at the College of Pharmacy at NOVA Southeastern University.

Our experience in the emergency department is very similar to what Dr. Dyer mentioned. We

have a lot of GHB overdoses. We had 48 overdoses associated with GHB in 1999. That number increased by 60 percent to 77 in 2000. We have more GHB overdoses than ecstasy. We have more GHB overdoses than oxicondon. I think it is important that I just underscore the immensity of the problem associated with GHB abuse. Most of our overdoses come in with people who have altered mental status and, basically, they just need a short period of supportive care, airway management. Most wake up. Many of them -- and I think this is important to point out, many of them mention that somebody had given them GHB, put it into their drinks, and so forth. As such, the media an many people have advised don't accept a drink from anybody but the bartender. We had a bartender up in our ICU about a month ago, and when he did recover I spoke with him and he said, yes, I chronically use GHB. A lot of my friends in the beverage industry also do. And, I think we can understand what the potential problems could be with that.

We have also treated five withdrawal cases and, again, the numbers might not be that big but this is just one hospital and, since it is a difficult thing to identify, we are probably

missing cases and I am sure there are cases missed throughout the country.

There have been nine deaths where, in the estimation of the medical examiner in Broward County, a county of 1.6 million people -- nine deaths were caused by GHB and I think it is important to point out that at least one of those deaths was with GHB alone, with no co-intoxicants and no alcohol level.

I guess my major concerns are with the scheduling and some of the off-label prescribing issues, and the voluntary nature of this distribution system. I kind of just want to summarize briefly by saying I think there are four questions that are major concerns of mine and I hope this committee addresses those concerns.

The first one is, is it really wise to rely upon an essentially voluntary, supposedly closed-loop distribution system, designed by the manufacturer, to prevent diversion of an increasingly popular, highly lethal, addictive and abused substance?

My second question is, is it prudent to require very little governmental regulatory oversight of such a system when the strict

adherence to that system may not be in the best financial interest of the entity responsible for that strict adherence?

My third question is, is it responsible to rely solely on those with a vested interest in demonstrating little or no diversion to verify that little or no diversion is occurring? It is my understanding that that is essentially what we may be doing here. I think there was an example of how this could be problematic just in today's proceedings. I certainly was under the impression by several people who spoke today that there was no diversion in the clinical trials. I think Dr. Mani, from the FDA, said that, indeed, there were some cases of diversion. So, I just think that is a potential concern.

My fourth question is does it demonstrate judicious foresight to establish a precedent for sort of circumventing existing scheduling and distribution processes, and couldn't such a precedent be used in the future to the financial benefit of pharmaceutical manufacturers and to the detriment of drug diversion prevention?

I would like to commend Orphan for their work and bringing a medication that they feel is

effective to those who could benefit from it. I think a mandatory, not voluntary, system of distribution, with adequate governmental regulatory controls and any restrictions on off-label prescribing would advance another one of their stated goals, which is reducing abuse and diversion. Thank you very much for having me.

DR. KAWAS: Thank you, Mr. Spillane. The next one is Ms. Mali Einen.

MS. EINEN: Hello, and thank you for the opportunity to speak before you today. I could tell you my story of my scars and bumps and bruises from my many falls from cataplexy, or I could tell you about my disappointment from having had to give up my career that I was dedicated to and loved, not to mention the loss of income and security. Instead, the part of my story I share with you today is the loss of the normal, everyday things that most parents take for granted.

My name is Mali Einen. I am a single mother from California with narcolepsy and what is considered severe cataplexy -- and a lot of nervousness. As a person with narcolepsy, I was fortunate to be diagnosed fairly quickly after the onset of my symptoms. I was diagnosed at the age

of 22 after first noticeable systems of narcolepsy, appearing at about age 22.

In the early years my cataplexy was triggered mostly by strong emotions -- a truly funny joke or my young daughter saying something adorable. As the years progressed, my cataplexy worsened, requiring less and less of an emotional trigger to cause a complete collapse -- unable to move or talk for seconds, sometimes even minutes at a time despite my daily medications.

As my daughter grew and my cataplexy worsened, I was unable to attend her performances, school programs or sports activities without several full collapses. My young, then seven or eight year old daughter would complain, why do you bother to come? You spend most of your time passed out. That is what she called cataplexy. I wondered would she ever understand that it was my joy for her success and my love for her that prevented me from participating in these milestones.

Several years later my daughter's simply relaying a story to me, excitedly, about her latest crush or her experiences with her friends would cause me to crumble, much like the film that Dr.

Mignot showed earlier today. It dawned on me that I had not only given up my experiencing anything that might involve positive emotion, it had become difficult for me to even participate as a spectator in my daughter's life.

During the years, I had been able to maintain success in my developing career as a money manager. My workaholic, nose to the grindstone withdraw kept me away from the usual office fun and water cooler moments, while allowing me to avoid embarrassing cataplexy. But this too had begun to erode. Although the various medications allowed me to keep my cataplexy partially in check, it seemed that my nighttime sleep became more and more disrupted, sleepy during the day, yet never able to sleep more than an hour or two at a time at night.

By 1996, my spotty nights of a few hours of sleep, my sneaking naps during the work day, and collapsing in exhaustion any time I sat still had affected my ability to continue to perform my job adequately. Long ago my daughter had given up on my being able to read her a story or to help her with her homework. My life had become dragging myself to and from work, attending to the basic needs of my daughter, while constantly working to

keep my emotions in check. There was little room for fun and interaction. Sole provider for my daughter and myself, I finally voluntarily left my job.

By this time I had become a complete slave to my next dose of medication to either control my cataplexy or to help keep me awake. The medications didn't make me feel well; they made me feel horrible, yet, I was their slave. I had never taken a back seat to finding better or best treatment options. I tried no less than five to seven different antidepressants over the years with varying degrees of success, but each with such a cost.

Within a year after I had left work, I became aware of a new medical study through Stanford, an experimental treatment for narcolepsy and cataplexy. I started Xyrem. My life changed! After a horrific washout period when, unmedicated, I was faced with my inability to care for myself, let alone my daughter, with mere thought causing collapse after collapse, I found that Xyrem controlled most of my cataplexy and I was thrilled how the better quality nighttime sleep allowed me to feel normal, almost good upon waking.

Although not required by the medical study, I began to voluntarily decrease my daily doses of amphetamines. The better, less disrupted nighttime sleep allowed me not to be a slave to my next dose of stimulants in order to make it through the next several hours. I now go many days without stimulants at all, and other days take 5 mg or less of Dexedrine.

I not only began to be able to listen to my daughter's glee-filled stories of her day, I started to volunteer at her school. I could joke with the kids; I could even watch Kelsey smash a winning serve across the volley ball court. I must admit, occasionally a funny story or my evening interaction with my daughter still causes my facial muscles to slacken with a bob of the head, but my daughter now uses these opportunities to give me a hard time, knowing that I will recover in a second or two and we will have fun and enjoy our life together.

I asked my now 17-year old, upon contemplating being here today, would you say my taking Xyrem has made a difference in your life? I had expected the usual teenage disinterested reply. Instead, Kelsey responded, as tears welled in her

eyes, as much as I hate it sometimes, you are really a part of my life now; you know everything that's going on with me.

It is for this that I am truly grateful to Orphan Medical and Xyrem -- and I think I forgot to say my conflicts of interest.

DR. KAWAS: That is the only reason we are going to let you go more over time.

MS. EINEN: I am a shareholder of Orphan Medical and a number of other stocks of products that I believe in. Narcolepsy Network has generously paid for my air fare and accommodations, but they have not compensated me for my time, nor am I paid for the time away from my brand-new job back in the career which I had to leave five years ago.

DR. KAWAS: Thank you, Ms. Einen. Next is Ms. Sandra Jones from California.

MS. JONES: Good afternoon, ladies and gentlemen. My name is Sandra Jones, and I am from Los Angeles, California. My travel expenses are being reimbursed by the Narcolepsy Network. I am 50 years old. It was only 19 years ago that my mother truly became a mother to me, my brother and sister. Nineteen years ago my mother began taking

what we now call Xyrem. Within a week after she started taking this medicine we noticed the incredible change in her. She could cook dinner without collapsing to the floor. She could sit down and eat dinner with us without falling asleep. She could make a sound that we hadn't heard in a very, very long time -- laughter, and more laughter without falling to the floor.

She became a totally new person to our family. That was not the case nearly thirty years ago. She quit her career as a nurse for fear of how the disease might affect her care of her patients. She became sort of a recluse in her home and we grew used to seeing her sleeping throughout the day and staying up all night. She was afraid she would fall and bring embarrassment to herself and especially to her family. People just did not understand her disease. She once collapsed at a party and people dismissed her as being a drunk. My mother didn't drink. It was what the narcolepsy had done to her.

This is an evil, evil disease and unless you have witnessed it firsthand you cannot understand the horrible ways it affects a person's live. Imagine having a newborn child, my sister,

and not being able to hold her for fear of dropping her. Imagine not being able to go to the grocery store for fear of falling in the aisle. Imagine not being able to read stories to her children because she would fall asleep, not us. Imagine not being able to drive a car for fear of collapsing behind the wheel. This was my mother.

But Xyrem changed all that. It was a difference between night and day and mother quickly rediscovered the joys that she had missed for decades -- playing games with us, going dancing, going to the movies, celebrating family birthdays and holidays. The day-to-day tasks that you and I take for granted, she could finally do as a normal person. This was the mother that we had never known until Xyrem gave us her life back and her family back. I have seen the difference. I have lived the difference. Please make this valuable medication available to people who have narcolepsy. They and their children will see the change in their lives. Thank you.

DR. KAWAS: Thank you, Ms. Jones. That concludes the section of open public hearing, and I want to thank everybody who expressed their views, information and helped the committee keep sight of

all the issues here.

We will now reopen the questions from the committee to the invited speakers, sponsor and the FDA. In particular, I would like to focus on the presentations that we had right before lunch involving the epidemiology, adverse medical events and the sponsor presentations on risk management and abuse liability. So, who wants to start the questions from the committee with regard to some of those presentations?

Continued Committee Discussion and Deliberations

DR. SIMPSON: I put up my hand under false pretenses because I had just one question really --

DR. KAWAS: We don't like false pretenses around here!

DR. SIMPSON: It was really relating to the efficacy. I mean, a lot of the presentations we have just heard give the impression that the cataplexy was, if not completely controlled, almost completely. Yet, when we look at the data we see that the median number of events at the end of some of the studies is about eight or so on drug. So, do we have any data about how many people actually had no cataplectic events?

DR. REARDAN: I think that this question

was discussed to some extent this morning. It dealt with complete cataplexy --

DR. SIMPSON: No, no, I am saying do we have data on the people who were, quote, cured? Were there any?

DR. REARDAN: We have a slide on that, I understand.

[Slide]

DR. HOUGHTON: This is an example of the long-term data, and one of the problems with the controlled GHB-2 trial is that it may be too short. The reason that the time was restricted is because of the imposition of patients on placebo for longer periods of time. But that represents a picture of the long-term response in terms of percentage change. So, we have a control across all doses, demonstrated here for a 12-month period, around the 90 percent or better mark. Now, that doesn't mean to say people don't have any cataplexy, but it is certainly very significantly reduced.

DR. KAWAS: Dr. Katz?

DR. KATZ: Yes, we have seen this slide a number of times. I just want to remind the committee that this is open, uncontrolled, non-randomized data, not the sort of data that we

would ordinarily rely on to draw any sort of conclusion about effectiveness of any sort.

DR. KAWAS: Maybe the sponsor could show us some of this data from one of the randomized trials?

DR. HOUGHTON: We could show you the change in the GHB-2 study again, which is the four-week study.

[Slide]

The data is median change from baseline. We had a median incidence of 23.5 in the 9 g group, a change from baseline of 16.1. If we present that again as percentage change -- because, once again, it is complicated by the spread in the data.

DR. SIMPSON: I guess my question is if the median at the endpoint is 8.7, it means 50 percent of the people were above it and 50 percent were below. Now, how many were below, say, 1 or 2?

DR. HOUGHTON: Well, it depends on what their starting level was, and the conditions of entry were 3 cataplexy or more attacks per week. We did have patients with very high incidence. So, in terms of absolute numbers, that is a very difficult response. I am not trying to be evasive.

DR. WOLINSKY: The other piece of that

data though that you presented and might be worth looking at quickly is the randomized stop component of the trial.

DR. HOUGHTON: Sorry?

DR. WOLINSKY: When patients were randomized to be taken off --

DR. KAWAS: The 21 study.

DR. REARDAN: Right. The question is on a-patient-by-patient basis, how many patients went from X amount of cataplexy to zero cataplexy. Is that what you are trying to get at?

DR. SIMPSON: Zero or close to zero.

DR. REARDAN: That is in the data listings for the trial. We didn't bring individual breakout of the data. We brought summary information for the committee. I don't know if Dr. Mani has a recollection or Dr. Katz.

DR. KATZ: You don't have a distribution of how many events patients had? In other words, you know, X percent had two or fewer events; Y percent had between two and five events.

DR. HOUGHTON: No, we didn't break it down like that. I think the slide that you were referring to was the one that I showed with individual patient plots, and I can show you that

quickly.

[Slide]

That is just an example of absolute numbers. These were individual patients plotted. That was their incidence at the baseline, and that was some two years after this was conducted. That is the sort of response they got when their active treatment was withdrawn. That is the group in active treatment. So, in terms of just absolute numbers, that is just a snapshot. That is not a statistical presentation. It happens to be every patient that came from that original trial through into this trial, and I show it as individual plots. It is the best impression of individual patient data I can give you to answer your question.

DR. BLACK: Just a comment on that. In this section we do have placebo-controlled data and we have the number of cataplexy attacks on placebo versus active medications after patients have been on treatment for a long period. Dr. Katz' comment is very good. The data that has been generated over the open label, though it does suggest there is a time course till optimal effect of at least two months, is open label. But this is placebo-controlled data, suggesting that the

average there of cataplexy attacks per day -- I don't know if you have the numbers of that, Dr. Houghton, but it is very low during the time of treatment unless they are taken off and then on the placebo-controlled portion.

DR. KAWAS: I have a question for the company as well as probably Dr. Dyer. I want to hear both sides of why we heard such very different descriptions of the potential for withdrawal syndromes with this disorder. I recognize fully that the company has studied individuals with narcolepsy and it is possible that alone could comprise the difference, but we do have a very nice withdrawal study in study 21, which is not typically the case, and the findings that were collected from that are in fairly sharp contrast to the stories that we have heard from Dr. Dyer with regard to withdrawal syndromes, and I wondered if both sides could tell me what the difference was. Is it dose? What is the difference here?

DR. REARDAN; I will ask Dr. Balster, but I believe it is dose and frequency. Bob, do you want to comment?

DR. DYER: I doubt that we disagree. Clearly, in my set of patients and what we use

nearly as a diagnostic parameter and which patients we should admit, even though their early symptoms are mild, is the frequency with which they are using it. So, the kinetics of the drug show us a duration of activity around three or four hours. When these patients increase their frequency so that their body constantly is exposed to GHB, those are the ones that we feel become severely physically dependent and then go through this withdrawal syndrome that can have an onset within hours of discontinuing the drug.

DR. KAWAS: So, in your opinion it is frequency of dosing, not even the number of grams per day.

DR. DYER: As far as I can tell, it is frequency because if I take the sponsor's information, and for years I have spoken to the investigators that are doing this and they have said they have had no trouble. Their patients have a 12-hour drug holiday daily, which is two to maybe three times what they are calling a half-life for this drug. So, the drug is completely eliminated from the body for a time period, and the patients have that become severely addicted, all of them -- I mean, that is kind of diagnostic for the severe

withdrawal, somebody who is taking it every three hours around the clock.

DR. BALSTER: Yes, I agree completely with that, and maybe the analogy that would help you understand it would be the analogy, for example, with alcohol where really alcohol can produce a very significant physical dependence but you can drink it every evening with your meal and you won't become dependent because between that evening use and the next day it has cleared the body. So, whatever physiological adjustments are necessary have corrected themselves. So, we are in complete agreement.

DR. KAWAS: Thank you. Dr. Katz?

DR. KATZ: Just as an extension of that, there was also the implication or the explicit statement that in some of those people who took it very frequently and ultimately, presumably, became addicted, they were compelled to take it more frequently. In other words, there was a tolerance that developed and they had to increase their frequency to get the same sort of pharmacologic effect.

So, I will just ask the same question that Dr. Kawas asked about withdrawal. We have heard

from the company that patients who have taken the drug for years and years and years don't develop tolerance; they don't have to increase their dose; they don't increase the frequency of self-administration. But, we are hearing that on the outside there are people in whom this phenomenon apparently does occur. So, I will ask the same question. Why the disparity?

DR. DYER: Again, there haven't been really good studies or anything scientific. It is kind of my thoughts or opinions but, again, it is accommodation because you are taking it around the clock. So you are accommodating. Also, in the patients that are taking it -- well, I don't know, they are not really patients -- in the people who are abusing it there is a lot of the feeling that if a little is good, a lot is better. They are taking it initially, these body builders, for this growth hormone burst. So, they really feel like they are doing the right thing. So, there is nothing to have them diminish their dose or hold their dose as it is. Then, once they start taking it more frequently, the duration of the drug as it wears off in three or four hours, we think, gives them kind of a dopamine surge for which then they

are going to feel a little depleted and want to take that next dose. Then there is also physical craving for that kind of high. They are awake and feeling that kind of high as opposed to the patients that are taking it immediately upon going to bed and then sleeping through this euphoric -- whatever the kids are trying to get that are abusing it -- if you can roll that into an answer.

DR. BALSTER: That is exactly the way I would see it too. Just to add one further thing to that, the way to look at tolerance, you have to understand that it occurs through different effects at different rates and in different ways. So, the therapeutic effect is one effect. The intoxicating effect is a different effect. And, commonly in abuse situations where persons are trying to maintain an intoxication, they have to escalate dose and frequency in order to do that, whereas the data obtained in these clinical trials, of course, is on the therapeutic effect.

DR. DYER: One other comment, in the alcohol abuse trials they did escalate their dose in more of a craving kind of manner. That was about 15 percent.

DR. KAWAS: Dr. Roman?

DR. ENGEL: I would like to add something, if I may, to this point that is based on the risk management system proposed by the sponsor. As you saw, the data collected by the specialty pharmacy will include dose by patient. And, because of that, the specialty pharmacy will be able to predict when is the appropriate timing for a given patient to have their prescription refilled. So, for example, there are patients attempting to refill too soon, so to speak, that will be identified and it will be an opportunity for the pharmacist to interact with the physician very quickly, before a patient might get into a situation like which Dr. Dyer is describing with an overuse syndrome.

DR. ROMAN: A question perhaps again for Dr. Balster. Is the pharmacology of GBL and 1,4-BD similar in animal experience to GHB? Number two, if there is a difference, did I understand correctly that GBL and 1,4-BD are not currently drugs of abuse?

DR. BALSTER: Well, the first question, pharmacological comparisons of GBL, GHB and 1,4-BD, these haven't been very extensively done. So, hopefully some of those NIDA grants that someone

was talking about will really take that question on. But let me say that in a number of those studies that were done to describe the pharmacology of GHB, in some of these studies actually GBL was administered to the animal with the view that it was a prodrug for GHB. I forgot who said it but someone said that so far as we know, all of the effects of GBL and 1,4-BD are really as a consequence of their conversion to GHB. I believe that would be the current state of knowledge about that although it is imperfect.

Now, the question about control, in a sense, yes, all of these drugs are potential drugs of abuse because they can be taken and basically are active in the case of precursors with metabolites. So, yes, all of these are potentially drugs of abuse. Only one of them is a controlled substance and one of them, by congressional action of last year, became what is called a listed drug, and I could explain that to you or, actually, Dr. Sannerud would know better than I what exactly that means. But it essentially means that there is limited distribution.

DR. ROMAN: So, with GBL and 1,4-BD there is no control.

DR. BALSTER: Well, as I say, for 1,4-BD, to my knowledge, there is no control. I need to step back a little bit from that because we could get into too long of a discussion about what constitutes an analog under the specific language of the legislation. So, it is possible for prosecuting attorneys to claim that one or another of these drugs are analogs of a controlled substance. The Controlled Substances Act, in a sense, regulates analogs. Now, 1,4-butanediol is questionably an analog, but that would be something that would be worked out in court. So, I am not trying to tell you that someone could absolutely, with impunity, sell 1,4-BD to children and say that it wasn't a drug of abuse because I am sure that there would be authorities and prosecutors who would try to do something about that. But in terms of the actual language of regulation, only GHB is a controlled substance.

DR. SANNERUD: GHB is a Schedule I controlled substance. Butanediol and GBL are considered controlled substance analogs under federal law, which means they can be prosecuted, as GHB, with penalties and other things would apply if someone is caught trafficking, distributing or

clandestinely manufacturing or selling these compounds as well. GBL is listed as a List I chemical, which means that there is record-keeping and registration required. There are no retail sales of butanediol, and there is a graph in here with the product. These are used in industrial uses. So, this comparison is really a little bit misleading. I don't know the numbers but GHB is not even marketed yet, so this number on production is only for clinical trials I assume.

As far as the GHB and Xyrem they are both GHB. There is no forensic analysis that is going to differentiate between the two. So, when samples are submitted to labs there is no way to tell if it is the product or if it is something that is made at home. So, for someone to say that there has never been any diversion of the product, there is no way to tell that because there is no way to differentiate between the two under forensic laboratory conditions.

Another question I wanted to address is the quota issue. Ms. Meyers brought up quotas for Schedule II compounds, the stimulants. DEA sets the quota, as it will with GHB as well. It has never been the case that drug has run out at the

end of the year because the quotas are set too low. If there is a problem with the drug manufacture the quotas can always be increased throughout the year, and they are done so on a regular basis. So, there has never been the case where a drug has run out.

DR. KAWAS: Dr. Mani?

DR. MANI: I would just like to touch upon the issue of drug diversion during the clinical trials once again briefly. Many speakers have asserted that there has been no evidence that Xyrem or GHB used in the clinical trials included in the database was diverted. That may very well be true, barring the one exception that I cited earlier, and I have no firm evidence to the contrary. However, I have gone through the NDA, reviewed the whole NDA, and I would be a little more hesitant in making that assertion, and I will tell you why, and that has to do with the way the drug was dispensed in the Scharf study which, as you know, occupied about 30 percent of the database in terms of patient numbers and about 70 percent of the database when you are talking about patient years of exposure.

What happened here was that patients saw Dr. Scharf in Cincinnati, at least for an initial

visit, and had an appropriate diagnosis made and were then enrolled in the trial and then went back to whatever part of the country they came from. Prescriptions for medication were filled based on their returning completed diaries. In some instances it appears, at least from my looking at the case report forms, that prescriptions were sometimes filled in advance or the diaries being returned, obviously to prevent the patient from running out of the drug. But the important thing is that patients were not required to return unused supplies of medication prior to getting a fresh prescription, or to provide any formal accounting of how much medication they used or did not use. In the absence of any active surveillance of that kind, as I said, I would be quite hesitant in making the assertion that no medication was diverted.

DR. REARDAN: I need to make a qualifying statement here. We do not disagree with Dr. Mani. However, under the company's clinical IND, our patients under IND didn't begin entering trials until 1996. Patients were required to document their dose; to return their bottles. The bottles were all qualified by volume in terms of what was

returned. The incident that Dr. Mani refers to, I believe, occurred in 1986, when GHB was available as a nutritional supplement and Dr. Scharf's trial, again, was clinical practice. There were a lot of issues on GCP compliance in that trial. We do not take responsibility for accountability of drug under Dr. Scharf's trial. So, I will just qualify that. Okay?

DR. MANI: I agree.

DR. FALKOWSKI: I have a question and it has to do with the fact that we are talking about a method of taking this drug where you take half the amount at bedtime and then you wake up several hours later, but don't really wake up, and take the rest of it. And, I am just wondering what would happen if you were confused. It also involves mixing it ahead of time to the right strength. I am asking this both to Dr. Dyer and the sponsor, what would happen if someone took 9 mg at once? You know, if someone got confused and took it all at once, what would be the expected outcome?

DR. REARDAN: I had a number of questions about this at the break from a couple of members of the committee -- how do they make it up, and so on. It might be worthwhile to ask Patti Engel to go

through that. The other point about narcoleptic patients waking up, maybe Dr. Black, you could comment on how they wake up and take their second dose.

DR. FALKOWSKI: Right, but my bottom line question is what would happen to a person who inadvertently took all of their dose at once, and I really insist on an answer to that. Thank you.

DR. BLACK: That question has been answered by patients who have taken inadvertently larger doses. As far as the waking up at night, the patients that are here could probably respond to that, but the overwhelming majority are awake actually before the four hours later on their own and they are fully awake. The medication is premixed so there is no mixing that needs to occur at that point. There are folks who have taken extra doses and there is more sedation that occurs with the extra duration and the period of sleep is longer with the higher dose.

DR. FALKOWSKI: Is the answer then increased sedation? Is that the answer to my direct question?

DR. BLACK: Yes, if the dose is increased there is increasing sedation and a longer sleep

period.

DR. FALKOWSKI: Okay. Dr. Dyer, could you respond to that?

DR. DYER: It is my opinion that the dose would be around 100 mg/k and at that point you are going to have coma and some of the other side effects that we see in our club goers are very likely to be what you would see. So, vomiting and aspiration is a possibility. You know, the ability to hear and react to fire alarms, children, whatever, that is all going to be blunted.

DR. FALKOWSKI: Is it a possibility then that some of these people who may have double dosed would be in a coma but who would know, you know? Is that a possibility, sponsor? I mean, who is to know?

DR. BLACK: I think that the question is a good one, and what I might call deep sleep someone else might call a coma. But when we look at the brain wave activity of the folks with the higher doses, they have nothing in the EEG that would be consistent with straightforward coma.

DR. FALKOWSKI: But you didn't take EEGs on these people when they were sleeping in situations like this.

DR. BLACK: Well, we have done EEGs on the folks when they have been sleeping at the 9 g dose but not on double the 9 g dose.

DR. FALKOWSKI: Okay.

DR. KAWAS: Dr. Katz, please.

DR. KATZ: Yes, a couple of things. Maybe the best way to get at this if it is possible is to ask the company to show us any data that they have about what happened to patients who took, let's say, a single 9 g dose. I don't know how many patients did that, but if there is data on that it would be nice to see.

So, I don't know, maybe you could look for that while I get to the second part which is, again, just another variant about the question we were talking about before, this perceived disparity between patients and non-patients who take the drug recreationally. We have heard again, not just in terms of withdrawal and addiction and tolerance but just in terms of serious adverse events, a number of the serious adverse events that we have heard about in the emergency room situation seem to have occurred at doses, presumably -- I don't know how reliable the dose information is in that setting, I am not sure, but presumably at doses that patients

routinely get and which they tolerate extremely well. So, I will ask the same disparity question again there.

DR. MIGNOT: I think you have to realize also that you are talking about narcoleptic patients who also experience daytime episodes of overwhelming sleepiness that sometimes lead to confusion, and there are a lot of horror stories about narcoleptic patients, independently of GHB, at any moment of their life where they can sometimes be in a risky situation just because they have what we call automatic behavior, this overwhelming sleep attack where they really don't know what they are doing, where they may be driving or doing something dangerous. I think that is also important to keep in mind. The danger of taking two doses at a time, if it is relatively well dispensed, for narcolepsy patients I think needs to be put in perspective for their other symptoms.

DR. REARDAN: I am only aware of one case in our database. It was a patient who inadvertently took 18 g and I think, Dr. Mani, you are well aware of that. He did fall on his head. So, it is confusing as to whether it was a result of his 18 g dose -- you know, that was the best

estimate we had -- or in the fall he hit his head, but he did end up being taken to the emergency department and did need supportive care. Oh, Bill is saying that was a normal dose. I am sorry, let me get him to clarify.

DR. HOUGHTON: Yes, I am sorry. That is one of the cases that we know very little about. It was a patient who was in the kitchen. There was a loud bang. His wife heard the noise and came in, and her husband was on the floor. So, we got no dose relationship to that event. We know nothing as to whether it is related to Xyrem.

The 18 g overdose was the patient who was supposedly sleepwalking, in the Scharf database, who supposedly then took 18 g on top of his normal dose and was taken to hospital and ended up on a ventilator.

Really, the best prevention we have of 9 g being taken together is the fact that the dose has to be made up into separate doses. The instructions to the patient are very clear. They make two doses up together, dilute it in the water; drink one when they get into bed and the other, in a sealed cup, put away. Now, if they took the second dose in ten minutes or two hours, we have

not done that study and it is very dangerous to extrapolate that sort of dosing. On one hand, I can quote the patient who took 180 g and was taken to hospital unconscious and walked out of hospital four hours later to be admitted to the psychiatric unit.

I certainly don't want to propose that as the normal pharmacodynamic response. We have not done a study that has escalated beyond the 4.5 g dose twice a night, and I think it is very dangerous to extrapolate. It is also very dangerous to extrapolate the anesthesia data or some of the data that Dr. Dyer talked about this morning. Doses were given up to 100 mg/kg intravenously. If we believe the bioequivalence data, the absolute bioavailability data, that is equivalent to at least 300 mg/kg as an anesthetic dose, and that would be the best dose relationship we could give to dose escalation. Again, without true data I am not prepared to extrapolate from that.

DR. KAWAS: Dr. Mani, do you still want the floor?

DR. MANI: Yes, very briefly, just as further evidence of how much individual variability

there is in response to this drug. There is a subject who Dr. Houghton had referred to in his presentation this morning, a healthy subject participating in a pharmacokinetic trial, a healthy young subject who received a single dose of 4.5 g and afterwards became obtunded, developed obstructed respiration perhaps because of his jaw falling back, became incontinent or urine and stool, and took a number of hours to recover but did not need any special supportive care. So, even a 4.5 g dose may not be entirely safe for everybody.

DR. HOUGHTON: That story is somewhat true but not quite accurate. The patient was easily arousable, walked to the bathroom after the event of passed urine, after resting back in bed had a normal sleep and, two hours later was awake and ate a normal lunch. So, again, I can't account for the degree of obtundation but that still represented the maximum single dose in our database. It was a single dose of 4.5 g after a 10-hour fast.

DR. MANI: Although those details about the patient being able to get up and go to the bathroom and eat her lunch, and so on, wasn't in the narrative that we have available.

DR. HOUGHTON: We were collecting urine samples every two hours and I can assure you the patient was walked to the bathroom. She certainly vomited at the time.

DR. KAWAS: Dr. Leiderman?

DR. LEIDERMAN: Very briefly because Dr. Mani raised one of the points that I wanted to, but the other question I had for the sponsor and the sleep neurophysiologists here, do you think that in some of the differential response that we are seeing in the narcolepsy patients as compared to the subjects who become dependent, addicted, have overdose problems that there may be a role not only of the basic neurophysiology of the narcoleptic brain but, of course these patients tended to be co-medicated with stimulants, and what role do you think that might be playing in the narcolepsy population?

DR. REARDAN: Is the concern that stimulants would still be present on board when they take their nightly dose of Xyrem? Is that what you are after, or what?

DR. LEIDERMAN: Well, I am asking for your thoughts on, shall we say, the differential effects of GHB on the two populations, and one of the sort

of clear differences, taking sort of the first cut, is that narcolepsy patients are co-medicated with stimulants generally, whereas the abusing drug population, if anything, is self co-medicating with other CNS depressants or using GHB at high doses alone.

DR. BLACK: I think there are a number of questions that surface. We have patients in protocols where they are wanting to remain on the protocols or wanting to be drug compliant. There are reasons that they wouldn't abuse in addition or outside of the fact of co-pharmacy with stimulants and so forth. So, it is hard to compare those two groups clearly.

I think the best we can do is speculate. We have a number of patients that were not co-treated with stimulants as well, that were on just Xyrem, and they didn't self-escalate the dose or abuse the agent either. I think the only way to do it would be to give high dose frequently to the narcolepsy patient population and see if they are similarly addictable, and then it would be also interesting to find out what percentage of the normal population is addictable as well. Obviously, those studies couldn't be done. But I

think we can't compare the two and it is real hard to try to extrapolate the information we have to do a comparison.

DR. KAWAS: Dr. Dyer, followed by Dr. Van Belle, followed by Ella Lacey, followed by the questions that the FDA has asked us to consider. In between, we will get a quick demonstration of the mixing.

DR. HOUGHTON: Could I just add one point of clarification to Dr. Leiderman's question? There were patients in all of the studies that were not on stimulants. In the GHB-2 study I think it was about 15 percent when we did a recent look at the database for Dr. Mani. So, there was at least a proportion of patients represented in the database that weren't on stimulants as concomitant medication.

DR. DYER: There was one study, I believe it was done in rats where amphetamines and then a second with caffeine, where those were shown to kind of be antidotal to GHB poisoning, where it prevents the rats' loss of riding reflex. So, there may be some of that issue if they are taking it concurrently. One of the other things about the disparity, where I don't see the disparity as being

so much is that the narcoleptics are taking their dose at night. We know pretty commonly from the surgical studies from what we see coming into the emergency room and from the adverse effects of the study, that GHB causes vomiting and incontinence. So, we are seeing that in both populations of patients.

DR. CHERVIN: Is anybody there?

DR. KAWAS: Yes, is that one of our phone consultants, Dr. Chervin or Dr. Guilleminault?

DR. CHERVIN: Sorry, it seems like we were completely cut off.

DR. KAWAS: Can you hear us now?

DR. CHERVIN: Just barely. If there is any way you can make this signal more than barely audible, it would be helpful?

DR. KAWAS: We can barely hear you but it sounds like we are going to have to get the AV people on it, if you give us a moment.

DR. CHERVIN: I do have questions if I have time to ask them.

DR. KAWAS: I know that you are on a timetable, so we will put you in the middle of the six-person pileup, if we could let the speaker that is going now finish though.

DR. DYER: So, there was another study where they took the patients and the patients that they gave the dose to and then forced or tried to maintain themselves awake, those were the patients that became confused.

The other thing is that in our emergency department study where we were trying to verify our ability to predict GHB by toxidrome, we looked at patients that came in with a GCS score less than 8 that were spontaneously breathing. So, unlike most CNS depressants that cause profound coma, generally the breathing is still spontaneous and maintained. You see mild respiratory acidosis but it is not very common that these patients need to be intubated. So, it is not contrary to be thinking that a patient might be comatose and survive the night.

DR. KAWAS: Dr. Van Belle, while we are still working on the audio, do you want to go ahead and ask your question?

DR. VAN BELLE: I just have a brief question with respect to age eligibility. Will this medication be available to people under 18 years old?

DR. REARDAN: The company has not

specifically developed data for pediatrics, and I think this would have to be something we work out with the agency but, typically, a medication approved for adults is not denied children. FDA and Congress have tried to put incentives in to get sponsors to develop pediatric information. In addition, narcolepsy is not generally a pediatric disease. I don't know if either Dr. Mignot or Dr. Black want to comment further. Dr. Katz?

DR. KATZ: Well, generally speaking, unless there is a good reason not to, we would limit the age that would be at least included in the indications or in labeling or dosage administration to the age of the lower limit of the age studied in the trials. I don't know exactly what the youngest patient was in these trials.

DR. REARDAN: Bill Houghton is saying 12.

DR. KATZ: Okay, 12. Again, if there was one patient who was 12 and everybody else was 18 and above, we would say adults or 18 and above, that kind of thing. It is true that there is no prohibition, obviously, from a physician writing a prescription for a drug for a child if it is only explicitly approved for an adult. It happens obviously all the time. But one of the questions

when we get to it with regard to risk management and that sort of thing is if there were no children studied, or children studied below a certain age, do you think attempts should be made to restrict it in this case? So, you know, it is open for discussion.

DR. MIGNOT: To answer the question, onset of the disease is roughly between 15 and 25. That is really when the bulk of the patients are coming in, especially for cataplexy, and I think it is very important to treat them early. As there is more and more knowledge about narcolepsy being an important disease and being recognized early -- I think you have heard a lot of testimony about how important it is to treat them early so that they can go through normal schooling. I think it will be very important to not be too restrictive towards the lower age.

DR. KAWAS: Dr. Lacey?

DR. LACEY: Two questions, one regarding the packaging. With the packaging being in a bottle and it is child-resistant dosing, and all, but hearing about adolescents and their involvement with GHB, I wondered if you considered other packaging. In deciding on this packaging, did you

consider individual dosage packaging at all, and what happened with that?

DR. REARDAN: We considered individual dosing packaging for sure. We thought that was a greater potential for diversion as it is easy to take those individual doses. I think maybe you would get some reassurance if Patti Engel can go through how we instruct the patients to dose and what the controls are for that. Patti?

MS. ENGEL: Thank you. To the point of individual dosing, we did speak quite extensively about that with law enforcement.

DR. LACEY: Yes, I am pretty convinced about the patient. I am more concerned about others in the household who are exposed to a bottle.

MS. ENGEL: Right. I will address that as well. On the individual dosing, law enforcement was concerned about small containers that could be stuck in a pocket or purse, or slipped in someone's drink more easily. One of the things I shared with you earlier is that the bottle itself comes with a child-resistant closure. What is difficult to see from this distance, but it is something called a press-in bottle adaptor. When the patient gets

this, there is a little well, if you will, in there. Even if a child can get this lid off, you can't drink it down. What has to happen is there is a metered syringe provided. It gets stuck in here and the patient removes a metered dose. Okay? They then have two child-resistant dosing cups and these aren't fancy. We took them because they are CPIS tested for child resistance, of course, and they put it in, preparing both doses by their bedside.

Now, the dose itself is metered. This Xyrem, to be frank, is not good tasting stuff. It is sodium oxybate. It is very salty. Many people will dilute it. How much they dilute it really is to their taste. We did not want to cherry flavor it or anything like that that may make it more attractive to children. Okay? Does that answer your question?

DR. LACEY: It really wasn't the small children that I was concerned about as I was about the older, the adolescents in the household who can open it the same as I could. So, I guess your answer was that law enforcement was concerned about the small dosages just being put in a pocket.

MS. ENGEL: That is right. Remember,

illicit use of Xyrem also falls under C-I penalties, like heroin or LSD. So, we will never be able to find a package that a 19- or a 21-year old will not be able to get into. What we do, however, is to educate the Xyrem patient on a number of occasions of the penalties should that occur. So, there is an element of patient responsibility with this.

DR. LACEY: Thank you. The second question I have is about the suicide attempts that were presented by Dr. Houghton this morning. That was in that list of adverse events I believe, and it has continued to bother me that we talk about it as a suicide attempt as though nothing else happened and I am just curious, I guess, in those attempts were some of the other adverse events also experienced by those persons who were suicide attempters?

DR. REARDAN: As you heard from Dr. Mignot, depression is very common in narcoleptics, but I will ask Bill to comment on that.

DR. HOUGHTON: In all the patients who attempted suicide there was preexisting disease. In terms of response to the dose taken, only one of the suicide attempts involved Xyrem, and that was

the patient who took a very large dose, about 300 ml of the drug which is equivalent to at least 150 g, and he became comatose, incontinent of feces and urine, continued to breathe spontaneously, was found by his wife in the bathroom, transported to the emergency medical care, did not require intubation or ventilation, and walked out of hospital four hours later to be admitted to the psychiatric unit. I certainly don't propose that as the norm. There will be certainly unconscious patients at much lower doses. So, please don't think I am proposing that as the pharmacodynamic profile of the drug. But you asked me what the side effects of the suicide event were and that is the only data that I can give you.

The second suicide event that was not fatal did not involve Xyrem. One of the fatal attempts did not involve Xyrem at all. The last suicide attack in the bipolar disorder patient was a real pharmacologic cocktail involving benzodiazepines, opiates, a number of drugs and some Xyrem.

DR. LACEY: But for those individuals who did have the suicide attempts, they did not have other -- not with the attempt directly but other

adverse events also in their report?

DR. HOUGHTON: No. One of those was a lady who had a group of people to her home. She asked them all to leave early, and when attempted to be contacted the next morning didn't respond, and when her attentions were sought she was found dead in the home.

The second attempt was a young lady who took an overdose of buspirone and told her father immediately. Her behavior was normal to that point. So, that is an example.

DR. KAWAS: Dr. Chervin or Dr. Guilleminault, can you hear us now? You guys are next in the line up.

DR. CHERVIN: Thank you. I have two questions. Please tell me if it has been covered and I just was not able to hear it, but I read in some of the material that was distributed prior to the meeting about comparisons of the therapeutic index or the therapeutic window for GHB to that of other drugs that are currently approved and used. I was wondering if perhaps Dr. Dyer or Dr. Falkowski or Dr. Balster could address that comparison.

DR. DYER: Is that the comparison of LD-50

in rats?

DR. CHERVIN: I guess it was rats, and it was LD-50 and effective dose, and they looked at the ratio.

DR. DYER: The problem I have with some of the rat data, lethal dose data, is the deaths we see are often secondary to coma. It takes high doses to cause pure respiratory depression. We have some patients that idiosyncratically have a pulmonary edema, but most of the deaths are secondary to unprotected coma and loss of airway. So, I don't know that that would extrapolate or come from rat data at all. I don't think you would see that.

DR. CHERVIN: Is there any other way to get at the issue of is Xyrem going to be more dangerous than other drugs that are used carefully when indicated?

DR. REARDAN: Dr. Chervin, I have some data on LD-50 that will help. Oral GHB has an LD-50 on the order of 9000 mg/kg in rats, and about 3500 mg/kg in mice. The IV LD-50 is about a third of that for GBL and for butanediol it is on the order of 2000 mg/kg. If you look at the effective dose, we are in the range, I believe, of about

50-120 mg/kg recommended for the narcoleptic patients. Now, that is just on an LD-50 basis. I don't know if Dr. Mani wants to comment on the therapeutic range, or Dr. Katz.

DR. KATZ: I don't think we really know. I am not sure if the animal data is relevant at all. And, I don't think we have data that, in a systematic, adequate way, explores the full dose response both with efficacy or tolerability. As you have said, you have done a trial where the maximum dose, fixed dose, was 9 g per night and, you know, we either decide that that was a tolerable dose or it wasn't. And, you have the dose response for the effectiveness, and that is all you have. As you acknowledge, you haven't explored higher doses so I don't think we really know, and I don't know how you would really get at the question of how the therapeutic window, if there is one, compares to other drugs that are in common use. Some drugs that are used, there is a belief that they have a very narrow therapeutic windows, and some are wide. I don't think you can say more than that.

DR. REARDAN: I don't disagree.

DR. GUILLEMINAULT: I have a question.

Narcoleptic patients have hypnagogic hallucinations. They may even shoot -- if a gun is available they may hurt their bed partner because they are keeping their hallucination. How much does Xyrem decrease hypnagogic hallucinations, which is a very significant side effect which may kill neighbors and may kill even bed partners?

DR. REARDAN: If I understand the question, Dr. Guilleminault, it is how much did Xyrem reduce hypnagogic hallucinations in our trials, and I guess my first response is the incidence was very low and we did not see a statistical significance in GHB-2. I don't know if Dr. Houghton wants to comment further on hypnagogic hallucinations.

Just while they are finding the data, it is fair to say that the incidence of hypnagogic hallucinations recorded in the four-week trial was very low. There was a trend towards improvement that certainly didn't reach statistical significance. There was a better representation in the long-term open-label study and we could show that but I am loathe to do so because I certainly don't want to claim it as efficacy. I think we will be able to find the GHB-2 data.

[Slide]

DR. HOUGHTON: In the Lammers study there was a reduction from 0.87 hypnagogic hallucinations per night over the 4-week treatment period to 0.28 incidence per night, with a p value of 0.008. That is one set of figures.

DR. MIGNOT: Just to sort of expand on what you said, if only about 40-60 percent of patients we narcolepsy/cataplexy have hypnagogic hallucinations as their symptoms or sleep paralysis, then obviously that must reduce the power for the trial because they have only about half of the patients they included who even had that symptom.

[Slide]

DR. REARDAN: This is a slide from GHB-3. I guess that is open label, I don't know if we want to go into that. What it shows is median change from baseline to visit number and out through 12 months. You see a median change in hypnagogic hallucinations, a reduction of 0.35 per day. Is that right?

DR. KAWAS: Dr. Penis and then Dr. Falkowski and then this committee will be looking at the questions that the FDA has asked us to vote

on.

DR. PENIX: I think we have to anticipate several different possibilities in the treatment of patients with any drug, and I am somewhat concerned about the fact that the effective dose of Xyrem appears to be the maximum dose available, number one. Secondly, in regards to the possible protective effects of stimulants on the side effect of sedation, and whether we should consider Xyrem as a monotherapy drug or as an adjunctive treatment, and the question I would like to ask -- I think Dr. Houghton may have presented this data of talked about it, of the 15 percent of patients who did not receive stimulants while on Xyrem whether there was a difference in the maximum dose escalation in those patients compared to the ones who were on stimulants. I am not sure if we can answer the question, but if there is data on that, if there is a difference.

DR. HOUGHTON: No, we don't have data separate for those on stimulants and those not on stimulants. There was only about 15 percent in that controlled trial that were not on stimulants. So, we hadn't plotted that at all. Remember that stimulants are taken in the morning and usually the

last dose at lunch because narcoleptics are really trying to sleep at night and stimulants really complicate that, and the half-life of the gama hydroxybutyrate is about an hour.

So, even after their second dose their plasma levels on awakening in the morning are extraordinarily low. So, a contribution of stimulants to change that is quite unlikely. We certainly didn't see an abnormal sleep response in the normal volunteers in any of the pharmacokinetic studies, except the one patient who became obtunded, and she was awake four hours later and ate lunch, and then went home that day. So, the only real suggestion of data I could give you in the absence or stimulants is the single dose response or the repeat dose response in the pharmacokinetic studies, and that certainly didn't appear to be different at all.

DR. BLACK: I would just comment on the notion of a potential protective effect with stimulants. With the traditional stimulants, they are relatively short acting and there is a phenomenon called rebound hypersomnia as the medication wears off -- well demonstrated in animals and humans -- where the individual becomes

more sleep than they would have been had they not taken a medication; often a problem for those with narcolepsy who are using those medications.

Rather than those stimulants keeping people more awake and less affected by the Xyrem dose, there is the potential for even greater sleepiness with that rebound hypersomnia. That has not been well explored, but I think it would be erroneous to assume that there is any protective effect from the traditional stimulants. From the longer acting stimulant, modafinil, sleep studies have been done to suggest that there is no impact one way or the other on sleep in terms of depth of sleep and so forth.

DR. KAWAS: Dr. Falkowski?

DR. FALKOWSKI: I have to take issue -- well, I already did with the statement that Xyrem will not contribute to the public health problem of abuse of GHB-like substances because I think it will and I want to take just a few minutes to elaborate on why that might be something I couldn't cover in the confines of my 15 minutes as well as covering those other points.

I had occasion last week, in Philadelphia, to present at a conference on drug abuse addiction

professionals from around the country, and since I speak about drugs of abuse, when I got to GHB I said, so, tell me about GHB in your community. Having heard from 15 people from 15 distinct parts of the country on this, a common theme emerged and that had to do with the fact that people who were abusing it couldn't quite get the dosing right because they kept passing out. Passing out became sort of a way of life. I think in Dr. Dyer's data we even saw that as well.

This is a drug that causes people to lose consciousness and in some cases respiratory arrest. Well, I think this is particularly relevant because if dosing is the problem I believe that this will only make more attractive a predictable dose as a known entity in a prescription product. "Gee, I can get around all these dosing problems by getting the prescription."

I am also concerned that none of the sponsor's packaging that I looked at even mentions the word gamma hydroxybutyrate, or did I miss that? I looked for it; I didn't see that. That concerns me because, as we have seen with oxicodon, we know, for example -- and I think it is a good case, we know that narcotic addicts will seek out

prescription narcotics for predictable dosing and for predictable purity. And, we have seen an increase once long-acting oxicodon was developed -- we have seen an expansion in its prescribing not just for chronic pain but for the treatment of even acute pain. That plays out to the tune of 300,000 oxicodon prescriptions in 1998 and over 5 million oxicodon prescriptions in the year 2000.

What people have to do, what drug seekers have to do to acquire it is go to a doctor and feign pain. This happens with unsuspecting doctors and it is happening in all parts of the country.

Now, diversion of drugs does not occur by people storming with machine guns the one central manufacturing. It occurs at the patient-doctor level. And, I am very concerned about the possibility of folks who are having trouble. Again, this is a diverse population; it is not just kids using drugs. This is weight-lifters, these are people seeking effects, going to a doctor and saying, gee, you can get around all that; just go to a doctor and tell him you are sleepy. Just go to a doctor and tell him you collapsed. This is really seriously my concern about this, and I don't think that these two issues are separate. This

drug has a huge following.

DR. KAWAS: I would now like to focus on the questions that the FDA has asked us to vote on. Do you feel very strongly that your comments are necessary before that?

DR. RISTANOVIC: I am going to make a comment extremely brief. The comment is very brief because in today's time we know how to diagnose narcolepsy. So, there is no way, even if someone is trying to malinger, to be given a diagnosis without appropriate testing in the sleep lab. That is a prerequisite.

DR. KAWAS: Thank you.

DR. RISTANOVIC: That is all.

DR. KAWAS: The FDA has given us three questions that they want this panel to vote on, and a whole page and a half of other items that they would like this committee to discuss.

So, I would first like to ask them if it is acceptable to facilitate the discussion, can I make the decision to split the first question into two?

DR. KATZ: Absolutely.

DR. KAWAS: Thank you. It might be the only thing that gets done quickly today. The first

question is going to be has the sponsor demonstrated efficacy of Xyrem for the proposed indication to treat cataplexy? I am opening the floor for discussion on that. Yes, Dr. Katz?

DR. KATZ: Again, I think it is very important for us to hear a discussion about dose and which dose. I mean, I mentioned that earlier in my comments this morning, but if you could address that it would be very helpful.

DR. KAWAS: Absolutely. In fact, maybe I would like to facilitate this part because I think this is the easiest thing that is going to happen in the next hour. To my mind, there have been two pivotal studies that have suggested efficacy for this drug in relationship to cataplexy at the 9 g level. Maybe by making that not overly provocative comment we can stimulate discussion. Does anyone want to comment on the dose or the effect on cataplexy before we vote?

DR. FALKOWSKI: Is that the recommended dose? It is not. That is why I am sincerely confused because the study seemed to show efficacy at 9 g, yet, the recommended dose is something other than that and that needs explanation. I don't understand that.

DR. KAWAS: Any other comments? Richard?

DR. PENN: I was going to make it a motion so we would save some steps. I think it is very clear that what you said is a good summary of the case that, in fact, they haven't set the dose at 9. They have suggested a different dose regimen and that has to be looked into very carefully. But the one thing I think we all we agree on is your statement. I would, therefore, put it as a motion, since we are supposed to do a motion so that that has been shown.

DR. KAWAS: Would you like to make a comment, Gerald, before we pick the motion that is about to be on the floor?

DR. VAN BELLE: Sure. Well, I think it is the issue of dose response that I am struggling with in this case in terms of the pharmacokinetic model. If you assume that there is a pharmacokinetic model that is dose related, I would say if evidence has been shown for an effect at 9 there is probably an effect at 8.5 as well. Well, where do you draw the line at that time, and I don't quite know where to do that. I think there is ambiguous evidence for an effect at 6 and one study showed that. So, if you want the technical

answer, I think there is only evidence for clinical effectiveness at 9 but that ignores, to my mind, the pharmacokinetic aspects of the data so I am struggling with this.

DR. KAWAS: Could we restate Dr. Penn's motion that this committee vote on whether or not there has been efficacy demonstrated of this drug for the treatment of cataplexy and, specifically at the dosage of 9?

DR. SIMPSON: This may be my ignorance, but when something is labeled, for example, that it is efficacious at a dose of 9, does that mean that a doctor would necessarily prescribe it at 9? He could prescribe it quite a lot higher, couldn't he?

DR. PENN: That is going to get us into the next thing, which is how this is going to be monitored. Because it sounds like we want to put an absolute dose limit and we don't want to allow variability in the population. By the technical way we are going to allow this out, if they are going to be watching how much a patient can take, then is a doctor going to be allowed the latitude a patient more, and you are asking can they be given less? I think the answer is usually the doctor makes that decision. Everybody understands that is

the mean does that you have to use but that doesn't mean your patient will respond to it. So, there is the latitude unless we put into force this voluntary program.

DR. KAWAS: I would like to focus this committee back on the questions or we will never -- well, we will have everyone on a plane without a quorum in order to vote on these issues.

The first question really isn't so much about safety and what a doctor will do, the FDA has just asked us have they demonstrated efficacy for this drug in either of the two indications.

DR. FALKOWSKI: I believe they have demonstrated efficacy for reducing cataplexy in cataplectic narcoleptics on stimulant drugs. I think that is what their studies have shown us today.

DR. KAWAS: Okay. We will be taking a vote and everyone's vote is going to count. Are there any other comments people want to make before we put Dr. Penn's motion on the floor?

DR. SIMPSON: I really agree that they haven't necessarily demonstrated efficacy in treating cataplexy but really in reducing cataplexy.

DR. KAWAS: Do you want to put your motion on the floor again?

DR. PENN: The company has shown efficacy at 9 g per day using a 4.5 divided dose for treating cataplexy in narcoleptic patients.

DR. KAWAS: These votes are going to have to be recorded individually I think. So, can we start with everyone who agrees that the sponsor has demonstrated efficacy of Xyrem for the proposed indication to treat cataplexy? Please raise your hands now.

I just want to remind everybody that the voting members of the committee actually are sort of in the central part of the table, beginning with Dr. Simpson and then going around to Dr. Penix. All who agree the company has demonstrated efficacy for cataplexy, raise your hand.

[Show of hands]

How about if we go around and identify, and start with Dr. Penix for the record?

DR. PENIX: I agree.

DR. KAWAS: Just your name.

DR. PENIX: Dr. Penix.

DR. VAN BELLE: Van Belle.

DR. PENN: Penn.

DR. KAWAS: Kawas.

DR. WOLINSKY: Wolinsky.

DR. ROMAN: Roman.

DR. KAWAS: All the people who do not feel the company has shown efficacy for the treatment of cataplexy, please raise your hand and start identifying.

[Show of hands]

DR. SIMPSON: Simpson.

DR. FALKOWSKI: Falkowski.

DR. LACEY: Lacey.

DR. KAWAS: I think that was everyone, so no abstentions in that case.

Moving on to the next hard one, has the sponsor demonstrated --

DR. KATZ: Dr. Simpson and Falkowski, I believe in your comments you said you thought there was an effect demonstrated, or something, but the vote went the other way. I just want to understand.

DR. FALKOWSKI: Right, I believe that they have demonstrated that there is some evidence of efficacy for reducing cataplexy in cataplectic narcoleptics on stimulant drugs. These studies have been conducted on people who were already on

stimulant drugs. We don't know about the cataplectic narcoleptics who weren't. So, I wanted to reflect what we actually looked at, the scientific evidence.

DR. KATZ: And, would that be the basis for your no vote as well?

DR. SIMPSON: Well, mine is really that they reduced cataplectic events. I guess my understanding of treating it is that they couldn't sort of cure it.

DR. PENN: May I just clarify? I didn't mean cure. My motion was not cure, nor did I say monotherapy.

DR. KATZ: Right. From the point of view of an effect, you know, that sort of language only being applied to a cure, the vast majority of things we treat and give claims for in indications are for symptomatic, non-curative treatment. So, it is perfectly acceptable for us -- and I think it was implied in Dr. Penn's motion that to vote yes you wouldn't necessarily have to conclude that the drug cures it or wipes these attacks out, but just that there is a decrease in these attacks compared to the control.

DR. FALKOWSKI: And you can call it

monotherapy but what the subjects were in these studies were subjects with the condition that were already under medication for this condition. So, to take that leap to say, well, therefore, if you have people with this condition who are not on stimulant drugs, does that follow? I don't believe it does.

DR. KATZ: We will take that under advisement.

DR. KAWAS: The next question, has the sponsor demonstrated efficacy of Xyrem for the proposed indication to reduce excessive daytime sleepiness in patients with narcolepsy? The floor is open for discussion on this point.

At the risk of putting myself back in the same place as last time, I would summarize what we have seen today with regards to excessive daytime sleepiness that there was one study, in a double-blind fashion, that showed subjective changes in sleepiness with the Epworth Scale, and that would be the GHB-2 study. The other study which is being held up as a pivotal study with regards to daytime sleepiness was the Lammers study, which is a small study. Otherwise, I feel that the evidence with regards to daytime

sleepiness was very weak at best, in particular, the only study that proactively made daytime sleepiness the primary outcome measure as well as using objective measures with the MSLT was, in fact, negative. All the other studies were open label. So, here I have a little more -- considerably more difficulty actually seeing that the sponsor has demonstrated efficacy for daytime sleepiness. So, what are the committee's thoughts on this? What are the committee's comments on this? Jerry?

DR. WOLINSKY: As I tried to point out before, I think this is such an enriched patient population for purposes of the endpoints that were studied, it is hard to know that one could generalize daytime sleepiness effects in a full population of narcoleptics. So, I agree that the data is weak and it is also in a very enriched population.

DR. KAWAS: I am not sure I understand. For clarification, enriched with what? You mean enriched for cataplexy?

DR. WOLINSKY: Enriched for cataplexy which is not present in all narcoleptics and is not always present at this frequency. So, I don't

think that we would know. I would not know as a clinical that if I had a narcoleptic with sleep attacks or daytime sleepiness but no cataplectic attacks whether I could expect the drug to work or not, and I saw no data to tell me that I could.

DR. KAWAS: Any other comments? Any other thoughts before we call the vote on this question?

DR. PENN: I move that the company has not provided information to prove that daytime sleepiness is affected by Xyrem, and I would make a comment on my motion, that if the company sees this as an important thing they can do a post-approval study on that specific item and that would be appropriate. I was leaning at the beginning of this to think that there was too much need for full proof on an orphan drug that this might be the case and I was going to give them the benefit of the doubt, but considering the potential for abuse in patients who will say they are just sleepy and the regulatory problems with that, I think we had better be quite strict on this.

DR. KAWAS: Can you make that motion without the addendum?

DR. PENN: No, no, the addendum is just my comment.

DR. KAWAS: Good. Give me the short motion.

DR. PENN: They didn't prove their point.

DR. KAWAS: The language is has the sponsor demonstrated efficacy of Xyrem for the proposed indication to treat excessive daytime sleepiness in patients with narcolepsy? So, a vote of yes the way I just worded it would suggest that the company has shown efficacy, similar to the last vote. A vote of no would suggest that the company has not shown efficacy for that particular indication. So, all in favor of yes, the company has shown efficacy for the indication of daytime sleepiness, please raise your hand.

[No show of hands]

All if favor of no?

[Show of hands]

Let the record show that it was unanimous. It might be the only time today.

DR. TITUS: And enter nine names please into the record.

[Drs. Penix, Van Belle, Penn, Kawas, Wolinsky, Roman, Falkowski, Simpson and Lacey voted against the motion]

DR. KAWAS: Now, the second question that

the FDA has asked us to vote on is has the sponsor established the safety of Xyrem when used for the proposed indication for which substantial evidence of effectiveness has been submitted?

Now, given our previous vote, we are talking about substantial evidence for the effectiveness to treat cataplexy, and I want to go ahead and put in here that I think most of the committee members have been of the opinion that the substantial evidence is almost exclusively in the 9 g dose range. So, I think we are talking about has the sponsor established safety of Xyrem when used for cataplexy at a dose of 9 g per day, for the most part. The floor is open for discussion on this question.

DR. SIMPSON: Could one of the physicians put the adverse events that one can see in the 9 g in perspective?

DR. KAWAS: Let me let Dr. Katz and Dr. Mani answer the question. Dr. Katz?

DR. KATZ: Yes, this is why the dose which you think is effective is important. It might be useful, before you decide whether or not the safety has been established at 9 g, to have a look at what the total exposure at the 9 g dose is and whether

or not you think that is acceptable, as a first step, independent of whether or not it seemed to have been tolerated, with enough people at 9 g with sufficient duration. So, I don't know if the firm could put up a slide. I think Ranjit has an overhead.

DR. KAWAS: Slide 67 from the company, updated ISS database, summary patient exposure by dose. By my calculations we are talking about 60 years, person years of exposure on the 9 g dose from the integrated data set.

DR. MANI: I am sorry, I don't believe it is patient years, is it? It is the number of patients.

DR. KAWAS: Well, I calculated it because there were 13 patients who had been on it for 2 years or more and 34 patients who had been on it 12 months or more. So, it was just 2 times 13 plus 34. That is the way I cam to the 60 person year estimate. I actually didn't give them any credit for the 6-month exposure.

Actually, I have a question to ask of the company, do each years subsume the others? So, the 13 individuals who were in the 2-year category, are they also included in the 62 who are in the 6-month

category and the 34?

DR. REARDAN: Yes, I believe that is correct, Dr. Kawas, the 13 patients would be included in the 34, and the 34 would be included in the 62.

DR. KAWAS: So, the math is more complicated than I made it out to be, actually. It still comes to about 47 patient years of exposure by my calculation. I believe that the standard generally if it is considered acceptable is considerably higher than that. Perhaps Dr. Katz would like to comment on that, particularly in the case of an orphan drug with a relatively small patient population.

DR. KATZ: Yes, the typical minimum requirements for an application for a standard drug that is not an orphan -- we will start there because we have such standards written, is at least 1500 patients total or subjects total, with at least 300-600 for 6 months for a chronic disease and at least 100 for a year. That is the standard ICH minimum data package for safety.

As you point out, this is an orphan condition. I guess the company estimates the prevalence of narcolepsy patients with cataplexy is

about 25,000 or 24,000, something like that. And, we had agreed prior to the submission of the NDA with the company that, because it is an orphan with a fairly small prevalence, that they wouldn't really have to have the full data set that a typical NDA would have, and we agreed that a total of about 500 would be in the ball park. It is understood that at least some significant percentage of those patients should be at a therapeutic dose because the safety accrued at the dose that is less than therapeutic isn't particularly contributory.

So, while I don't believe -- the company can correct me if I am wrong, but I don't believe we set in stone what would the minimum numbers be that would be sufficient for either 6 months or a year or total active therapeutic dose. I don't believe we signed a contract about that, but I think the implication is that a big chunk of the data ought to be at therapeutic dose. So, I can't give you an absolute answer but I will throw it back to you and ask would you think that the exposure at the therapeutic dose that you have seen is sufficient to characterize the safety profile reasonably and that we could write labeling that

would adequately inform prescribers about what the panoply of risks is at 9 g?

DR. ROMAN: Could that be solved with a post-release very strict follow-up on these patients, Dr. Katz?

DR. KATZ: We really have to be assured that the drug is safe in use at the time of marketing. We cannot rely on post-marketing data to say, well, we will find out if it is safe in use. We have to make a decision about whether it is safe in use as described in labeling, whatever that is going to look like, at the time of approval. There may be additional information we would like to have in Phase IV but the fundamental finding of whether or not it is safe in use must be made prior to approval.

DR. ROMAN: A second point that I would like to make is that probably you can say that up to 9 g per day, not that there is sort of the middle of the road -- probably it would be recommended to start with a lower amount and increase according to tolerance and effects, but it is up to 9 g per day. That is sort of the upper limit. It happens to be the most effective one and sort of therapeutic dose but probably you would

like to start with the lowest possible amount.

DR. KAWAS: I think the company shares your interest, but my take on this is we don't want to put out there that a drug is efficacious at one dose and safe at another. I mean, I think it is incumbent on us to feel confident that both of those characteristics go with whatever dose we think is appropriate.

In response to your question, Dr. Simpson, and I don't know if I understood it correctly but you said what is the clinical significance, is that from the perspective of a clinical?

DR. SIMPSON: Well, that is part of it. Just speaking as a statistician though, the safety evidence isn't there with those kind of numbers, obviously. I mean, I think everybody knows that.

DR. KAWAS: I think that is really more the question that is on hand here --

DR. SIMPSON: Yes.

DR. KAWAS: -- because from the perspective of a clinical, this drug actually -- you know, if you didn't tell me what the drug was and just showed me ten safety profiles that have gone by this committee in the last decade, or whatever, I suspect this would look like one of the

best ones. Nobody died from it. No major laboratory abnormalities were detected. But it is very, very, very few subjects that we are talking about, and I think that is considerable concern to us.

DR. SIMPSON: There actually was one suicide which could be attributed to this.

DR. KAWAS: It still puts it in probably the best of the ten. Dr. Katz?

DR. KATZ: Dr. Racusin, on our safety team, just reminded me of sort of a simple rule that we use to decide what sort of size of a risk you can cap with a given exposure, it is called the rule of thirds, but basically with a cohort of 60 patient years you could be comfortable with ruling out a risk of no greater than 1/20, which is --what? -- 5 percent. So, in other words, there could be a rate of 5 percent of something bad with a cohort of 60 that you would not have even seen in that cohort. So, just to sort of give you an idea of what sorts of potential risks are there that we might not have seen yet with this cohort size.

DR. VAN BELLE: Just a small correction, Dr. Katz. I believe that it should be 3/60, which is 15 percent rather than 20 percent.

DR. KAWAS: Do we have any other comments before we give a shot at trying to vote on the safety?

DR. WOLINSKY: I very much share your concern about approving the drug at one effective dose and then saying the safety is really at a lower dose than what is effective. On the other hand, I do think that we have some reasonable data on the efficacy side that says that the dose ranged somewhere between 6-9 g is effective for a substantial proportion of patients, which we then give us not roughly 50 years of patient exposure but closer to 200 years of patient exposure.

DR. KAWAS: I agree with that comment, Dr. Wolinsky, but I really would want to point out that almost all of the SEs appear at the 9, not at the 6 range. So, you know, you are stacking the deck a little.

DR. WOLINSKY: I thought actually, as I saw the listing of the adverse reactions, they clustered in two modal distributions. One was at the high range and one was, surprisingly, below 6.

DR. KAWAS: Actually, maybe we will take a look at that. Could Xyrem put up slide number 70 for us, updated ISS database does distribution of

adverse events?

[Slide]

I think that is what you are talking about. It is not a perfect dose response. I mean, something pops up in the middle, the 6 range actually in terms of SAEs at 12 percent for the 6 g dose.

DR. WOLINSKY: And if I heard correctly, and I don't know how they were distributed, at least some of those serious adverse events were cataplectic episodes.

DR. KAWAS: But even then, I mean, I would point out that we are talking about a 3-fold increase in discontinuations due to AEs in the 9 versus the 6. I mean, it is a 3-fold difference.

DR. WOLINSKY: I take your point.

DR. PENN: On the other hand, once again, that looks like a pretty safe drug to me when you are only talking about 15 percent of people dropping out for AEs, and the real-life situation is that these patients are going to be titrated up to the 9 and, as we saw from that graph of the unacceptable information from the standpoint of the study results, in experience over a number of years you can run patients certainly at lower doses than

9. So, I think that should be influencing our opinion of the safety data.

DR. KAWAS: Thanks. Dr. Katz?

DR. KATZ: Yes, I think the critical question here is not whether those numbers at 9 g are acceptable or not, although that is an important question, but to me the question is -- and you have certainly been talking about that, do you have enough experience to be comfortable at the dose you think is effective. I think, I mean my sense of what people are saying -- you didn't vote on it yet, but my sense is that you felt that at 9 g there just isn't really that much data. I don't want to preempt your vote, but it sounds like the general consensus was there wasn't enough data there -- forget about what the data actually showed, but there just wasn't enough to be able to be comfortable that we have adequately characterized the safety at 9, which is what we have to do. The only vote you took on effectiveness was effectiveness at 9 g. So, if you think it is useful to reopen a discussion about whether or not you think there is effectiveness at 6 g, and if you do, then you have considerably more exposure to think about. So, that is your call. I

mean, Dr. Wolinsky suggested that he thought there might be some evidence of effectiveness at 6. I don't know how the others feel, and I leave it up to you as to whether or not you want to reopen that question because if you do think there is effectiveness at a lower dose, it increases your N from the point of view of safety. So, I just throw that out.

DR. KAWAS: I actually think that is probably worth our doing. With regards to effectiveness at 6 g, what are the thoughts of the committee? I will start by saying that I suspect that there is effectiveness for at least many patients at 6 g, partly for all the reasons that other members of the committee have said, but also because there appears to be a fairly prominent dose-response curve not only in terms of AEs but also in terms of efficacy. And, what isn't factored into a total dose is the levels of particular patients, the weights of particular patients or whatever, but the data shows me that at least a subset of patients appear to be responding at least in some of the trials to 6 g. Dr. Katz?

DR. KATZ: Study 21, the withdrawal study.

DR. HOUGHTON: That is the slide that I

would really like to show if I could.

DR. KATZ: The dose there was 50 mg/kg, is that correct? What was the distribution of doses in that study?

[Slide]

DR. HOUGHTON: This is shown here. There was an equal distribution of patients at the 6, 7.5 and 9 g and if you look at that paradigm of acute withdrawal, the response to placebo randomization is obviously very robust at 6 and 7.5 g, as it is at the 9 g. The problem with the GHB-2 study is that it is only a 4-week study and the slope of the line hadn't plateau'd at the end of 4 weeks. When we did apply that to open label, even though it was open label we still saw the maximum nadir at 8 weeks. So, if you then take a group of patients who have been on active treatment for a very long time and are then randomized to placebo, if you believe that is a support for long-term efficacy then efficacy is supported at 6 g and 7.5 g.

DR. KAWAS: Would members of the committee like to comment on this data or any other data showing efficacy or non-efficacy at 6 g? Yes?

DR. SIMPSON: I do think that this trial, in fact, is very impressive. I just want to remind

everybody of the caveat of this, that the people that you were looking at long-term exclude all those people who have dropped out for adverse events.

DR. KAWAS: I think that is a very good point. I mean, this was a study done in responders rather than just random narcoleptics. Individuals in this group represented probably are individuals who felt they were getting benefit or saw benefit.

DR. SIMPSON: And provided the drug is safe, then in fact this might be a fair rule to look at to say, yes, the drug is effective.

DR. MANI: I would just like to point out that these comparisons are not of randomized groups.

DR. KATZ: They are not randomized to dose.

DR. MANI: They are not randomized to dose.

DR. KATZ: It is obviously a randomized study. So, they are not randomized to dose in the sense of typical dose response. These are doses that presumably they had been responding to in open experience, and there is not as balanced across the doses, that is true. And, the numbers are quite

small on each dose. On the other hand, you have already decided that in toto it is a study that demonstrates effectiveness.

DR. KAWAS: I mean, I think even though we all recognize these are responders, the fact that a group of individuals on 6 g who, when withdrawn, showed this effect at least told me that there was a subgroup that did respond, as I said before, to 6. The question is how big is that subgroup, and when we are talking about indications and efficacy do we feel that on the whole 6 is a dose to which people respond based on all the evidence that we have seen so far?

DR. FALKOWSKI: And I would also like to say I am a little uncomfortable with the idea of saying that we have so many patient hours for most drugs but, because this is orphan status, we have it but we don't have -- Dr. Katz' remarks -- but we don't have any numbers. Well, that, to me, puts the sponsor in a difficult situation about, you know, what is adequate in trying to develop a new drug and it makes it very difficult for us here to try to reach a conclusion. Enlighten me, here.

DR. GUILLEMINAULT: Can we make a comment, as a sleep expert, on the issue?

DR. KAWAS: I am sorry, who is speaking?

DR. GUILLEMINAULT: Yes, can we make a comment on that issue as sleep experts?

DR. KAWAS: Please. Yes, you are on the air.

DR. GUILLEMINAULT: Okay. The comment that I want to make is that currently there is no drug for cataplexy which is at a fixed dosage. None. Because there is a certain amount of variability from patient to patient, and a patient, for example, can respond at 20 mg of fluoxetine or 60 mg of fluoxetine. In general terms, it is unrealistic to believe that there will be a single dose which will control all cataplectic attacks for all narcoleptic patients. So, you have dose ranges, and I think that that is what these studies are showing. Looking at the data that you have, efficacy for some patients is at 6 or for some patients at 9. And, that is the clinical experience, 20 years of clinical experience. That is the best that you are going to get. So, your efficacy for some is 6 and for some is 9. All drugs used for cataplexy are like that. All patients respond following that scheme.

DR. KAWAS: Thank you. Dr. Katz, would

you like to comment on Dr. Falkowski's concerns about the orphan status?

DR. KATZ: The only written rules that I am aware of which talk about numbers that are adequate, or are potentially adequate, for an NDR, or for a typical NDR, there are no numbers written down anywhere as policy or guidance.

So, as I say, had agreed that a total of 500 was appropriate -- we, the company and the division.

DR. FALKOWSKI: So they came up short.

DR. KATZ: Well, that is the question we are asking. There was, on our part, that at least a big chunk of that would be at a therapeutic dose. So that is why we are asking you whether or not you think it is adequately chararacterized.

I just want to make one other comment with regard to the 6-gram effectiveness and to ask the company just -- should make this explicit, although I think Dr. Trout said it a couple of times.

In Study 2, the p-value for the 6-gram versus placebo contrast was 0.0529, or 0.053, I believe. That was including a correction for multiple comparisons given the three doses.

So you have one study which, basically,

has a p-value of 0.05 at the 6-gram dose; right? And then you have what you have seen. So I just remind the committee of that.

DR. FALKOWSKI: And that was the four-week study, the GHB-2 study; right? Okay.DR. KATZ: i

DR. KAWAS: Any final comments before we take a vote on the sponsor establishing the safety of Xyrem when used for the proposed -- well, actually --

DR. SIMPSON: Would it be appropriate to do a revote on the efficacy?

DR. KAWAS: Not revote, but we can do another vote on whether or not the panel thinks that there was efficacy demonstrated at --

DR. SIMPSON: A dose between 6 and 9.

DR. KAWAS: Well, I think we will have to say either a dose of 6 or a dose of 7.5 or something like that.

DR. KATZ: Well, if you conclude it is effective at 6 and you have already concluded it is effective at 9, it would be sort of odd if it wasn't effective at 7.5. So, if you just want to vote it at 6, we will take it from there.

DR. KAWAS: Okay. We are voting on 6.

Has the sponsor demonstrated efficacy of Xyrem for the proposed indication to treat cataplexy at the dose of 6 grams per day? All in favor? All who agree that the efficacy has been demonstrated, raise your hand.

[Show of hands.]

DR. KAWAS: Let's start and identify yourself as we are going around.

DR. SIMPSON: Simpson.

DR. ROMAN: Roman.

DR. WOLINSKY: Wolinsky.

DR. LACEY: Lacey.

DR. KAWAS: All who do not feel that the company has demonstrated efficacy at 6 to treat cataplexy, raise your hand. Start identifying at that end.

DR. PENIX: Penix.

DR. VAN BELLE: Van Belle.

DR. PENN: Penn.

DR. KAWAS: And I am the lone abstention, I think.

DR. FALKOWSKI: Over here.

DR. KAWAS: Oh; and Falkowski. So we have a split committee for you on 6. If I vote, I break it. Actually, I am fairly convinced that there is

efficacy at 6. So Kawas.

Now, safety. We are now talking safety between 6 to 9. We are now talking about a lot more patient hours, patient years. The floor is open for discussion for safety between 6 and 9 grams a day.

DR. PENN: Can the company give us the number of patient years exposure 6, 7, 9, total because we can't do it from your data that we have seen here. How close to the magic 500 are you? Patient years; excuse me.

DR. KATZ: Not patient years. 250 patients greater than six months, if I added that up correctly. That is without Dr. Scharf. This is now with, so the numbers are bigger. Without Dr. Scharf, I calculate about 250 patients for at least six months. Is that about right?

DR. VAN BELLE: I got 399.

DR. KATZ: Greater than six months?

DR. VAN BELLE: Yes.

DR. KATZ: At 6 and above? We can just split the difference.

DR. VAN BELLE: How many Ph.D.s does it take to add nine numbers?

DR. KATZ: I am not a Ph.D. I can't be

expected to. Can you put the slide back without Dr. Scharf?

DR. KAWAS: I come to about 150 patient years of exposure just looking at the individuals who were on at 12 months or more.

DR. REARDON: This is the data without Dr. Scharf included from the ISS.

DR. KAWAS: I think it is important that we know exactly what we are looking at so thank you for pointing that out to us. On the other hand, I will say that it is to -- my personal impression was that Dr. Scharf's data, although it was the most extensive and the longest term, was collected the least systematically. Given some of the other issues that were brought up about it, it is probably to your advantage to stick with this dataset in terms of AEs.

Okay; then the vote is about to be called for. If the sponsor has established the safety of Xyrem when used for the proposed indication at the dose of 6 to 9 grams per day. All who think yes, raise your hands.

[Show of hands.]

DR. KAWAS: Wait a minute. Something very funny just happened here. It seemed like more

people were willing to say it was safe at 9 than are willing to say it is safe at 6 to 9? Let me try again. Who thinks it is safe, raise your hands now.

[Show of hands.]

DR. KAWAS: Identify yourself from that end.

DR. ROMAN: Roman.

DR. WOLINSKY: Wolinsky.

DR. PENN: Penn.

DR. KAWAS: Kawas in there. Anyone else? Who does not think it is safe, raise your hands, that safety has been demonstrated, established safety at the dose from 6 to 9 raise your hand now?

[Show of hands.]

DR. KAWAS: Has not been demonstrated to your satisfaction. Falkowski, Simpson, Lacey, Penix? Anyone else?

DR. VAN BELLE: Van Belle abstains.

DR. KAWAS: And one abstention. We are really helping a lot.

DR. KATZ: I didn't count. Was that a split?

DR. KAWAS: Right down the middle. Really helping.

The third question that the FDA has asked us to consider is the adoption of a risk management plan necessary for the safe use of Xyrem. I would like to focus us on that question. First, in a yes/no way rather than the details of whether or not, of what belongs in a management program if we think yes, or what doesn't belong if we think yes.

DR. FALKOWSKI: I thought part of our discussion was going to be different elements of that.

DR. KAWAS: That is the next part. First, let's decide do we need a risk-management program, yes or no. And then, if we do, what should be the elements. Jerry?

DR. WOLINSKY: I think there are really two issues here. I wish there weren't, but there are two. One is the risk-management program and whether it is critical for the patient population in which the drug seems to be indicated. I actually don't think that is important.

Then the question is is there a risk-management program that is necessary for the concerns about the societal risk at large. There, I think the answer is absolutely yes. Because of that conflict, we may be in an unusual position if

we favor this drug, favoring, potentially, making a precedent step in which we put unusual controls on physicians and patients, more so than we have had in the past.

I am not sure there is anything wrong with that, but I am not sure that this is a large enough forum in which this question should be addressed.

DR. KATZ: There certainly are precedents for risk-management programs being necessary for the safe marketing of the drug. I don't know that there are many, but there are certainly -- and I think you heard about some. So there is this precedence for a risk-management program.

Now, the details--I don't know specifically which details you are thinking about--may make this more of a precedent. But, certainly, risk-management programs of this type or similar type have been used and have been approved.

DR. WOLINSKY: I don't disagree with that, but I think we are talking about whether or not there is an inherent problem with the drug in terms of the efficacy, safety level that we are seeing. Most of the risk-management programs that I am aware of that have been put in place have been put in place for the protection of the patient not the

protection of society.

DR. KATZ: Again, you have made a distinction which we have not yet explicitly made. It is a fair distinction. I am not sure everyone agrees that there would be no need for a risk-management program if it was just--if you weren't worried about the societal questions. But it is a fair point for sure.

DR. PENIX: Also, isn't it the difference in the fact that this is a controlled substance and the other drugs are not that the safety measures that are put in place for the protection of the patients are usually not controlled substances. So that may be a difference in this particular case.

DR. WOLINSKY: This is controlled, but I am not sure that the controlled substances have this much potential control on them is what we are suggesting here.

DR. FALKOWSKI: I have a question which is has the FDA ever been in a position where they have a drug coming before them that has already been scheduled? This seems to be unique.

DR. LEIDERMAN: Could I just answer a couple of these questions?

DR. KAWAS: Please, Dr. Leiderman.

DR. LEIDERMAN: Let me refer you to a table. It is actually the last page in your blue FDA briefing package book. It actually lists several examples of risk-management plans for different drugs that come from different classes and for different therapeutic indications that are all in place for various safety reasons within the FDA, and they range from other controlled substances, potent opiates in the case of Actiq and fentanyl, to mifeprex and thalidomide. The risks and the intended protected individuals may be different in each case. Obviously, in thalidomide, the risk isn't to the patient but to the accidental fetus. Similarly, much of the consideration in Actiq, which is a potent opiate, was concern for other individuals within the household and, again, not for an opiate-tolerant severely debilitated pain patient.

So, to answer Dr. Penix' question, in fact, or Dr. Falkowski's, some of these have been already scheduled drugs. I think what is unusual but not absolutely unique is to start out with a drug that is basically in Schedule I and then to be bringing it into the therapeutic arena but, again, it is not entirely unprecedented either.

DR. KAWAS: Thank you. I can't help but point out that it is probably unprecedented, but this drug has gone from over the counter, a completely unregulated food supplement that could be bought by anybody ten years ago to Schedule I, which seems to me even more unusual.

So we are back to the question about the adaption of a risk-management plan necessary for the safe use of Xyrem. I think the comments that have been made, that Dr. Wolinsky made, was it may not be necessary for the safe use but it is necessary for other reasons.

Can we amend what we vote on, whether or not it is necessary, period, for whatever reasons and vote on it in that regard?

DR. KATZ: Yes; I would prefer you did, actually.

DR. KAWAS: Okay. The real question is is a risk-management program necessary. I have a feeling we are ready to vote on that. So I will call the question. All in favor say aye.

[Chorus of ayes.]

DR. KAWAS: No?

DR. PENN: No.

DR. KAWAS: Let the record show that Dr.

Penn voted no. Any abstentions?

[No response.]

DR. KAWAS: Dr. Penn, do you want to give your comments, since you were the descending opinion.

DR. PENN: I think this is a very complicated issue and I don't think we can resolve, at the end of a committee meeting, the responsibilities toward the general population of controlling the drug and the FDA controlling it for a group of patients.

I see that the whole issue is being distorted in the same way that drugs for treating pain have been a problem and that is if we limit the drug with all these regulations, that the patient population, which is quite small, will not be served.

That certainly has been true with narcotic drugs over the years, that many, many physicians have underprescribed narcotics for a long period of time. I think we will see the same here except there won't be the same push to get it accepted by cancer patients. The narcolepsy group is much too small.

So it is going to be a very hard balance.

I also worry about the idea of "voluntary" ways of doing this. They are not voluntary on the company. The company wants to get the drug out and they realize that they can't do it unless there are societal controls on the drug and they are willing to do it.

But I don't like the precedent of the drug company deciding for a physician whether, for example, somebody 17-years old will get the medication or whether somebody, because of different metabolism of the drug, might not be used on a slightly higher dose than 9.

Those are things that we have traditionally let the treating physician do and we have also not let the company choose who are the treating physicians. So I think this is something that needs a large amount of debate and that is why I was being obstinate and voting no on this without qualification.

DR. KAWAS: Thank you. Rusty?

DR. KATZ: Just as far as the dose and the limitations, that is something that can be discussed in the context of what type of risk-management program you think needs to be in place. You could have a risk-management program that

doesn't say you cannot ever give a dose greater than 9 grams.

In a typical drug, when we have labeling, we have information that the drug is effective or safe only up to dose X, we don't usually say, "You can't possibly give any more." We just say, "Here is the data. There is no data above dose X."

So it isn't part and parcel of any risk-management program that you would automatically limit the dose. I supposed you could, but it is not presupposed that that must be the case.

DR. PENN: But you might limit age. The other thing is who is going to make these decisions. We were given this in the context of a very particular type of risk management. I think the devil is in the details in these types of situations and to vote yes or no is very difficult without knowing exactly what details we are talking about. They make major substantive differences.

DR. KAWAS: Let's go on.

DR. KATZ: That is why I wouldn't ask you to vote on the details.

DR. KAWAS: That is what I was going to say. Let's go on to the details. I want to remind the committee, particularly because of the lateness

of the hour, if there is a detail that is not important to you, please don't fill up too many of the airwaves with it so we can get to the ones that are important to you.

So the first one is should there be a requirement for additional safeguards; i.e., keeping drugs in a locked storage space in the patient's home. Just for a straw vote to begin with. How many people think that there should be the requirement for a locked cabinet in the patient's home? Anyone who thinks yes? Straw vote. Anyone who thinks no? Straw vote.

I think we have got a clear preponderance here. I think I will at least express my thinking is that we don't require patients to keep Demerol or Valium or Halcion or anything else in a closed cabinet, many of the drugs that are potentially at least as abusable as this.

Having said that, I think that almost all drugs belong in a locked cabinet. That is the real issue here and I am not sure to what extent requiring it would make one difference or another.

So, should there be a requirement for additional safeguards? Can I say, in general, that the committee felt that that was not essential, necessary.

Should there be additional warnings on the labeling of the dose cups and/or bottle? Any comments?

DR. WOLINSKY: I heard something that I thought was very insightful from one of the people who talked to us in the public session and that it would be useful if there was some distinguishing feature about the bottles that could not easily be counterfeited and this was be in everyone's best interest.

DR. KAWAS: Thanks. I assume that would be something that the company would do to the bottle rather than something the patient--

DR. WOLINSKY: I assume so.

DR. DYER: Are the dose cups to be labeled because those are not? So additional would be additional to that or additional to what is required by law, because they should definitely be labeled.

DR. KATZ: If I can just interject. I don't think there is anything required by law. This is what the patient keeps at home. Right now, I think they are just as you see them. There is nothing on them. There is no labeling of any sort; is that right? They are just blank?

DR. KAWAS: Would the company like to comment? Is any additional labeling planned for the dose cups? Or maybe it is about to be planned for the dose cups?

MS. ENGEL: Actually, no. As you know, the poison-control system nationwide is going to a central 800 number as well as having a logo that is "Mr. Yuck" like but better tested for kids. That we expect to be ready in October. At that point, the central pharmacy will put into each of the packages three stickers, one for the bottle and one for each dose computer that will include that "Mr. Yuck" type symbol plus the central 800 number for the entire poison-control system nationwide.

DR. DYER: My concern is that if the bottle ever leaves the little dose caps--if you go away for a night, I am going to take my two doses with me. If they are separated from that bottle, no one is ever going to know what it is.

MS. ENGEL: As I said, there are three of those labels that will go, so one for each--no; it does not.

DR. DYER: It needs to say what it is. If you go stay at a friend's for the night and you have narcolepsy and you take those two bottles with

you, child-resistant caps are designed to keep children out for one to two minutes. That is it. Somebody will get into that and, if they do, there is no way to know what it is.

When they call that number to the poison center, they say, "I have a bottle with a "Mr. Yuck" sticker on it." It needs to say Xyrem and now many milligrams.

DR. KAWAS: I would like to call the question. Should there be additional warnings on the labeling of the dose cups and the bottle of GHB? Do I need to separate those two out or can I put the dose cups together with the bottle.

Let's start with should there be labelings on the bottles. All in favor raise their hands?

[Show of hands.]

DR. KAWAS: Is that almost unanimous? No? Labels on the dose cups saying that it is Xyrem or GHB or something. That is unanimous, please note on the record.

How about should there be additional warnings on the dose cups and/or bottle of GHB? I am not sure, maybe I should ask, what is the definition of additional? What is supposed to be on there already? Dr. Katz?

DR. KATZ: I think we are probably mostly thinking of the cups. There was supposed to be nothing on cups. So anything you put on is additional. I don't know about the bottle. I don't know if we were thinking specifically about the bottle. I assume that has all the usual required statements, whatever they are.

DR. KAWAS: Are you satisfied by our vote that there needs to be labeling on the dose cups? I think, though, I am starting to feel from the committee that there is some expression of wanting certain kinds of warnings added? No?

DR. DYER: If I could just add in, by law, you have to have "Keep out of reach of children," "Don't take with depressant drugs," "Avoid hazardous machinery." So those kinds of standard things would be on there and I don't know that anything else would be required.

DR. KAWAS: Dr. Lacey?

DR. LACEY: If this is a scheduled substance with implications for--legal implications, why wouldn't we put that type of warning in as few words as possible there. Maybe it would deter someone.

DR. DYER: There is already a requirement

for "Federal law prohibits dispensing of this drug to other than who it is prescribed." There is already a label like that required on prescriptions.

DR. PENIX: It could also attract certain people as well, I think.

DR. KAWAS: Yes; these warning labels have a mixed response. Can we move on to special concern or advice regarding limitations on the quantity supplied at any one time. Perhaps the sponsor can correct me but my recall is that it is going to be dispensed at one month and then--a maximum of one-month supply at a time? Is that correct?

DR. REARDON: We had proposed to the agency initially to start at one month with each patient. As the patients and pharmacists get experience, that might be extended to three months or could be kept to one month.

I think the FDA is asking should there be a regulatory or legal description on the length of period that a Schedule III drug should be prescribed.

DR. KAWAS: Rusty?

DR. KATZ: I am not sure we meant that

question to be generic with regard to any Schedule III. We want to know whether or not, in this particular risk-management program, there ought to be a provision that says you only get one month at a time, or you only get three months at a time. We just wanted to know what you felt about that.

DR. KAWAS: The floor is open for discussion. First, do people think there should be any restrictions on the amount, period, and then we can discuss the timing. So straw vote. All people who think that we should be talking restriction of some sort or another raise their hand. And people who don't think we need to be talking restriction on length of time, raise your hands.

We have got a roughly split straw vote with the probable preponderance on the no time limit. Does that help enough?

DR. KATZ: Sure. If that is what you think, it is helpful. I can't guarantee we will agree.

DR. KAWAS: Having worked in sleep laboratories as well as doing other physician things where certain drugs--I mean, my personal rule has been that drugs that have the kind of potential for trouble, of which there are many,

many, many of them already in our armamentarium, I never give out more than one month's supply with three refills.

DR. FALKOWSKI: That is why I think that, particularly with this, we need to be cognizant of that and that there should be a limitation on that. That is all I wanted to say. And I also don't know where it comes in, or where this discussion happens, but I really believe that a drug, if you look at the third page from the back of the materials the FDA provided about just the scheduling criteria for drugs, that this drug, although it is efficacious for people with cataplexy, with narcolepsy or else on stimulant drugs, that it clearly--

DR. KAWAS: Your point it getting lost.

DR. FALKOWSKI: It should be in Schedule II. I believe it should have the dispensing restrictions that are more consistent with a Schedule II drug and I don't believe that would put undue burden on the patients because most of them are already on Schedule II drugs because they are on methamphetamines or other drugs.

Somehow, I wanted to say that today. Thank you.

DR. KAWAS: Do you feel satisfied with what you have heard on that question, Rusty?

DR. ROMAN: Claudia, one more point is how are the patients going to be selected. I think would should at least mention that the patient should have a clear diagnosis of narcolepsy with polysomnogram and MSLT

DR. KAWAS: You are jumping to Question 6, but why don't we go ahead and do that since I agree that is an important point and I am worried we won't get to it.

So what are your thoughts?

DR. ROMAN: That patients should have a recent polysomnogram followed by MSLT in order to confirm the diagnosis of narcolepsy.

DR. PENN: Who is going to decide whether it really is narcolepsy or not? The government? The company? The person who reads the test? The doctor that is taking care of the patient? That is why I mean the details are very important. You can say that it sounds good that we should have a diagnosis, but these are important points.

DR. KATZ: Can I just clarify what we meant?

DR. KAWAS: Thank you.

DR. KATZ: We meant the treating physician, in other words, would make the diagnosis. We certainly, obviously, are not going to get involved in the diagnosis of a patient from where we sit. The company didn't anticipate that they would either if I can speak for them.

No; we just meant do you think that the patients have to have a bona fide diagnosis, does the physician who is writing the prescription have to assert, in writing, before the prescription will be filled that, yes, this patient has narcolepsy.

Then you can throw this apart and say do they have to assert that the patient has cataplexy and that is what you have decided the effectiveness data supports. So that is a subtlety or nuance of the question you can get to. But specifically with regard to who is going to make the diagnosis, if you meant that question seriously, we meant the prescribing physician.

DR. KAWAS: Response to that? Dr. Roman, do you want to give your opinion and then Dr. Wolinsky has a question or comments.

DR. ROMAN: I think that there are diagnostic criteria that are sort of fairly well accepted, at least here in the USA. The question

of should it be a certified polysomographer or should it be one of the certified centers in the nation, we will start getting into the problem of what happened with the patient who lives in the in the middle of nowhere and has no way to get to the next sleep center at 500 miles.

DR. KAWAS: Excuse me, but that is not what Dr. Katz asked you. He wants to know do you think the physician needs to certify, however they come to this decision, that the person has narcolepsy, that they need to certify up front, this person definitely has narcolepsy.

DR. ROMAN: One of the speakers mentioned that it is relatively simple to get a sleep attack and narcoleptic episodes that are real enough to fool the best unsuspecting doctor. So, since we have objective ways of making a diagnosis of narcolepsy, I think we need to use that for the protection of the public at large.

DR. KAWAS: Thanks. Jerry?

DR. WOLINSKY: I think this actually frames what is my concern from before about protecting, or treating patients and protecting society. Now I want to get back more to protecting people who are treated. That really gets to an

issue that we run away from in this country and that is, if we want to be able to push the envelope to be able to provide drugs that may be helpful for patients with true orphan diseases, we probably also have to say that we are willing to make sure that those people have what they say they have and that the drugs are being used in the context of the set of patients in whom they were originally tested.

It is one thing to talk about hemorrhoid cream but it is another thing to talk about a drug with a narrow therapeutic window and a diagnosis which can be made with accuracy by experts most of the time and could be misapplied by others a lot of the time.

This becomes a critical issue so that if someone is not willing to monitor this, all that we do, in looking at the hard science of what is presented to us, flies out the window as soon as the drug gets approval.

DR. HAGAMAN: Can I make one quick comment? I think, as a physician treating these patients, if they have had a PSG and MSLT in the past, there is really no need to bring them back in for another one. At that point, you have to trust

the physician's judgment that yes, they do have a diagnosis of narcolepsy, they have had the PSG MSLT done.

DR. WOLINSKY: I don't think the panel was questioning that at all.

DR. MIGNOT: Especially because, in such cases, you will have to stop medications which is another problem.

DR. KAWAS: I don't think that was being suggested. So let's move on if we could, please.

DR. SIMPSON: I don't know if this fits under it, but the way the question is worded, should there be restricted prescribing for the product. I just want to put in a plea for prescribing for children. As far as I can see, there have been no pharmacokinetic studies in children and children's pharmacodynamic and pharmacokinetic profile can be very different from adults.

So, given its complex pharmacokinetic profile, as it is, I would be very concerned if it was prescribed in children based, as is usual, on a way to a BMI.

DR. KAWAS: I am not sure that we have answered your question. Actually, I still have a

question that I want the committee to focus on unless Dr. Katz feels otherwise. Is it important that we decide whether or not it needs to be restricted to people with cataplexy as a component of their illness?

DR. KATZ: I am not sure whether or not you think you have made some sort of recommendation about whether or not it needs to be restricted to patients with narcolepsy globally yet. Do you think you have, because I didn't hear it if you--

DR. KAWAS: No; I don't think we have. You are talking now about certifying that the person has narcolepsy, at least on some signature level.

DR. KATZ: We did not put in how we you would know that the patient has narcolepsy. We anticipated that the physician would make the diagnosis appropriately. We didn't ask--I don't think we did anyway--about whether or not there should be specific diagnostic criteria that they have checked off or they have had a recent, or ever had a polysomnogram.

We anticipate, for purposes of this question, that the diagnosis would be up to the physician to make appropriately without any

additional specific requirements, but I suppose you could say patients must have a history of polysomnography and other tests, a multiple sleep latency test or an MPT before they can be prescribed this.

You could decide that you think that that is appropriate. We left it open intentionally.

DR. KAWAS: I think the committee needs to discuss that particular point. I want to make the comment, though, before we get too far, I would tend to leave it open and I recognize all of the things of modern medicine that all of the people in this committee are familiar with because we sit at major medical centers.

But there are people with narcolepsy and cataplexy at places that do not have access to sleep-disorder centers and polysomnography. I think that needs to be kept in mind or discussed on some level as we are cogitating about this.

DR. ROMAN: The problem is that you need to go through the differential diagnosis of excessive daytime sleepiness and the differential diagnosis of cataplexy. In most cases, that is going to require at least a polysomnogram, a sleep test, to rule out obstructive sleep apnea,

restlessness, and what have you.

So, in most patients, at least those who present for the first time to get this medication, I don't see how you can avoid doing these tests.

DR. BLACK: I hate to interrupt, but a point that I think is worth bringing up is that the condition indication here is cataplexy. Cataplexy is a clinical diagnosis not confirmed by any testing or MSLT. If you are going to limit it to cataplexy, I think it is important to recognize that you can't make any verification on the diagnosis with MSLT as far as the cataplexy goes.

DR. KAWAS: Since we have you up there, what percentage of people have isolated cataplexy without narcolepsy and sleep attacks?

DR. BLACK: It is incredibly rare.

DR. KAWAS: Thanks.

DR. BLACK: Incredibly so. But, on the other hand, the incidence of cataplexy and sleepiness without an MSLT that confirms it is a modest subset. In other words, if you have cataplexy, you won't necessarily have two sleep-onset REM periods on your MSLT, so we need to keep that in mind so that we don't potentially limit folks with true sleepiness and cataplexy and

narcolepsy that don't show the MSLT findings.

It is not 100 percent specific or sensitive.

DR. KAWAS: We have some people over on this side who wanted to--

DR. LEIDERMAN: I just wanted to be clear about the question that I think we were asking. What was discussed internally within the agency was the concern about off-label use. We all know that drugs are used often more frequently for other than their labeled indications. The question we wanted to pose for this specific drug, does the committee recommend restricting its prescription to the labeled indication.

DR. KAWAS: So, actually, I think maybe, put in that context, we could call the question and try a vote here. In the opinion of this committee, are we recommending that this drug needs to be restricted in some fashion to on-label use? All in favor?

[Show of hands.]

DR. KAWAS: Almost unanimously. Negative?

[One hand raised.]

DR. KAWAS: One negative vote from Dr. Penn.

DR. VAN BELLE: I am going to abstain because I was out of the room.

DR. KAWAS: Dr. Van Belle is abstaining. Everyone else voted yes; am I correct? So, did we give you a better answer this time?

DR. KATZ: Yes. All your answers are good.

DR. PENN: Isn't this the first time anybody has ever suggested that the FDA should be restricting off-label use of drugs?

DR. KATZ: I doubt. I don't know.

DR. PENN: Isn't it stated in the FDA, all of your regs, that you do not regulate medicine and off-label use is up to the physician?

DR. KATZ: I don't know if it says we don't regulate medicine but, certainly, I think we have the authority to do, I think, plenty of things that some people might consider practice of medicine. So I don't think, as far as I know, there is any--as far as I know, there is no legal bar to this if that is the question you are asking. I think we have done it in the past.

DR. KAWAS: I think that I want to make the comment that even if it was the first time that the FDA was doing this, it certainly is not new to

medicine. Now, insurance companies routinely make us do this.

DR. FALKOWSKI: I have one question, I guess, or one concern, and I just want clarification. Did I not read this correctly? I tried to read it all, but nowhere does it says gammahydroxybuterate. Is this correct, sponsors, that there is not the word gammahydroxybuterate in any of these doctor or patient things.

In terms of issues here, I think it is very important that the doctor information says what this is.

MS. ENGEL: As we worked with our colleagues in law enforcement, they urged us not to put gammahydroxybuterate as the generic name of the materials, et cetera, because they felt, for example, if you are a patient, and you have something in your home that says gammahydroxybuterate, that might actually be an attractant to a babysitter or someone else.

So the attempt, based on the advice of law enforcement, was to separate that out.

DR. FALKOWSKI: I am not talking about patient materials--to the doctors. Will the doctors get to know? They don't have their

materials sitting around their home.

DR. KAWAS: Excuse me. Dr. Katz, is this a question you would like the committee to discuss?

DR. KATZ: I think it is an interesting question. I think we can work it out. The point is well taken and, as the company says, they have gotten conflicting advice for good reasons as well. I think we can work it out.

DR. KAWAS: Great. Thanks.

DR. LEIDERMAN: I just wanted to respond to Dr. Penn's comment about restrictions on prescribing. Actually, there is some very recent precedence in the non-CNS drug arena. The drug, mifepristone, in fact, was approved under very restricted distribution. It requires signed documents by both physician and patient to be returned to the distributor before--and only a restricted group of physicians who certify to a certain ability to handle the complications are, in fact, allowed to prescribe the drug.

So that is a precedent in the non-CNS arena.

DR. KAWAS: I am told that somebody on one of our phone lines would like to make a comment? Can you hear us?

DR. CHERWIN: Yes; I had wanted to make a comment several comments ago, just to briefly reiterate. I agree with Dr. Black said which may be important that not all patients with cataplexy have positive sleep studies. So, in addition to, perhaps, in some cases, sleep studies not being available, this is another concern.

DR. KAWAS: Thank you.

DR. CHERWIN: Another thing is that cataplexy is not always a crystal-clear diagnosis. Not too many people have talked about that, but there can be cataplexy in the eye of one physician that does not exist in the eyes of another physician. That is a potential problem.

Finally, the International Classification of Sleep Disorders, which is to the sleep field similar to what the DSM is to psychiatrists, does not specifically require a sleep study diagnose narcolepsy.

I thought those three things might be salient to the discussion especially--since we sort of jumped to the appropriate prescribing section, maybe we can run through the questions there and see how many of them we can quickly comment on for Dr. Katz and the agency.

Should physicians document that they read the material sent to them before the pharmacy fills the initial prescription? If we took a straw vote right now, how many people would say yes? How many people would say no? Since we have got a split here, of the people who are on the yes side right now, would some of you like to comment on what kind of documentation you want?

I mean, are we talking a signature saying, "I have read the materials that were sent to me," or are we talking about something more than that?. Jerry?

DR. WOLINSKY: Again, it sort of depends what we require or what might be expected for a diagnosis rather than what would be required. I think if a sleep specialist is comfortable with the diagnosis in that patient, and refers the patient back to treatment to that physician who is back in North Dakota that you keep mentioning that can't possibly have all of the diagnostic tests around, then I think it is important that that physician in North Dakota knows what they have signed on to.

If it is the sleep specialist who has got 150 patients on treatment because they are very expert at this, if they have signed the document

once, that is probably enough for me.

But I think these are details that I am not sure that we need to work out today. There are plenty of things that can be worked out by Russ and his people.

DR. KAWAS: Russ and his people gave us this question.

DR. KATZ: And we didn't anticipate, necessarily, a vote. But right now, as I understand the program, the initial prescription is filled and then the physician and the patient have to send back a card that says, "Yes; I read this stuff." It was just some sentiment internally for all of that documentation that, "Yes; I have read it. Yes; I understand it," that is to happen even before the first prescription was filled.

We are going to get into major problems if we try and apply a different standard to different types of treating physicians, the expert versus the non-expert. Actually, this was one of the issues that I actually did want. A lot of them are not necessarily that critical but this was one of the few that I really wanted some discussion on. There are a lot of other details I think we can take care of.

DR. WOLINSKY: But I guess I was saying that, that even the expert would sign it. He just wouldn't have to sign it every time he gives out a new dose.

DR. KATZ: No, no, no, no. We don't anticipate that.

DR. KAWAS: Once.

DR. KATZ: I just meant the first time you give a dose to a particular patient, you would sign a card before the initial prescription was filled for that patient. That is what I think we anticipate.

DR. FALKOWSKI: On a patient by patient?

DR. KAWAS: I want to make the comment that I am comfortable with the notion of physicians having to sign for this potentially, but I am not comfortable with what was suggested as a mechanism to have it happen by the sponsor and that is sending a drug representative to the physician's office. I really feel very strongly that is not the way this should be done.

Dr. Penix?

DR. PENIX: This is a question for Dr. Katz. What is the purpose of the physician signing such a document?

DR. KATZ: It is just to acknowledge that they have read the material and that they are familiar with its safe use and that they have spoken to the patient about its safe use. Actually, that is a separate question, but it is all combined--that they know how the drug should be used, what its risks are, what the penalties are for inappropriate use.

DR. KAWAS: Doesn't it also sort of acknowledge that this is a somewhat unusual drug in some sense because every drug has all these risks in prescribing and we don't ask any physician to sign for all those drugs.

I sense on the committee a growing concern that the more drugs we have to sign for, the more uncomfortable they are becoming. But I think, really, it points out to the physician who is signing it that there is something different here.

DR. PENIX: I think, also, in that sense, it is important for the physician-information packet that they are aware that this drug is GHB and so, therefore, they may understand why it is required for them to sign this information.

I think that is really the bottom line. So I think it would be useful for a treating

physician to know what type of drug this is.

DR. FALKOWSKI: I would say yes only if it says it is GHB.

DR. DYER: Wouldn't CII make that implicit to know that this is a drug that has illegal implications and would be dangerous?

DR. KATZ: It is Schedule III.

DR. DYER: I am saying it belongs in Schedule II.

DR. KATZ: I think that question has been dealt with definitively. It has been legislated as Schedule III by Congress.

DR. FALKOWSKI: Right. That was legislated at another time.

DR. PENIX: Not to belabor this, but I agree with that drug company's position not to let the patient information--or not include GHB in the patient information. But I think the treating physician should be aware of that.

DR. KAWAS: I think that is a very important point because physicians do have a knowledge base of GHB even if it is from the newspaper or whatever to insure that they understand what it is.

DR. ROMAN: It also has the legal

implications of a physician somewhere who has been prescribing this at a higher rate than expected for that population. He may find his licensing--and a problem if they find that he is prescribing more of these, let's say more than a couple of patients in a year, or whatever it is that delimits.

So we need to look into that because there is potentially a risk for medical licensing.

DR. KAWAS: Can we see if we have shifted the straw vote from about a 50:50 split to something that is more consensuslike for the agency? On the question, should physicians document that they read the material sent to them before the pharmacy fills the initial prescription, presumably, some of those materials would incorporate the fact that what this drug really is is GHB whether or not it is on the bottle.

All in favor?

[Show of hands.]

DR. KAWAS: Nos?

[Show of hands.]

DR. KAWAS: And no abstentions. So let the record show that nos were Dr. Richard Penn and Dr. Gerald Van Belle. The remainder of the committee voted yes. No abstentions.

Should physicians be required to demonstrate safe use and appropriate dosage preparation to patients before the first prescription and be required to document that it has been accomplished? Do we want to try a straw vote and see if we can keep on going?

I think I will make the comment that patient education is too important and sorely underdone in this medical world that that is true for everything. I think, personally, that it would be the hope that, with all drugs, that the healthcare team will insure these demonstrations. I am going to suggest that we do not need to require any specific demonstration or any specific certification of this process.

I see some heads going in different directions. Let me get a straw sense on this one. Should physicians be required to demonstrate safe use and dosage? How many people are going to say yes? Straw vote.

DR. FALKOWSKI: Is the intent here that it just be demonstrated regardless of who does it, whether it is a nurse or a physician? What is your intent?

DR. KATZ: The intent was that--I don't

think we necessarily meant the physician but someone responsible in the physician's employ. It shows them how to draw it up and how much your dose is.

DR. FALKOWSKI: Should somebody demonstrate how you administer this drug before the patient takes it. So I think that is a good question. Can we take a vote on that?

DR. KAWAS: You mean someone in the physician's office should be required to demonstrate it and, in some way, ascertain it. The question is called on that. Who votes yes?

DR. VAN BELLE: Before we vote, there is a further addition to that statement here, and it says, "And be required to document that it has been accomplished." Are you intending to have that included as well?

DR. KAWAS: I think everything that happens in a physician's office needs to be documented. So, yes. That is why we are writing twenty-seven page H&Ps right now.

So we have got one vote yes? Is that all? Dr. Falkowski. No votes?

[Show of hands.]

DR. KAWAS: Abstentions.

[One hand raised.]

DR. KAWAS: We have got one abstention with Dr. Simpson and the remainder of the committee voted no.

DR. WOLINSKY: Having voted no on that in terms of the office personnel and the physician, it seems to me that it would be advantageous to the company to have first doses shown in the home when medication arrives. This is actually the effective education.

What goes on in the physician's office, my bias is, may not be as effective as with home nurse agents.

DR. KAWAS: I think we are not going to repeat the restricted prescribing for the drug question. We have gone over that adequately, I hope.

But the next one, does the risk-management program assure appropriate prescribing or sufficiently reduce the risks of misuse or overdose. I am not quite sure where to start with this one. Actually, Dr. Katz, which components of the risk-management program are you asking us to comment on?

DR. KATZ: That is a fair question. This

is sort of a global question, I think. To the extent that you have seen the details of the proposal, is there anything that leaps out at you as being absolutely inappropriate, or is there something that is not there that is a glaring omission that you all believe absolutely should be there?

I think that is sort of the sense of the question.

DR. PENN: Yes. I don't think the potential problems of the drug are explained to the patient adequately. That is, the narcoleptic patient won't necessarily know that this is an abused drug or if they take it in the wrong way that they can get into a lot of trouble and that the real education has to be to the patient in some manner.

I usually think that is the responsibility of the physician to do that, but I don't see that--I mean, we are protecting the patient from knowing what the name of the drug is. We are protecting them from knowing what the real side effects might be.

It doesn't say that if you take double the dose, it may have more than double the effect and

that you may go into coma and become incontinent and have seizure--well, probably not seizure but stop breathing or something unpleasant like that.

I think the emphasis should be on the patient understanding the medication and how to use it. The narcoleptic community suffers enough and has pretty good ways of letting each other know about the disease. Maybe you should use their ability to instruct patients on the proper way to do it and combine it in some way.

But that is where I think the glaring error is. This is a drug with very little leeway for dosing and people have to understand they shouldn't use it during the day, for example, because they won't have this period of time off.

So I think there is a huge amount to be done. I just don't like to see it done in this mandatory fashion because I don't think it will work. You will get a lot of signed papers, but you won't get the education you need done.

DR. KATZ: But I just want to clarify. I understand your reservations about the entire process but, given that there is a document that goes to the patient that ostensibly tells them what they need to know about using the drug safely, you

believe that that document that is currently written really needs to be beefed up as far as communicating to the patient what the risks are and how to use it?

DR. PENN: Yes; I think that the patient has to know what it is, that it is an abused substance that potentially can be abused. It would be like our not telling patients who use oxicodon not to chop it in two and take it. That gets them into trouble and they ought to know about that.

So there is a lot of education that has to be done with this medication.

DR. FALKOWSKI: I think I already addressed this question by saying I think the word gammahydroxybuterate should appear for patients and particularly for the physicians, the prescribing physicians. What is the secret? The way to have a drug come into the market when it is already a substance of abuse is not to pretend it doesn't exist and not even call it what it is.

I don't think that is an informed approach for physicians to know what it is.

DR. LACEY: Just as one presenter, and I don't remember who, today gave us the common names, the club names and everything. I think the patient

actually should be provided with as much of that information as possible. To not want to put it on the printed book or something because it is exposed to someone else is one thing. But the patient should be provided as much information as possible to know what they are dealing with.

DR. KAWAS: Any other comments before we move on to the next question? Jerry?

DR. VAN BELLE: Let me just make a comment. I agree with that and, also, from the practical point of view, we have already heard this afternoon that the narcolepsy website network is just far flung. If this is going to be approved by the FDA, the word will be out in the next fifteen minutes.

So to play coy and not put it on one set of labels is just not going to work.

DR. ROMAN: I completely agree. The USA Today had the title, "Company wants date-rape drug approved for a sleep-disorder treatment." If that is in the newspapers--

DR. FALKOWSKI: This question is--it is my understanding, and I asked for clarification for this prior to the beginning of this meeting today--that we are voting here on specific questions. Is

the determination of approval made upon FDA's consideration of what we talked about today?

DR. KATZ: Well, sure.

DR. FALKOWSKI: Is it made today?

DR. KATZ: Is the decision about what to do with the application made today? Absolutely not, no. Your opinions are all advisory. We take them very seriously and then we go back and we discuss it internally and we come to a decision, by the PDUFA due date.

DR. KAWAS: Going to the next question, can I ask, Dr. Katz--tell us what do you mean by certification and certification of physicians for prescribing?

DR. KATZ: There was some sense, internally, on the part of some people that physicians should--first of all, that it might be restricted to use only by sleep experts or physicians would have to somehow take a test to show that they know about narcolepsy, that sort of thing, that they are appropriate prescribers in some sense.

DR. KAWAS: So we are not talking about the same thing that we were talking about previously, documenting that they have read

whatever materials with the first prescription that they write?

DR. KATZ: It is something more than that.

DR. KAWAS: Okay. Let's take a straw vote on that. I think we can get past that one potentially fast, then. We are talking about more than just documenting that you have seen materials. Should certification of physicians, or some other restrictions, for prescribing Xyrem be required? Straw vote. How many people think yes? How many people think no? How many people are abstaining?

Let the record show that Dr. Wolinsky abstained. I am not sure, but I need to know why.

DR. WOLINSKY: Well, I am internally conflicted on this. When I say conflicted, I don't mean that I have some stockholdings anywhere but that I am--

DR. KAWAS: Anyone knows when they use that word they have time on the floor.

DR. WOLINSKY: I haven't come to a final decision in my own mind, but I would lean towards, I guess, certification of physicians when the circumstances are special. That doesn't actually keep patients from assessing care. It may mean that they have to be diagnosed in an appropriate

situation and then can be cared for by a physician who is willing to educate themselves about how to best use the drug.

I know that most of my colleagues won't like this but I think that this is where we have to go if medicine is to maintain credibility with an increasingly complex medical world that we live in.

DR. KAWAS: Now to go backwards to No. 5, which the questions deal with safe use by the patient. Should the patient sign an informed consent form before receiving the initial shipment of the drug? Straw vote. How many people think yes? How many people think no?

I won't ask Dr. Penn.

DR. PENN: I am worried about the medical-legal implications of informed consent in this situation. What does informed consent mean? Who signs it? All the things we get to in the controlled trials and that we deal with daily in the university setting.

It seems to me that, unless we work out the details, I can't feel comfortable voting for it.

DR. KAWAS: Actually, I abstained on the straw vote. My concern, and maybe my question is,

informed consent about what? Presumably, we are talking about some version of the education that we have said they need to have. So is this just an acknowledgment of that education? What is it we want to make sure that they are informed about and get a signature to verify that?

DR. KATZ: Usually, informed consent is--it mostly emphasizes the potential risks. There are drugs, of course, that have informed consent as part of their approval. So that was the question. Given the potential risks of this particular treatment, do people think that patients need to sign an informed consent.

It is unusual, but there certainly are precedents for it.

DR. PENIX: I think informed consent does imply a certain medical-legal situation but, perhaps, a contract like they use in many pain-management centers so that the patients acknowledge the problems with the dispensing of the drug and that type of thing. So maybe a contract would be a better idea than an informed consent.

DR. KATZ: Again, we put it on the list because it was raised internally at several discussions that we had. It doesn't mean that we

necessarily, as a group, endorse it or most of us think it is a good idea. It was an option. We wanted to see what you thought about it.

DR. WOLINSKY: Call that question again.

DR. KAWAS: Does that mean you want to change your vote?

DR. WOLINSKY: I would like to withdraw my yes because this is much more complicated than immediately meets the eye and goes beyond what we really need, given all the other things that are already in this package.

DR. KAWAS: Okay. Do we need any more discussion before we call the question the second time? Any other comments people want to make? Should patients sign an informed-consent form before receiving the initial shipment of the drug. All who think yes, raise their hand.

[Show of hands.]

DR. KAWAS: Let's go around the table and identify the yes votes.

DR. SIMPSON: Simpson.

DR. FALKOWSKI: Falkowski.

DR. ROMAN: Roman.

DR. LACEY: Lacey.

DR. VAN BELLE: Van Belle.

DR. KAWAS: All who think no.

DR. WOLINSKY: Wolinsky.

DR. KAWAS: Kawas.

DR. PENN: Penn.

DR. PENIX: Penix.

DR. KAWAS: Okay; we are set there.

Furthermore, should the patients be required to return a registry form before receiving the first shipment? Now, I assume that a registry form that we are talking about is kept by the sponsor?

DR. KATZ: Again, this analogous to what we talked about with the physician. The idea here was right now, the plan calls for such a form to be submitted after the first prescription is filled, that they have read the materials, they have received them and they have read them.

The question here was just whether or not you think that all has to happen before they even get the first dose.

DR. KAWAS: To my mind, that simplifies it considerably, then. Straw vote. How many people think yes, it should be done before not after or with the first dose.

DR. SIMPSON: Is this in addition to the

consent form?

DR. KAWAS: This is different than the consent form; yes.

DR. SIMPSON: So, would it be in addition? I mean, if they did the consent form, would they need to fill out another form and send it in?

DR. KAWAS: I am not sure I am the right person to answer that because I don't know whether or not there is going to be a consent form. But maybe Dr. Katz could--

DR. KATZ: We asked it separately. They are two different things, although they are very closely related, I suppose. If you sign a informed consent that says, "I know what the risks are. "The card--what do we call it--a registry card. That presumably could be something that says, "I have read the material. I assert that I know how to draw the appropriate dose up. I know how to mix it. I know that I have to mix both doses first."

They have a sense of how it is supposed to be taken. So you would imagine it would have different information, could have different information, than an informed-consent form.

DR. KAWAS: So the registry, actually, has--it is not just a name, address, serial number

of a person who is getting the drug. That is not what we are talking about in the registry form? We are talking about--

DR. KATZ: I think the idea here was, as I said before, whether or not, analogous to the question with regard to the physicians, that they have read the materials, what I intended, anyway, for this question was the exactly analogous situation for the patient.

Should the patient have to send the form back. It would be a registry form, I suppose, in terms of who they are, but the pharmacist already knows who they are so they get into the registry that way, I suppose.

But whether or not they have read the material and they understand what the risks are and they understand how to take the appropriate dose, just before the first dose.

DR. KAWAS: Okay. Now I think we can better take a straw vote.

DR. SIMPSON: I just wanted to say I thought the consent form was that.

DR. KAWAS: But, having rephrased it for us, I think essentially what we are saying is now we have said that we want the physicians to certify

that they have read, know and understand some of the issues, the question is, should we ask the patients to do the same thing.

All who think yes, raise your hand.

[Show of hands.]

DR. KAWAS: And nos?

[Show of hands.]

DR. KAWAS: I think we have got a bunch of abstentions, mostly. Would you like to comment no your thinking?

DR. PENIX: I think it is just pretty complicated. I am not sure what a registry is going to do, what the drug company is going to do, with the information, who should keep the information. There are a lot of different issues, so I guess, in the late hour, I am going to abstain.

DR. LACEY: I would think these two things could be combined into one some way or the other. If they can't, it is just getting to be too complicated in terms of all the forms and whatever, so they are losing interest in it.

DR. KAWAS: Are you talking about the patient or the committee? No; I think that something really important was just said here,

actually. I think that if we put too many layers that nobody is going to pay attention to any single layer here. The whole idea is to do exactly the opposite, to have both the patients and the physicians taking this seriously.

Anybody can write in a patient's chart, "I have demonstrated how to do a safe dosage through the patient," and signed their initials. That only takes a few seconds. Getting them to spend the time to do it in the office is quite a different thing.

Obviously, what is more important is what is actually done and not what is certified. But let me see if I am getting the flavor from this committee that, in general, they think there should be one certification, registration, informed-consent process or whatever for both physician and for patient. Is that the gist of what we have been saying?

All who agree with that statement, straw vote, yes. All who think no.

DR. PENN: I abstain.

DR. KAWAS: Oh, gosh. And Dr. Penn abstains and we are not going to even bother finding out why.

Dr. Katz?

DR. KATZ: Given the late hour and the list that still remains, I don't think we really need much in the way of discussion or even a vote, or a straw vote, on any of the other remaining issues.

I would ask, though, the committee members to just sort of quickly glance at it, or not, as you wish. But, again, if there is anything that strikes you as being a glaring omission in the program as proposed and as amended by your previous votes, just sing out. But I don't think we need any detailed discussion of the rest. I think we can sort of work it out.

DR. KAWAS: I would like to make the comment that, at least on the postmarket surveillance, I think there should be required postmarketing reporting, surveillance, monitoring.

DR. PENIX: In addition to the usual adverse effects, of course.

DR. KAWAS: Are there any other comments or thoughts from the committee particularly on the items we didn't specifically discuss like central pharmacy, postmarketing surveillance or other recommendations on protecting--

DR. SIMPSON: I guess there was just one issue brought up about who would police the policemen.

DR. KAWAS: You want to more specific in which policemen we are talking about?

DR. SIMPSON: The issue was whether the drug companies should be policing the correct usage of the drug and then, if that were the case, who would be policing that the drug company were doing it right. And, if the physicians are supposed to be making sure that the patients are doing it right, and so on. That is what I mean. There is layer on layer here.

DR. KAWAS: Let's start with the first layer about if there is a surveillance or whatever from the company.

DR. KATZ: Again, in some sense, we are always in a position to oversee what the companies do in terms of meeting their appropriate reporting requirements and this sort of thing.

I think there is an understanding that what comes out of this registry and the experience will be reported to us. It will have to be reported to us. We will be working in close cooperation with the company to make sure that this

happens.

We won't be down at the first line making sure that the pharmacist is calling the patients within 24 hours. But, like many other things, there is an understanding that the company is responsible for making sure any given system of surveillance is working appropriately and we have interactions with them periodically.

So that is as far as we have gotten.

DR. LEIDERMAN: There are also precedents, at least for independent monitoring committees. And that has certainly been in approval agreements in the past. So that is the kind of thing that I think we need to work out.

DR. KAWAS: Unless there are any more burning comments or thoughts or theories, I would really like to thank the company, the agency, the members of the panel and all the invited speakers as well as the speakers from the public forum for this interesting and challenging day

This meeting is now adjourned.

[Whereupon, at 6:00 p.m., the meeting was adjourned.]

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Xyrem Prescription and Distribution Process

Video Script 2/2/01)

Audio	Video	Titles
1. [Fade in music]	Graphic texture of oranges and yellows	
[Up music.]	logo of Xyrem emerges	Fade in first title/logo graphic.
		Xyrem® (Sodium Oxybate) Oral Solution
[Fade out music.]		Fade out first title/logo graphic. Fade in video title.
		Prescription and Distribution Process
2. Narcolepsy, it is a serious debilitating condition that diminishes the quality of life for approximately 125,000 Americans.	Fade to head-to chest shot of narrator.	
3. Xyrem is a promising new medication that, for some patients with narcolepsy, can significantly reduce the incidence of cataplexy, as well as improve symptoms of daytime sleepiness.	Fade to table-top shot of Xyrem box and a display of its contents.	
4. But, because Xyrem is a controlled substance, Orphan Medical wants to make certain that "only" patients for whom it is prescribed have ongoing access to this important treatment.	Fade back to shot of narrator sitting on desk.	

5. Orphan Medical is committed to a distribution plan that is both safe and effective for patients and also protects the general public by minimizing opportunities for the diversion of Xyrem to unauthorized individuals.	Fade to shot of Orphan representative making a presentation about success plans—perhaps pointing to a bullet point on an overhead screen.	
6. To achieve that goal, Orphan Medical--after extensive consultation with law enforcement, prosecutors, field law enforcement personnel, pharmaceutical distribution experts, forensic experts, DEA consultants, and drug diversion experts-- has developed a comprehensive, restrictive distribution program.	Fade to build graphic that begins with shot of Xyrem box in center of screen.	Fade in titles as mentioned. • **law enforcement** • **prosecutors** • **field law enforcement personnel** • **pharmaceutical distribution experts** • **forensic experts** • **DEA consultants** • **drug diversion experts**
7. In addition to thorough patient and physician education about Xyrem,	Fade to shot of narrator holding up a variety of patient/physician education material and, then, setting it down on the desk.	
8. As well as multiple security checks before, during and after prescription fulfillment.	Cut to split-screen shot showing a) pharmacist assistant verifying doctor's license b) pharmacist unlocking cabinet, c) patient signing for delivery by Federal Express.	

9. The purpose of this video is to outline, step-by-step, all of the security measures that will occur whenever a prescription of Xyrem is written and filled.	Cut back to narrator.	
10. When Xyrem first becomes available, a select group of physicians with a documented history of prescribing medications for patients with narcolepsy will receive an educational module, in the mail, called the Physician Success Program.	Fade to freeze-frame shot of a physician consulting with a patient. Begin action	Fade in title with freeze frame. **Notify A Select Group of Physicians about Xyrem®** Fade out title
11. This program will introduce these selected physicians to Xyrem and includes a videotape, Physician Success Program contact information, a patient education presentation, templates for medical records and patient contracts, and information about third-party payor reimbursement. This mailing will be documented and no medication samples will ever be provided.	Fade to table-top display of Physician Success Program materials.	Fade in titles when mentioned in narration. • **Documented mailing** • **No physician samples**

12. Complementing this effort, a representative from Orphan Medical will visit each targeted physician and reinforce the information provided in the Physician Success Program. The representative will ask the physician to sign a receipt if any additional Physician Success Program materials are left for the physician's office.	Fade to shot of rep and physician meeting and discussing Physician Success Program materials.	
13. A crucial component of the secure distribution of Xyrem is the use of a specialty pharmacy. The specialty pharmacy is a single, centrally-located facility that will have a variety of distribution, documentation, and security responsibilities.	Fade in narrator	Fade in title **Specialty Pharmacy** Fade out title.
14. A staff of dedicated pharmacists, reimbursement specialists, and customer service representatives will provide a closed-loop distribution system that will not only serve patients and prescribers, but will also be able to generate data, recording prescribers, patients and dosing that could provide information for any possible investigations and prosecutions for state and federal authorities.	Fade to shot of pharmasist	

15. This distribution system begins with a secure holding warehouse area where an inventory of Xyrem is kept, according to scheduling requirements by federal and state laws and checked several times a day.	Fade to shot of pharmacy employee unlocking holding warehouse to reveal Xyrem supply.	Fade in benefit title. **Secure inventory storage**
16. On a regular basis, a small supply of Xyrem is moved from the gated and locked warehouse to a gated and locked area within the same pharmacy. Only qualified pharmacists and pharmacy technicians, dedicated to the Xyrem Program will be allowed access or will handle Xyrem.	Cut to shot of pharmacy employees transferring inventory.	
17. Both Orphan and the pharmacy acknowledge and document every time any inventory is moved.	Slow fades shot of a) pharmacy personnel signing some transaction documentation b) Orphan personnel at computer screen documenting the same.	
18. Now, let's take a step-by-step look at how the specialty pharmacy provides verification and documentation of both the prescription and the prescribing physician before preceding to fill any requests for Xyrem.	Fade to shot of narrator.	
19. When a physician determines that Xyrem is an appropriate medication for a patient,	Fade to shot of physician in the office using Orphan Medical's materials to educate a patient about Xyrem.	
20. The prescription is faxed or mailed, depending on each states pharmacy board regulations, directly to the specialty pharmacy.	Fade to shot of physician faxing prescription.	

21. Upon receipt of the prescription, the specialty pharmacy first verifies if the prescribing physician is on Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data from the physician's home State Board of Health to determine if there are any pending or previous actions against the physician.	Cut to shot of pharmacy employee picking up prescription fax and sitting down at a computer to verify physician's eligibility. Freeze frame.	Fade in title with freeze frame. **Physician verification**
22. Next, the pharmacy calls the physician's office to verify the origin of the prescription.	Fade to split-screen shot of pharmacist and physician on the phone. Freeze frames.	Fade in title with freeze frames. **Prescription verification**
23. If it is the physician's first time prescribing Xyrem, the specialty pharmacy will ship a Xyrem Physician Success Program to the Physician's office to ensure that the physician is given every opportunity to become thoroughly familiar with a prescriber's responsibilities regarding Xyrem.	Fade to table-top display of the Physician Success Program components.	
24. Another important benefit of using a single, specialty pharmacy for the distribution of Xyrem is that it's possible to keep all the data about inventory, physicians, reimbursement, patients, and delivery in one efficient and quickly-accessible location.	Fade to shot of narrator.	Fade in benefit title. **All data in one location**

25. Some of the data available include prescriptions by physician specialty, prescriptions by patient name, prescriptions by volume or frequency, and prescriptions by dose.	Fade to build title graphic.	Fade in title. **Data Available** Fade in bullet points when mentioned. • **Prescriptions by physician specialty** • **Prescriptions by patient name** • **Prescriptions by volume (frequency)** • **Prescriptions by dose**
26. The specialty pharmacy will also be responsible for contacting the patient's third-party payor to research benefits, file claims, appeal denials, and collect reimbursement.	Cut to shot of pharmacy employee on phone with insurance company.	
27. The specialty pharmacy will also follow specific procedures for communicating with the patient both before and after the Xyrem is shipped.	Fade to shot of narrator.	
28. First, the specialty pharmacy will contact the patient directly to make specific arrangements for the patient or the patient's authorized designee to personally receive the package containing the Xyrem and to discuss or verify third-party payor reimbursement.	Slow fades of patient and pharmacist discussing arrangements over the phone.	Fade in title. **Patient communication**

29. Throughout this entire process of verification and documentation, if any of the data or behavior suggests the possibility that Xyrem may be used inappropriately, the specialty pharmacy is empowered to contact the appropriate authorities.	Pharmacy finds a doctors that does not verify.	
30. The patient's medication will be shipped overnight by Federal Express utilizing a tracking system designed specifically for the specialty pharmacy.	Fade to shot of pharmacy employee putting Xyrem in Fed Ex packaging.	Fade in title. **Overnight delivery**
31. And, if it is the patient's first time receiving Xyrem, the specialty pharmacy will also include the Patient Success Program in the package.	Cut to close-up shot of pharmacy employee adding the Patient Success Program to the Fed Ex packaging.	
32. This program will introduce the patient to their responsibilities pertaining to Xyrem and includes a videotape, Patient Success Program contact information, advice for safe in-home storage and disposal, advice for traveling with Xyrem, and information about third-party payor reimbursement.	Fade to table-top display of Patient Success Program materials.	
33. Shipments of Xyrem can only be left with the patient or the patient's authorized designee. Therefore, if the patient or the patient's designee is not available to receive or sign for the Xyrem, the package will be returned to the specialty pharmacy. Also, if the package is somehow lost, the specialty pharmacy will initiate an immediate investigation.	Fade to shot of Fed Ex employee with package knocking on a patient's door. Patient—answers the door and they have a brief conversation. The Fed Ex employee shakes his head and gets signature. At the same time, the person closes the front door.	

34. Because the specialty pharmacy provides next-day, follow up through their in-house FedEx computer stations, they will telephone the patient within 24 hours after receiving the shipment of Xyrem.	Fade to shot of specialty pharmacy employee working at an in-house FedEx computer station.	Fade in title. **Real-time tracking**
35. During this call, the specialty pharmacy will confirm receipt of the Xyrem prescription and the Patient Success program,	Cut to split-screen shot of pharmacy employee and patient on the phone. Patient has all the Xyrem materials spread out on a table.	
36. counsel the patient about Xyrem dosing and compliance,	Cut to close-up shot of patient removing contents of the Xyrem box.	
37. and ensure the patient's understanding of the Patient Success Program as well as the patient's legal responsibilities and liabilities relating to the bifercated scheduling of Xyrem.	Cut to slow fades of pharmacy employee and patient on the phone. Patient is holding and reading a patient education brochure.	
38. The specialty pharmacy also keeps track of expected prescription refill dates and will contact the patient ahead of time. Patients who request a refill before their refill date will be flagged and their physician contacted. The physician verification process is repeated before every refill is sent.	Pharmacy finds a patient that does not verify on getting a refill	
39. As you can see, the Xyrem prescription and distribution process is a comprehensive program that ensures the responsible distribution of this important medication.	Fade to shot of narrator.	

40. Both physicians and patients will receive a thorough education about the use and safe handling of Xyrem.	Fade to shot of physician and patient in the office reviewing patient education materials.	Fade in title. **Thorough physician and patient education**
41. Strict adherence to security and verification protocols will minimize diversion of the medication to unauthorized individuals.	Fade to shot of Fed Ex employee at patient's door. Patient is signing the Fed Ex receipt and receiving the package of Xyrem.	Fade in title. **Helps prevent diversion**
42. A staff of dedicated specialists provide a closed-loop distribution system that will not only serve patients and prescribers, but will also have information to support any possible investigations and prosecutions.	Fade to shot of pharmacy employee entering data on a PC.	Fade in title. **Prosecution assistance**
43. And, most importantly, the Xyrem prescription and distribution process will ensure that this life-changing medication will be available to the thousands of patients who so desperately need it.	Fade to shot of happy patient after talking on phone at home with the success program.	
[Fade in music.]		
44. [Up music.]	Fade to black.	Roll credits, disclaimers, contact information, copyright, etc.

CHAPTER 5

The Verification and Information-Gathering Process

OVERVIEW

The verification and information-gathering process may be the most time consuming of the credentialing steps. Once a credentialing application is received and determined to be complete, verification and information gathering are initiated. The purpose of these activities is to obtain information that will support the credentialing and privileging decisions. In most cases, the accrediting organization specifies information to be obtained and information that must be verified according to either standards or standard intent. The Joint Commission on Accreditation of Healthcare Organizations (Joint Commission) and the National Committee for Quality Assurance (NCQA) also identify how information is to be verified. It is the responsibility of the credentialing professional to request, obtain, review, and file all information required by the organization's bylaws, rules and regulations, plan, and/or policy and procedure. Because many items can be verified or obtained by numerous methods, it is important that the organization determine which is the most productive and cost-effective for their program, at the same time meeting the intent of the applicable accreditation standards.

Information in this chapter relates to credentialing standards for Joint Commission and NCQA-accredited/certified organizations only, since the two of them together represent the majority of accredited/certified health care–related organizations.

VERIFICATION AND INFORMATION-GATHERING ACTIVITIES

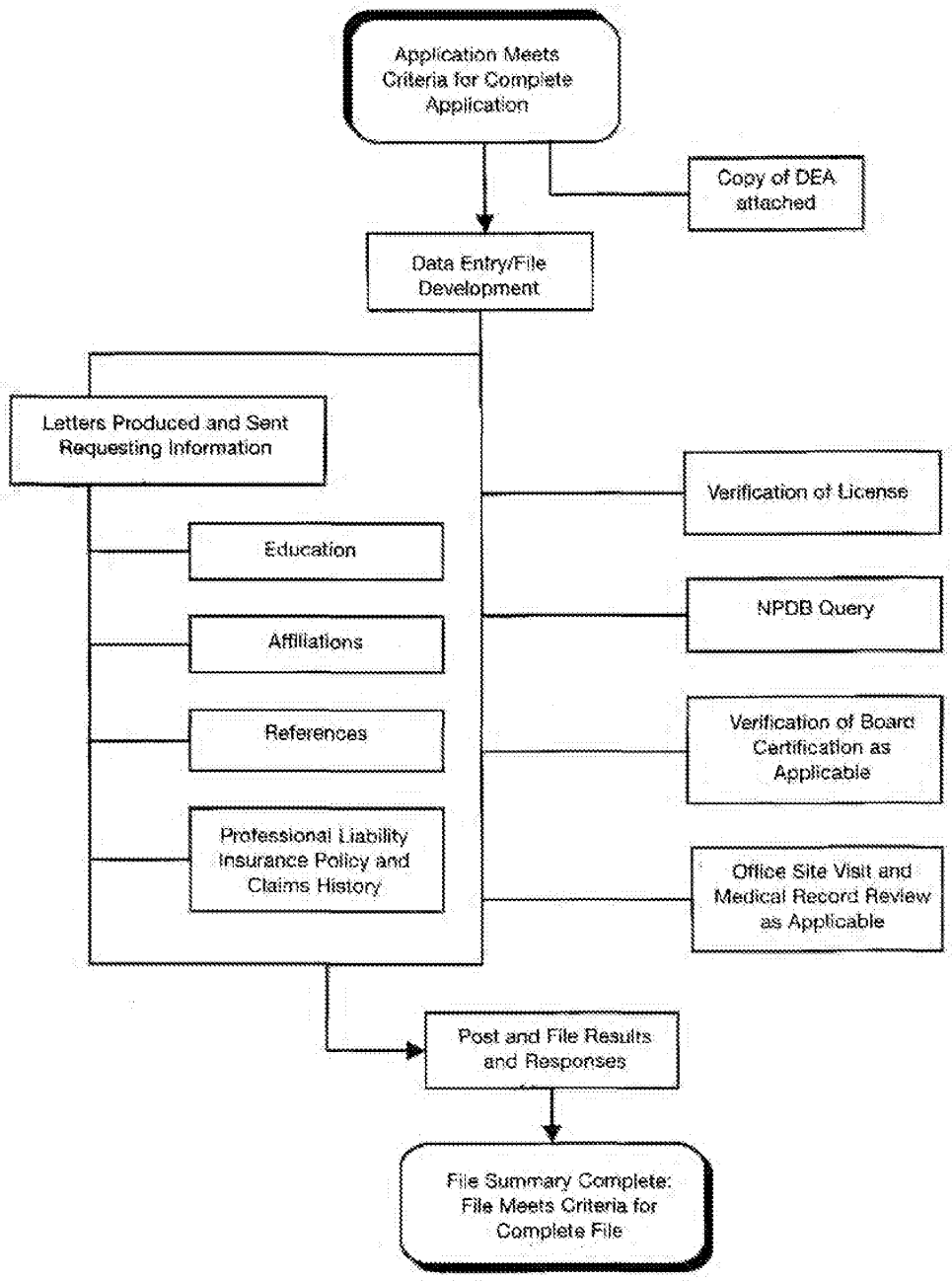
Verification is the process of validating information. Health care organizations usually validate, to the extent possible, the credentials of the practitioners and providers who submit applications. Most accrediting organizations, including the Joint Commission, NCQA, the American Osteopathic Association (AOA), and the Utilization Review Accreditation Commission (URAC), require that specific credentials and information be obtained, reviewed, and verified.

Process steps in a verification and information-gathering process are outlined in Figure 5–1.

A number of acceptable methods may be used for verification, including:

- *written*—the verifying entity forwards a written response to a request
- *copies*—a copy is submitted/obtained that is usually reproduced from an original document
- *verbal*—the verifying entity provides a verbal response (usually by phone) to a request
- *on line*—information is verified through use of an on-line service
- *visual inspection*—a document is provided for visual inspection but not for inclusion in the credentials file

Accreditation standards may require primary source verification and may specify the source(s)



Note: DEA, Drug Enforcement Administration; NPDB, National Practitioner Data Bank.

Figure 5–1 Verification and Information-Gathering Flowchart. Courtesy of C. Mobley & Associates, LLC, and Quality Management Options, LLC, Colorado Springs, Colorado.

that can be considered primary. Most standards require that verifications be obtained in a timely manner, and NCQA specifies time frames in which they must be obtained. It is important that credentialing professionals understand the requirements, activities, and the options available for verification and information-gathering activities.

Primary Source Verification

Primary source verification is defined by NCQA as "the process in which an organization validates credentialing information from the organization that originally conferred or issued the credentialing element to the practitioner."[1] The Joint Commission defines it as "the original source of a specific credential that can verify the accuracy of a qualification reported by an individual healthcare practitioner."[2] When information is verified, a primary source is the preferred source, but at times verification from a primary source is not feasible or timely. For example, physicians trained in other countries may provide names, addresses, and phone numbers for educational institutions attended, but responses to requests may not be printed in English, may not be obtained in a timely manner, or may not be received at all. In this case, the Educational Commission for Foreign Medical Graduates (ECFMG) provides information that, although not primary source, is considered acceptable for verification of medical education by most organizations. Accreditation requirements relating to primary source verification differ from one accrediting agency to another. The credentialing professional should be cognizant of all verification requirements of applicable accreditation standards.

Verification and information may be obtained using one or a combination of resources. The entire process may be completed internally, or all or a portion of it may be outsourced. Credentials verification organizations (CVOs), centralized verification services (CVSs), and the American Medical Association (AMA) Physician Masterfile are currently the resources most commonly used to support this process.

The AMA Physician Masterfile

The AMA Physician Masterfile (also known as the AMA profile) meets some of the specific primary source verification requirements of the Accreditation Association for Ambulatory Health Care (AAAHC), the Joint Commission, URAC, and NCQA. AMA Physician Masterfiles are available for doctors of medicine (MDs) and most doctors of osteopathic medicine (DOs). Information on the Masterfile includes

- medical school (date of graduation)
- residency training history
- licenses granted (initial years)
- current licenses (status)
- national board certification
- American specialty board certification—American Board of Medical Specialties (ABMS) board, sub-board, etc. (initial year granted and expiration dates)
- disciplinary actions taken by state licensing boards and federal agencies, including Medicare/Medicaid
- Drug Enforcement Administration (DEA) status
- government service affiliation (as a physician)
- gender, birthplace, birth date[3]

The Physician Masterfile does not include any competency verification, so if it is used by Joint Commission–accredited hospitals, additional information will most likely need to be obtained.

Use of a Physician Masterfile may decrease costs of verification activities. A paper or diskette file can be obtained for $12 with a turnaround time of 10 to 15 business days and an express fax copy for $20 with a turnaround time of three business days.[4] Organizations may find a cost benefit analysis to be effective in deter-

mining the most productive and cost-effective method of verification.

CVO and CVS Profiles

Many CVOs (external to a system) and CVSs (internal to a system) verify information and then provide summary information about the verification (in the form of a profile) to clients. The profile indicates what elements were verified, gives the method used, date verified, and the source. Copies of any information related to competency, as well as questionable or negative findings, are usually forwarded with the profile. Some clients (usually managed care organizations) accept the profile and negative findings only, and other clients (usually hospitals) want copies of all information received in addition to a profile.

COMMUNICATION

Requests and responses may be obtained verbally, on line, or in a written form. Usually, any communication method is considered acceptable but must be documented.

Verbal versus Written Verification

Verbal verification (usually by telephone) is considered acceptable by most organizations. Documentation of verbal verification should include

- the element being verified
- the source, including name and title of person providing the verification
- the date the verification is obtained
- the name of the person requesting/obtaining verification

Verification by telephone is usually used on a limited basis because of the time involved and the expense of playing long-distance telephone tag. But it can be very effective when turnaround time becomes a factor. Exhibit 5–1 is a sample form used to document telephone verification. NCQA considers electronic credentialing files acceptable as long as appropriate evidence of verification within acceptable time periods can be identified.

Letters

Computer-generated standard form letters are the most common method used to request verifications not available on line. Exhibits 5–2 through 5–7 are sample letters used to request verification of license, medical education, board certification, affiliation, professional peer reference and training. If a credentialing software program containing standard verification letters is not available, letters can be developed and entered into word-processing software as templates.

When a letter or written documentation is obtained or returned, it should be stamped as "received" with the date. Some organizations also require an initial or signature of the person responsible for receipt and review/file/data entry or next activity step.

Considering the vast amount of paperwork involved in verification, the credentialing professional should not get bogged down in extra pieces of paper. Verification requests do not require a cover letter or a separate questionnaire. "Simple and quick" should always be the motto for this task. Inclusion of a self-addressed stamped return envelope increases the possibility that the information will be completed and returned.

On-Line Verification

Some specialty certification boards and state medical boards now have on-line verification available. If the credentialing professional has on-line capability, this verification option is worth pursuing. Exhibits 5–8 and 5–9 list boards with on-line verification services as of this writing.

Exhibit 5–1 Documentation of Telephone Verification

Practitioner Name: _____ Specialty: _____

Element; Organization or Institution Contacted	Source: Name and Title	Verified by	Date and Time	Comments
Medical School: _____ Year graduated: _____			Date _____ Time _____	
Internship: _____ Dates: From _____ To: _____			Date _____ Time _____	
Residency: _____ Dates: From _____ To: _____			Date _____ Time _____	
Medical License: _____ Number: _____ Effective Dates: _____			Date _____ Time _____	Restrictions/Actions ☐ Yes ☐ No
Hospital Privileges: _____ _____ Date of Appointment: _____			Date _____ Time _____	Status: _____
Board Certification: _____ Date Issued: _____			Date _____ Time _____	
Professional Liability Insurance: _____ _____ Policy Number: _____ Amounts of Coverage: _____ Dates of Coverage: _____			Date _____ Time _____	Claims History ☐ Yes ☐ No

Courtesy of C. Mabley & Associates, LLC, and Quality Management Options, LLC, Colorado Springs, Colorado.

Exhibit 5–2 License Verification Request

Letterhead

Date

Board of Medicine
Address
City, State, Zip

RE: _____ (Physician)
_____ (License Number)

We have received an application from the above-referenced physician. Please provide information and confirmation regarding licensure. A Release from Liability statement and a self-addressed stamped envelope are enclosed for your response.

License number above is correct: Yes ___ No ___

License was granted: _____
Date

The license will expire: _____
Date

Is the license current and in good standing? Yes ___ No ___

Has the license for this physician ever been suspended or revoked or has any other action been related to it? Yes ___ No ___

If yes, please explain: _____

_____

Verified by: _____

_____ _____
Title Date

Courtesy of C. Mobley & Associates, LLC, and Quality Management Options, LLC, Colorado Springs, Colorado.

Exhibit 5–3 Medical Education Verification Request

Letterhead

Date

Registrar
Medical School
Address
City, State, Zip

RE: _____ (Physician)

We have received an application from the above-referenced physician. We require verification of the information provided by the applicant regarding your institution.

Thank you for your help. A self-addressed stamped envelope and a Release from Liability statement are enclosed.

Date of graduation: _____

Degree obtained: _____

Comments: _____

_____

_____

Verified by: _____ _____

_____ _____

Title Date

Courtesy of C. Mobley & Associates, LLC, and Quality Management Options, LLC, Colorado Springs, Colorado.

Exhibit 5–4 Specialty Board Certification Verification Request

Letterhead

Date

American Board of _____
Address
City, State, Zip

RE: _____ (Physician)

We have received an application from the above-referenced physician. Please confirm the status of certification. A Release from Liability statement and a self-addressed stamped envelope are enclosed for your response.

Dr. _____ was board certified by this organization on _____
Date
in the specialty of _____.

This certification will expire on _____
Date

Verified by: _____

_____ _____
Title Date

Courtesy of C. Mobley & Associates, LLC, and Quality Management Options, LLC, Colorado Springs, Colorado.

Exhibit 5–5 Hospital Affiliation Verification Request

Date

Hospital
Address
City, State, Zip

RE: _____ (Physician)

We have received an application from the above-referenced physician stating that he/she has been affiliated with your hospital. Please provide confirmation of this information and comments regarding your experience.

Your help is greatly appreciated. A Release from Liability statement and a self-addressed stamped envelope are enclosed.

Dr. _____ was granted privileges on _____
Name Date

He/she has current privileges: Yes ____ No ____

If no, please give date and reason: _____

Staff category: _____

Were privileges or medical staff membership ever suspended, revoked, or limited? Yes ____ No ____

If yes, please explain: _____

Please indicate competence:	Outstanding/ Very Good	Average	Fair/Poor
Knowledge and understanding in his/her field	_____	_____	_____
Interpersonal relationships with patient, staff and peers	_____	_____	_____
Maintenance of medical records	_____	_____	_____

Comments (including explanation of average, fair, or poor checks): _____

Signed: _____ Title: _____ Date: _____

Courtesy of C. Mobley & Associates, LLC, and Quality Management Options, LLC, Colorado Springs, Colorado.

Exhibit 5–6 Professional Peer Reference Request

Date

Name
Address
City, State, Zip

RE: _____ (Physician)

Dear Dr. _____:

We have received an application from _____ in which the physician lists you as a reference. Your completion of the following questionnaire will be greatly appreciated.

A Release from Liability statement and a self-addressed stamped envelope is enclosed. Thank you for your help and attention.

1. Number of years I have known this physician: _____

2. We are: social friends ____; friends from medical school, internship, or residency ____; professional associates ____; other _____

3. For the following categories, I would rate this physician to be:

	Outstanding/ Very Good	Average	Fair/Poor
Ethical conduct	____	____	____
Sense of responsibility	____	____	____
Medical knowledge	____	____	____
Professional judgment and skills	____	____	____
Recordkeeping	____	____	____
Patient management	____	____	____
Physician/patient relationship	____	____	____

4. My perception of this physician's dedication, integrity, and honesty is: _____

5. I am aware of problems that might affect this physician's ability to care for patients related to:

Health/Disability	Yes ____	No ____
Emotional stability	Yes ____	No ____
Alcohol or drugs	Yes ____	No ____
Other _____		

6. Additional comments (including yes answers and average, fair, or poor evaluation): _____

Signature _____ Date _____

Courtesy of C. Mobley & Associates, LLC, and Quality Management Options, LLC, Colorado Springs, Colorado.

Exhibit 5–7 Training Verification Request

Letterhead

Date

Program Director
Address
City, State, Zip

RE: _____ (Physician)

Dear Dr. _____:

We have received an application from _____ in which the physician indicates completion of (internship, residency, fellowship) at your institution. A copy of the clinical privileges requested is enclosed. Your completion of the questionnaire will be greatly appreciated.

A Release from Liability statement and a self-addressed stamped envelope are enclosed. Thank you for your help and attention to this matter.

1. _____(program) from_____(mo/yr) to____(mo/yr).

2. Was program completed? Yes____ No____

3. For the following categories, I would rate this physician to be:

	Outstanding/ Very Good	Average	Fair/Poor
Basic clinical knowledge	____	____	____
Competence and skill	____	____	____
Professional judgment	____	____	____
Medical recordkeeping	____	____	____
Patient management	____	____	____
Cooperativeness	____	____	____
Ethical conduct	____	____	____
Ability to understand/speak English	____	____	____
Sense of responsibility	____	____	____

If your evaluation is fair/poor, please clarify with further comments: _____

_____

4. I am aware of problems that might affect this physician's ability to care for patients related to:

Health/disability	Yes____	No____
Emotional stability	Yes____	No____
Alcohol or drugs	Yes____	No____
Other	Yes____	No____

continues

Exhibit 5–7 continued

5. Has the applicant ever been subject to any corrective or disciplinary action such as admonition, reprimand, suspension, or termination? Yes ____ No ____

6. Has the applicant ever been a defendant in a medical malpractice action? Yes ____ No ____

7. Is the applicant qualified for the privileges requested? Yes ____ No ____

8. REPORT IS BASED ON:
   A. Close personal observation ____
   B. General impression ____
   C. Composite of evaluations by supervisors ____
   D. Other (explain below)

9. RECOMMENDATION:
   A. Recommend highly without reservation ____
   B. Recommend as qualified and competent ____
   C. Recommend with some reservation ____
   D. No comment ____
   E. Do not recommend ____

10. Additional comments (including explanation of any adverse answers): ____

Signature: ____ Date: ____

Title: ____ Printed Name: ____

Courtesy of C. Mobley & Associates, LLC, and Quality Management Options, LLC, Colorado Springs, Colorado.

TIME FRAMES AND TRACKING SYSTEM

Organizations should identify turnaround time standards for response to requests for verification or information, as well as a procedure for second requests on follow-up actions. One missing piece of information can stop the entire credentialing procedure if it is vital to the decision-making process. A tickler file or tracking system should be in place to ensure that all requests are tracked and that a follow-up action occurs for any information not received within the time frame specified by the organizational standards. The procedure should also outline consequences or alternatives if a response is not received. Some organizations enlist practitioner support in obtaining information.

NCQA has very specific requirements for verification time frames that are outlined in their scoring guidelines. NCQA surveyors review dates of verifications that require a time frame and determine if they were obtained within the 180 days before the credentials decision. If a written verification is obtained, the 180-day time limit starts with the date on the letter or document, not the date the information is received. If a managed care organization delegates to a CVO, NCQA standards require that verification be no older than 120 days at the time it is submitted to

Exhibit 5–8 Medical Specialty Boards with On-Line Verification

American Board of Family Practice	www.abfp.org
American Board of Internal Medicine	www.abim.org
American Board of Medical Genetics	www.faseb.org/genetics/abmg/abmgmenu/htm
American Board of Pediatrics	www.abp.org
American Board of Preventive Medicine	http://members.aol.com/abmnet/indes.html

Exhibit 5–9 State Medical Boards with On-Line Verification Available

Arizona	www.docboard.org/doc_find/doc_find.htm
California	www.docgoard.org/doc_find/doc_find.htm
Colorado	www.dora.state.co.us/medical/main_verification-htm
Florida	www.fdhc.state.cl.us
Georgia	www.sos.state.ga.us
Indiana (password registration required)	www.ai.org./hpb
Iowa	www.docboard.org/doc_find/doc_find.htm
Kansas	www.docboard.org/doc_find/doc_find.htm
Maine	www.docboard.org/doc_find/doc_find.htm
Maryland	www.docboard.org/doc_find/doc_find.htm
Massachusetts	www.docboard.org/doc_find/doc_find.htm
Minnesota	www.docboard.org/doc_find/doc_find.htm
Missouri	www.ecodev.state.mo.us/pr.healarts
New York	www.nysed.gov
North Carolina	www.docboard.org/doc_find/doc_find.htm
Ohio	www.state.oh.us/med/
Oklahoma (DO)	www.docboard.org/doc_find/doc_find.htm
Oklahoma (MD)	www.osbmis.state.ok.us
Texas	www.docboard.org/doc_find/doc_find.htm
Utah	www.commerce.state.ut.us
Vermont	www.docboard.org/doc_find/doc_find.htm
Virginia	www.dhp.state.va.us

Note: Information also can be accessed through www.docfinder.com.

the managed care organization; this allows 60 days for review and decision by the managed care organization.

VERIFICATION AND INFORMATION-GATHERING ELEMENTS

An organization may obtain information or verification for numerous elements. Some are directed by accreditation standards, others by regulation, and many by standard practice or needs of the organization.

Verification Guidelines for the Joint Commission and NCQA

Table 5–1 outlines the verification guidelines for the Joint Commission and NCQA. As previously stated, verification and information-gathering activities are the most time-consuming activity of the credentialing process. It is important to carefully review regulatory and accreditation requirements to ensure compliance. Those items not required should be reviewed on a periodic basis. Identification of the value added, cost to produce and maintain, and reason the information is obtained should be included in the evaluation.

The elements most commonly verified or obtained are:

- ability to perform privileges requested/ability to perform essential functions
- application for membership/application or reapplication form
- board certification status
- civil and criminal history
- clinical privileges
- continuing medical education
- disciplinary actions
- DEA certificate and State Pharmacy certificate
- hospital references
- licensure
- malpractice history
- medical record review
- Medicare and Medicaid sanction activity
- member satisfaction/member complaint information
- NPDB query
- office assessment/site review
- peer references
- professional liability insurance coverage
- quality performance improvement activities/data
- training—professional and postgraduate school
- training—internship, fellowship, residency, postdoctoral
- utilization management
- work history/experience

Following is a grid, for each item listed above, of information that is commonly verified or obtained. The reader should reference the most recent accreditation standards, as they may have changed. The verification and information elements are outlined to include information related to

- purpose/description
- sources for verification or information (Unless otherwise indicated, sources pertain to both Joint Commission and NCQA.)
- Joint Commission and NCQA accreditation requirements/guidelines
- frequency of verifying/obtaining
- applicability
- comments/considerations/issues

Table 5–1 Initial Verification Guidelines of the Joint Commission and NCQA

Verification	*Joint Commission Guidelines*	*NCQA Guidelines*
Education		
Medical school	Yes	If no residency or board certification
Internship	Yes	No
Residency	Yes	If program completed and no board certification
Fellowship	Yes	No
ECFMG	If applicable	If no U.S. residency completed and graduated from a foreign medical school after 1986
Licensure and certification	Yes	Yes
Current appropriate state licensure	Per medical staff bylaws, rules, and regulations	
DEA certificate	Per medical staff bylaws, rules, and regulations	As applicable
State pharmacy certificate	If applicable	If applicable
Specialty board certification		If stated on application
Professional liability insurance coverage	Per medical staff bylaws, rules, and regulations	Yes
Experience	For evaluation of privileges	No
Work history	No	Yes (stated on application or CV. Gaps over one year should be clarified in writing.)
Malpractice history of claims resulting in settlement or judgment on behalf of practitioner	Per medical staff bylaws, rules, and regulations	Yes
Competence/ability to perform clinical functions	Per medical staff bylaws rules, and regulations	No
All hospitals		
Individuals personally acquainted with professional and clinical performance	Yes	No
Continuing medical/ professional education	Per medical staff bylaws, rules, and regulations	No
Affiliations	Per medical staff bylaws, rules, and regulations	Status of clinical privileges at primary hospital

continues

Table 5–1 continued

Information and Data Gathering	*Joint Commission Guidelines*	*NCQA Guidelines*
Completed application for membership	To include a statement that – no health problems exist that could affect practice – practitioner agrees to abide by bylaws and rules and regulations and to provide continuous care for patients – practitioner consents to inspection of records/documents and interview (if requested) – any challenges to any licensure or registration, or voluntary or involuntary relinquishment of such licensure or registration – any voluntary or involuntary termination of medical staff membership, or limitation reduction, or loss of clinical privileges	To include statements regarding – reasons for any inability to perform essential functions (with or without accommodation) – lack of present illegal drug use – history of loss of license and felony convictions – history of loss or limitations of privileges or disciplinary activity – attestation to correctness and completeness of the application
National Practitioner Data Bank query	Yes, per Health Care Quality Improvement Act of 1986	Yes
Sanctions or limitations on licensure	Yes	Yes
Medicare/Medicaid sanction activity	Per medical staff bylaws, rules, and regulations	Yes
Confirmation that no health problems exist that could affect practice	Yes	See statements to be included in application above
Structured site review of offices of all potential primary care and ob/gyn practitioners	No	Yes
Medical recordkeeping evaluation of all potential primary care and ob/gyn practitioners	No	Yes

Courtesy of C. Mobley & Associates, LLC, and Quality Management Options, LLC, Colorado Springs, Colorado.

Ability To Perform Privileges Requested/Ability To Perform Essential Functions

PURPOSE/DESCRIPTION

To evaluate and/or determine if any health problems exist that could affect clinical practice and whether further corroboration or investigation is needed on the basis of the information provided.

SOURCES FOR VERIFICATION/INFORMATION	ACCREDITATION
• Questions included on the application/reapplication forms and information must be completed by the applicant. • At appointment, the answers must be confirmed by a training program director/or chief of services or chief of staff at another hospital where applicant has privileges or a currently licensed physician designated by the hospital (Joint Commission). • At reappointment, the answers must be confirmed at least by a countersignature by the department director (or by the chief of staff at a nondepartmentalized hospital) (Joint Commission).	• The Joint Commission requires that the applicant's ability to perform privileges be evaluated. • NCQA does not require verification, but a statement is to be included on the appointment and reappointment form regarding any inability to perform the essential functions of the position, with or without accommodation.
FREQUENCY	**APPLICABLE FOR**
• At initial review • At reappointment/recredential or reapproval	• Medical staff and allied health practitioners (AHPs) as applicable (hospital) • Physicians and other licensed independent practitioners (LIPs) (managed care)

ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES

- Both accreditation organizations address the Americans with Disabilities Act (ADA) with regard to this requirement; statements made on an application may vary according to applicable legal requirements of the ADA (NCQA), and allowing the hospital to determine the applicability of the ADA to its medical staff will not be inconsistent with that hospital's efforts to comply with the (Joint Commission). (See also information on the ADA in Chapter 9 of this book.)
- In this area, NCQA also asks for a statement on the application regarding lack of present illegal drug use, with the same notation regarding the ADA. It has issued a classification regarding an acceptable statement to fulfill this requirement that reads, "Is there anything that may currently adversely affect your ability to exercise, or would require an accommodation in order for you to safely and competently exercise, the clinical privileges requested?"
- Information may be obtained by use of questions on the application/reapplication forms or comprehensive health questionnaire. It is up to the organization how much or how little information they will require and how they will interpret the ADA requirements. (The ADA refers to employees, and in many cases health care practitioners are not employees.)
- The Joint Commission standards related to this requirement include any LIPs with clinical privileges. The hospital determines if it is going to ask the same questions of an AHP who is not independently licensed and whether it will request confirmation by any listed reference or by a supervisor or sponsoring physician.

Application for Membership/Application or Reapplication Form

PURPOSE/DESCRIPTION	
To obtain data and information from the practitioner. All practitioners must complete a standardized, approved application form before initiation of the credentialing process.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
The application form and related attachments provided are compared with information and verifications obtained by the organization.	Both the Joint Commission and NCQA require an initial application and specify the components to be included (see below).
FREQUENCY	**APPLICABLE FOR**
• At initial review/appointment • At reappointment, recredential, or reapproval	• Medical staff and AHPs as applicable (hospital) • Physicians, other LIPs, and providers (managed care) • Providers (managed care)
ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES	
• The Joint Commission requires that the medical staff bylaws, rules and regulations, or policies define the information on the application to include challenges to or relinquishments of licensure or registration; termination; limitation, reduction, or loss of privileges at another hospital; and involvement in a professional liability action. • NCQA requires an application that includes a statement regarding reasons for any inability to perform the essential functions of the position, lack of present illegal drug use, history of loss or limitation of license and/or privileges or disciplinary activity, felony convictions, and an attestation. A faxed, photocopied, scanned or electronically reproduced attestation is acceptable to NCQA, but a stamped signature is not. • At reappointment or recredentialing, many organizations will use a computer software program profile that is sent to each practitioner in lieu of a blank form to be completed. The practitioner makes any corrections to the form, attests to its accuracy with no corrections or as corrected, and returns it to the appropriate source.	

Board Certification Status

PURPOSE/DESCRIPTION	
To verify that a practitioner is board certified, has recertified, or has been accepted to sit for the boards in the appropriate specialty.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• ABMS Directory of Board Certified Medical Specialists (Compendium) • AMA Physician Masterfile	• The Joint Commission does not require board certification, but if a physician is certified or "qualified," the intent state-

• AOA Physician Masterfile or AOA Director of Osteopathic Physicians (NCQA) • Confirmation from appropriate specialty (written or verbal) • Confirmation from the state licensing agency if the managed care organization provides recent evidence that the state agency conducts primary verification of board statutes (NCQA) • Primary source website (NCQA)	ments for the standards related to relevant training, experience, and competence mention board certification/qualification and the sources to verify. • NCQA does not require board certification but does require primary source verification if the practitioner is board certified. The only exception is that board certification is not applicable for chiropractors.
FREQUENCY	**APPLICABLE FOR**
• At initial review/appointment • At reappointment, recredentialing, or reapproval if recertification was due to expire during cycle	• Medical staff (hospitals) • Physicians (managed care)
ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES	
• NCQA requires that if a document source (e.g., ABMS) is used for verification, this source must be the most current available. The verification date is the date that the source is accessed. This is good for as long as the certification is current. • Organizations will need to monitor those specialties whose boards require recertification. This information is available from each specialty board. • Most specialty boards do not acknowledge the term *board eligible,* but it is still used by some hospitals in bylaws and/or privilege delineation. The term is often used by older practitioners who have completed a training program but have not chosen to sit for the boards. Many boards specify a time period after which the practitioner is no longer eligible to apply to take the boards without some continuing medical education and in some cases a formal training program of some length determined by the board. Because of these time elements (and additional requirements in some cases), it is difficult to track eligibility. • Some boards require a waiting period of several years after postgraduate training is completed before a physician can qualify to apply to take the boards. Therefore, if a hospital's clinical privileges are worded such that board certification is required, it must also identify the time line to take the boards and/or become certified. If this is the case, it must also define what happens if the boards are taken and failed. This may not necessarily mean that privileges are revoked, but the physician may require additional medical education, additional proctoring, a reduction in privileges previously granted, and/or a focused peer review to determine equivalent qualifications. • NCQA considers a letter from the Accreditation Council for Graduate Medical Education (ACGME) acceptable to confirm foreign board certification if the MCO also has a letter from the ACGME that states the foreign board primary source verifies training and education for each physician.	

Civil and Criminal History

PURPOSE/DESCRIPTION	
Some states require completion of a form and/or an inquiry regarding past criminal history or convictions as part of employment and/or the credentialing process.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• State-specific records • Statement of applicant on the application form • Criminal record check by an investigative firm	• The Joint Commission and NCQA accreditation standards do not specifically address verification of civil and criminal history.
FREQUENCY	**APPLICABLE FOR**
• Per state-specific statutes • Per organization bylaws or policies	• State-specific statutes indicate applicability.
ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES	
• A state-specific requirement to obtain a criminal history may also include a requirement to obtain a civil and/or financial crime history. • A release form or a disclaimer that a criminal history will not necessarily disqualify a job applicant may be required. • Pending Health Care Financing Administration (HCFA) changes to Medicare conditions of participation for home health care require a criminal background check for home health aides. All Medicare conditions of participation should be checked for applicability.	

Clinical Privileges

PURPOSE/DESCRIPTION	
To verify that a practitioner has clinical privileges in good standing and/or to obtain documentation to support a request for specific clinical privileges.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• Hospitals where clinical privileges have been granted (written or verbal with documentation) • Training programs (written or verbal with documentation) • Programs that offer limited training for specific privileges, such as new procedures (certificate of completion or letter outlining training as defined in criteria)	• The Joint Commission requires primary source verification of current competence in teaching facilities or other hospitals for clinical performance, partly related to clinical privileges granted at those institutions. • NCQA requires verification from the practitioner's primary inpatient admitting facility that the practitioner has clinical privileges in good standing, including any

	restrictions on the scope of privileges. NCQA does not require the practitioner to have clinical privileges, only that they be verified if they exist.
FREQUENCY	**APPLICABLE FOR**
• At initial review/appointment • At reappointment, recredential, or reapproval or for renewal or revision (addition) of individual clinical privileges	• Medical staff and AHPs who have clinical privileges (hospital) • Physicians and other independent practitioners who have or are requesting admitting privileges (managed care)
ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES	
• Also see the section "Hospital References" below for additional information. • If a practitioner does not have clinical privileges, the managed care organization should have a written statement describing the inpatient coverage arrangement and should credential/recredential those providing the coverage. • NCQA does not require verification of hospital privileges for dentists if they have a strictly office-based practice. • The 180-day verification time limit by NCQA applies to this element (120 days for NCQA-certified CVO).	

Continuing Medical Education

PURPOSE/DESCRIPTION	
To identify and collect information relating to continuing medical education as an adjunct to maintaining clinical skills and current competence.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• List of continuing medical education courses/hours that is submitted in those states that require continuing medical education hours to renew a license • List provided by hospital to practitioner of continuing medical education activity provided by the hospital • Copies of continuing education units (CEU) certificates from courses attended • List of continuing medical education courses/hours submitted to AMA for Physician Recognition Award	• The Joint Commission requires that individuals with clinical privileges participate in continuing education. • NCQA does not have a continuing medical education requirement.

FREQUENCY	APPLICABLE FOR
At reappointment, recredential, or reapproval, or for renewal or revision of individual clinical privileges	• Medical staff and AHPs who have clinical privileges (hospitals)

ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES

- At least some of the continuing medical education that practitioners participate in should relate to the privileges granted.
- Physicians may apply for the AMA's Physician Recognition Award, which requires 150 hours of continuing medical education for a three-year period. The list that is sent to the AMA may be submitted with a reappointment and application as long as it includes a time period that coincides with the two years being evaluated at reappointment. The AMA award certificate itself should not be accepted as evidence of continuing medical education, since there is no way to evaluate the type of education received (i.e., whether anything learned relates directly to the clinical privileges granted). The same is the case for those state-licensing boards that require CEUs to renew a license. The list that is submitted to the state is acceptable. Department chairs can then compare CEUs with the privileges requested.

Disciplinary Actions

PURPOSE/DESCRIPTION

A regulatory and accreditation requirement to identify practitioners and providers with disciplinary actions (sanctions and/or limitations on scope of practice) that might affect ability to render competent, quality patient care/services.

SOURCES FOR VERIFICATION/INFORMATION	ACCREDITATION
• State licensing boards • Organization taking action • National Practitioner Data Bank (NPDB) • Federation of State Medical Boards (FSMB) database • AMA Physician Masterfile (Joint Commission)	• The Joint Commission references medical staff bylaw requirements, the NPDB query, and verification of state license. • NCQA requires that applicants provide information regarding history of loss or limitation of previous five years or disciplinary activity; obtain information from state board or FSMB; complete NPDB query; and check for Medicaid/Medicare sanction.
FREQUENCY	**APPLICABLE FOR**
• At initial review/appointment • At reappointment, recredential, or reapproval	• Medical staff (hospitals) • Physicians and other LIPs (managed care) • Others required by statute, accreditation, or organization bylaws, policies, and procedures • Providers (if specified in policy)

ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES
• An NPDB query may reveal disciplinary actions. This information should be clarified with the practitioner and the organization that imposed the action before any decision about the possible impact on privileges or affiliation. • Primary source verification of disciplinary actions is required only for state board actions. • NCQA does not currently recognize NPDB as an acceptable verification source for state board queries and actions. • The 180-day verification time limit by NCQA applies to this element (120 days for a CVO).

Drug Enforcement Administration (DEA) Certificate and State Pharmacy Certificate

PURPOSE/DESCRIPTION	
To verify practitioner registration with the DEA and, if applicable, with the state pharmaceutical licensing agency. A DEA certificate authorizes a practitioner to prescribe controlled substances. Some, but not all, states also require a state pharmacy license.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• Copy of certificate from practitioner (NCQA) • Documented visual inspection of original certificate (NCQA) • Confirmation with CDS (NCQA) • National Technical Information Service tape: printout or on line with documentation (NCQA) • Confirmation with the state pharmaceutical licensing agency, where applicable (NCQA)	• The Joint Commission requires primary source verification of current license or registration, but its intent statements reference only state licensure. The only standard reference to DEA is the requirement for the applicant to provide any information on previously successful or currently pending challenges on DEA license or the voluntary relinquishment of such license. • NCQA does not require primary source verification of current certificate or registration.
FREQUENCY	**APPLICABLE FOR**
• At initial review • At reappointment, recredential, or reapproval—DEA must be current at time of peer review (NCQA) • At time of expiration—every three years	• Every practitioner who administers, dispenses, or prescribes a controlled substance must be registered with the DEA.

ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES
• A DEA certificate may be obtained by a physician, dentist, podiatrist, or other practitioner who is authorized by the jurisdiction in which he or she is licensed. • Documentation of visual inspection should include date of inspection and name or initial of inspector. • In the hospital setting, the hospital pharmacy may maintain copies of the DEA certificate or other accepted form of DEA verification. • NCQA does not require that the 180-day verification limit be applied to DEA verification, but the DEA must be effective at the time of the credentialing decision. • State pharmacy certificates are not applicable for chiropractors or dentists; DEA is not applicable for chiropractors, but it may be for dentists. • A practitioner may request registration for all or part of the five DEA schedules. If all five schedules are not listed (II, IIN, III, IIIN, IV, and V), the practitioner may not prescribe in unlisted categories. Most organizations require that practitioners have all schedules. • If a practitioner dispenses and/or administers narcotics in more than one office, he or she must have a DEA for each location. Only one certificate (copy) is generally collected or verified.
Definition of DEA Schedule Codes
– *Schedule I:* No accepted medical use in the United States (e.g., LSD) – *Schedule II:* Substances with high abuse potential and with severe psychic or physical dependence liability (e.g., opium, morphine, codeine) – *Schedule II N:* Non-narcotics with high abuse potential (e.g., amphetamine, pentobarbital) – *Schedule III:* Substances with less abuse potential than those in Schedules I and II (e.g., suppository forms of secobarbital) – *Schedule III N:* Non-narcotics with less abuse potential than those in Schedules I and II (e.g., derivatives or barbituric acid) – *Schedule IV:* Substances with less abuse potential than those in Schedule III (e.g., barbital, phenobarbital) – *Schedule V:* Substances with less abuse potential than those in Schedule IV (e.g., narcotics used for antitussive and antidiarrheal purposes)

Hospital References

PURPOSE/DESCRIPTION	
To verify current competence and/or to verify that a practitioner has clinical privileges in good standing in a hospital.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• Letters from hospitals • Documented verbal hospital references • Hospital roster, provided that it includes a cover letter stating that the practitioner is in good standing and including any restriction on the scope of privileges (or separate letter on restrictions, etc. is attached)	• The Joint Commission requires verification of current competence from authoritative sources on applicant's scope and level of performance. Hospitals can comment on clinical performance in general terms, satisfactory discharge of professional obliga-

	tions as a medical staff member, and ethical types of operative procedures/complications/outcomes for surgeons of record and applicant's clinical judgment and skills. • NCQA requires oral or written confirmation from practitioner's primary inpatient facility that the practitioner has clinical privileges in good standing.
FREQUENCY	**APPLICABLE FOR**
• At initial review/appointment • At reappointment, recredential, or reapproval	• Medical staffs and AHPs with clinical privileges; other AHPs optional (hospital) • Physicians and other LIPs (managed care)

ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES

- Hospitals have the option of whether to request letters of reference from hospitals at reappointment. Some request letters only if a practitioner is not active at the hospital and they have little or no performance activity to evaluate. Other hospitals want to obtain references from all current hospital affiliations. The argument for not obtaining references from all hospitals is that any required adverse action would be contained in an NPDB report, and the hospitals would not be gaining much by also soliciting information from other hospitals. The other argument is that many hospitals use a generic letter for routine responses, which provides very little information. The best methods to obtain the needed valuable information are asking hospitals to complete a questionnaire that provides more specific information than a generic letter (assuming that the hospital will complete the questionnaire); asking the appropriate questions on the application regarding actions taken by hospitals; and obtaining NPDB reports.
- As verification requests for hospital references increase, and because NCQA addresses the acceptable use of rosters (with qualifications), many hospitals are now willing to provide a partial roster or list of medical staff to requesting organizations. The rosters/lists should contain the practitioner's name, license (MD, DO, etc.), appointment date, and staff category. Any practitioners on the list with adverse actions should be underlined or otherwise marked with a notation in the cover letter that a practitioner release is required before further information is provided. Some hospitals do not want to use rosters and/or require a release form for every practitioner. Other hospitals are comfortable with providing the very basic/in-good-standing information suggested above without a signed release. Some of these hospitals include in their "consent to release of information" a statement like "From time to time, this hospital receives requests from other health care organizations to verify your membership/clinical privileges inclusive in a roster provided by this hospital. Your signature on this release allows that information to be released. If any adverse action has been taken against you, a specific release signed by you will be required from the requesting hospital." Check with legal counsel for assistance in wording the release.
- NCQA states that verification of privileges at a designated participating hospital may be interpreted by the MCO as verification of status at the MCO's designated participating hospital or the primary admitting hospital of the practitioner.

Licensure

PURPOSE/DESCRIPTION	
To verify current licensure to practice and previous current state sanctions, restrictions, and/or limitations on scope of practice.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• State licensing board via printout, letter, modem, verbal (documented), or licensing board reports for license and/or disciplinary actions depending upon state resources available • At reappointment, viewing the applicant's current original license (Joint Commission) • FSMB (disciplinary actions) • AMA Physician Masterfile (Joint Commission)	• The Joint Commission requires verification of current licensure, including any disciplinary actions. Also, each applicant (for appointment and reappointment) must provide information related to previously successful or currently pending challenges or voluntary relinquishment of licensure. • NCQA requires verification of current licensure, previous or current sanctions, restrictions, and/or limitations on scope of practice. Review of information should be for a five-year period and should include all states.
FREQUENCY	**APPLICABLE FOR**
• At initial review, appointment • At reappointment, recredential, or reapproval • At time of expiration (see issues below)	• Medical staff and licensed AHPs (hospitals) • Physicians and other licensed practitioners (managed care)
ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES	
• The 180-day verification time limit by NCQA applies to the element (120 days for CVO certified by NCQA), and the license must be in effect at the time of the credentialing decision. • Each state has different methods available for verification and reporting of disciplinary actions. And some states license everyone through one board, while others have a licensing board for each category. • If a practitioner is licensed in more than one state, each current license should be verified or at least the FSMB should be queried and/or the NPDB report should be reviewed (if the organization is qualified to do this) for any disciplinary action. • Licenses expire at different times (annually, on birth date, etc.) and are valid for different lengths of time (one to three years usually). • Even though licenses are verified at initial appointment and reappointment/recredentialing, licenses should be reverified (with the state licensing board) at time of expiration. Many organizations collect copies of a license but a copy from the practitioner does not constitute verification. • The Joint Commission requires evidence of a current verified license at all times.	

Malpractice History

PURPOSE/DESCRIPTION	
To identify the professional liability claims history of a practitioner or provider.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• Malpractice carrier • NPDB • The application form identifies history	• The Joint Commission requires that bylaws, etc. define the information to be obtained related to professional liability action(s) and, at a minimum, final judgments or settlements are reported. • NCQA requires verification of malpractice settlements or judgments paid by or on behalf of the practitioner.
FREQUENCY	**APPLICABLE FOR**
• At initial review/appointment • At reappointment, recredential, or reapproval	• Medical staff (hospitals) • Physicians and other LIPs (managed care) • Providers (see below)
ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES	
• NCQA requires either an NPDB query or written confirmation of the past five years of malpractice settlement history from the malpractice carrier; NPDB is not recognized as a source for dentists, podiatrists, or chiropractors. • The 180-day verification time limit by NCQA applies to this element (120 days for a CVO). • At the time of reappointment or recredentialing, only history for the past cycle is applicable; information reviewed previously should not be re-reviewed. • If the past five years include residency or fellowship covered by hospital insurance policy, it is not required by NCQA that information be obtained from that carrier. • A practitioner does not have to be convicted of malpractice for an organization to use malpractice information as part of the credentialing decision. • If a provider is not accredited, the organization's standards of participation may address malpractice history even though Joint Commission does not require verification of the malpractice history; industry standard includes verification either through the malpractice carrier or the NPDB.	

Medical Record Review

PURPOSE/DESCRIPTION
Evaluation of medical recordkeeping practices and practitioner documentation in medical records.

SOURCES FOR VERIFICATION/INFORMATION	ACCREDITATION
• Medical records—hospitals • Medical records—physician office (NCQA) • On-site evaluation of recordkeeping practices—physician office (NCQA)	• The Joint Commission requires medical staff involvement in the accurate, timely, and legible completion of records. • NCQA requires documentation of an evaluation of medical recordkeeping practices.
FREQUENCY	**APPLICABLE FOR**
• At initial review • At reappointment, recredential, or reapproval	• Medical staff (hospital) • Primary care practitioners (PCPs) and obstetrics/gynecologists and high-volume specialists at time of recredentialing for medical recordkeeping practices and of primary care for medical record documentation (managed care)

ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES

- The Joint Commission outlines the information to be included in the medical record review in its information management standards.
- Only individuals with appropriate qualifications should evaluate medical practice and health management.
- The Joint Commission requires that medical staff provide leadership for the measurement, assessment, and improvement of the accurate, timely, and legible completion of patient medical records and that records be reviewed at least quarterly.
- Ambulatory documentation and recordkeeping practices should be reviewed with office staff, including
  - forms and methods used for medical record file/filing system
  - means of ensuring confidentiality
  - organization of files and forms within the file
  - documentation practices
- NCQA
  - states that high-volume specialists are determined by the managed care organization
  - allows a site visit/medical record review to occur within a two-year period before the credentialing decision
  - indicates that the managed care organization should have specific standards by which the medical record is reviewed

Medicare and Medicaid Sanction Activity

PURPOSE/DESCRIPTION

Identification of sanctions imposed by the Office of the Inspector General (OIG), which may be criminal with a fine and /or imprisonment, civil monetary, civil liability, or exclusion from Medicare or Medicaid programs, due to such offenses or fraud, excessive claims, failure to furnish medically necessary items, default on a health education loan, or violation of limitations on physician charges.

SOURCES FOR VERIFICATION/INFORMATION	ACCREDITATION
• NPDB (as of March 3, 1997, the NPDB established a data link with the OIG to provide cumulative sanction information) • Cumulative Sanctions Report—Internet • FSMB • Medicare intermediary • Medicaid agency or intermediary • Medicare and Medicaid sanction report distributed to federally contracted managed care organizations	• The Joint Commission standards are silent in relation to verification or collection of information about Medicare or Medicaid sanctions. • NCQA standards require managed care organizations to review for previous sanction activity by Medicare and Medicaid.
FREQUENCY	**APPLICABLE FOR**
• At initial review • At reappointment, recredential, or reapproval	• Managed care organization physicians and other LIPs

ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES

- In 1976, Congress established the OIG at the Department of Health and Human Services (DHHS). The OIG is charged with identification and elimination of abuse fraud and waste in DHHS programs. OIG work is carried out through inspections, audits, and investigations.
- Query is not applicable for dentists.
- The NCQA 180-day verification time limit applies to this element (120 days for CVO certified by NCQA).
- Verbal verification requires a dated and signed/initialed note in the credentials file indicating source (how and who).
- Verification by review lists or information on line should be documented in the credentials file to include date, signature/initials of staff member, source, and report date if applicable.
- As with other NPDB information, if a report states "no information found," it may be assumed that the practitioner has not had Medicare or Medicaid sanction activity; a specific statement will not be found.

Member Satisfaction/Member Complaint Information

PURPOSE/DESCRIPTION	
Data that may be incorporated into an NCQA-accredited managed care organization's decision-making process for PCPs.	
SOURCE FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• Members enrolled in the managed care organization	• The Joint Commission is silent on the topic of collection and use of information related to satisfaction or complaints. • NCQA requires that three of six sources of information be used at the time of recredentialing; complaints and satisfaction are two of the six identified sources.
FREQUENCY	**APPLICABLE FOR**
• At reappointment, recredentialing, or reapproval	• PCPs only
ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES	
• There should be documentation of an affirmative assessment even if there are no findings (e.g., if member complaint information is reviewed as part of a practitioner's recredentialing evaluation and no documented complaints are found, the absence should be documented).	

NPDB Query

PURPOSE/DESCRIPTION	
The Health Care Quality Improvement Act of 1986[5] established NPDB as an information clearing house. NPDB is primarily an alert or flagging system that assists in review of credentials through collection and release of certain information related to the professional competence and conduct of physicians, dentists, and some other health care practitioners. State medical and dental boards, hospitals and other health care entities, professional societies, and medical malpractice payers must report certain actions that relate to competence and conduct and payments made for a claim or judgment against a practitioner. Hospitals *must* query NPDB, and other eligible entities *may* query when they employ or contract with a practitioner. To be eligible, the entity must provide health care services and engage in professional review activity through a formal review process.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• The only source is NPDB. Fees are charged for all queries, except for self-query by a practitioner. Queries are completed electronically using a modem and QPRAC, the software developed by NPDB.	• The Joint Commission mentions the requirement for hospitals and encourages a query in a timely manner to ensure that all relevant information is available before appointment or granting of privileges.

	• NCQA has a specific standard that the managed care organization has received information from the NPDB and includes it in the file.
FREQUENCY	**APPLICABLE FOR**
• At time of initial application and every two years • If practitioner wishes to add or expand existing privileges at a hospital • At time of application for temporary privileges • At time of application for locum tenens privileges	• Medical staff (hospitals) • Physicians and other licensed independent practitioners (managed care) • May be applicable for some licensed AHPs (with clinical privileges)

ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES

- The 180-day verification time limit by NCQA applies to this element (120 days for CVO).
- The NPDB help line at 1-800-767-6732 accepts calls seven days a week, 24 hours a day (excluding federal holidays) and includes recordings for common topics. Weekdays from 8:30 A.M. to 6:00 P.M. (5:30 P.M. on Fridays) Eastern Time, an information specialist is available for questions.
- Hospitals do not have to query NPDB on medical and dental residents, interns, or staff fellows (house staff) in structured programs of supervised graduate medical education. But if a resident, intern, or fellow is appointed to a medical staff or is granted privileges to practice outside of the education program, a query must be completed.
- NCQA standards note that an NPDB query is not required for chiropractors and podiatrists.
- The NPDB query is a federal regulation; hospitals must query at least every two years regardless of accreditation status or affiliation.
- A self-query by a practitioner does not constitute a required query by an organization.
- Only eligible entities or their authorized agent may query NPDB. The report may *not* be shared with any other entity, organization, or agent. Reports may be shared only when two or more hospitals share a single, unified medical staff and shared peer review process with a joint governing board. Improperly sharing information could result in an $11,000 fine for each offense.[6]

Office Assessment/Site Review

PURPOSE/DESCRIPTION
To assess an applicant's office setting; to evaluate the site against managed care organization standards.

SOURCES FOR VERIFICATION/INFORMATION	ACCREDITATION
• On-site review of the facility in which care is provided	• Joint Commission: not applicable • NCQA: requires initial visit to offices of all potential PCPs, obstetricians/gynecologists and, at recredentialing, a visit to all PCP offices in which there are more than 50 members and obstetrician/gynecologists (if considered PCPs) and other high-volume specialists (as identified by the organization)
FREQUENCY	**APPLICABLE FOR**
• At initial review/appointment • At reappointment, recredential, or reapproval	• PCPs • Obstetricians/gynecologists • High-volume specialists (as determined by managed care organization)

ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES

NCQA standard rationale indicates that
- review should be structured
- review should be focused on the quality of the facility
- assessment of the following should be included:
  - –physical accessibility
  - –physical appearance
  - –adequacy of waiting and exam room space
  - –availability of appointments
- criteria should have goals or standards for acceptable performance

- If a practitioner practices at more than one location, each location should be reviewed by the managed care organization.
- A separate site visit for each practitioner in a medical group at one location is not required.
- The recredentialing site visit is focused on changes in the facility, equipment, and staffing.
- The managed care organization develops the site visit tool, and it is to be completed at the time of or shortly after the visit. No standard or example format is provided by NCQA.
- The site visit should occur before the initial decision and then within a two-year cycle before the recredential decision.
- For practitioners affiliated with a facility accredited by AAAHC or the Joint Commission, the managed care organization may use accreditation in lieu of a site visit; if the MCO obtains a copy of the survey report, the report clearly includes the office, that the survey meets the MCO quality assurance criteria, and that the survey was conducted during the two previous years. This is not interpreted by NCQA to be a delegation.
- Use of information from statewide site visit programs (such as currently established in Oregon and Washington) is considered to be delegation by NCQA.

Peer References

PURPOSE/DESCRIPTION	
To obtain recommendations from individuals in the same discipline (e.g., physician and physician, podiatrist and podiatrist) who have firsthand knowledge of the practitioner.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
* Reference letter (Joint Commission) * Documented phone conversation (Joint Commission) * Internal medical staff committee performance improvement, credentials, and executive committees (Joint Commission)	* The Joint Commission requires peer recommendations as part of the credentialing process and should refer to relevant training or experience, current competence, fulfillment of obligations as a medical staff member, and any effect of health status on the privileges being recommended. * NCQA does not address peer references.
FREQUENCY	**APPLICABLE FOR**
* At initial appointment * At reappointment, recredential, or reapproval	* Medical staff and AHPs with clinical privileges (hospital)
ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES	
* If no peer exists within the hospital environment, a recommendation is obtained externally. * When possible, the Joint Commission recommends that the peer be in the same specialty, but this is not required. * Some hospitals opt to get peer references at reappointment as well as at the initial peer review process. The only time that is necessary (other than if it is stated policy) is when there are no peers who are part of the department/committee review process.	

Professional Liability Insurance Coverage

PURPOSE/DESCRIPTION	
Verification that the practitioner has coverage for professional liability with limits to comply with organizational standards.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
* Insurance carrier * Copy from malpractice insurance carrier that is provided by the practitioner * Copy from practitioner	* The Joint Commission does not specify professional liability insurance coverage but does require compliance with bylaws, rules and regulations, and policies. In most

	areas, if is a community standard to require some level of coverage. • NCQA specifies verification of current adequate malpractice insurance according to the managed care organization policy.
FREQUENCY	**APPLICABLE FOR**
• At initial review/appointment • At reappointment, recredential, or reapproval	• Medical staff (hospitals) • Allied health, if specified in bylaws or policies (hospitals and managed care) • Practitioners (managed care) • Providers, if specified in policy
ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES	
• Coverage must be effective at time of the credentialing decision. • Copy should indicate dates and amount of coverage.	

Quality Performance Improvement Activities/Data

PURPOSE/DESCRIPTION	
At time of reappointment/recredential/reapproval, information from performance or quality improvement activities is considered as part of the decision-making process and in support of evaluation of competence for granting privileges.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• Practitioner-specific information identified as part of performance improvement activities (hospital) • Practitioner-specific information identified as part of quality improvement activities (managed care)	• The Joint Commission requires that the results of peer review activity be considered at reappointment and that findings of the assessment process that relate to individual practitioners be used in evaluation, renewal, or revision of privileges. • NCQA requires the managed care organization to use performance monitoring information when recredentialing PCPs. Use of three of six sources of information, one of which is information from quality improvement activities, is required.
FREQUENCY	**APPLICABLE FOR**
• at reappointment, recredential, or reapproval	• Medical staff and AHPs with clinical privileges (hospitals) • PCPs (managed care)

ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES
• Practitioner-specific information identified during quality/performance improvement activities should be used in determination of competence. • The Joint Commission identifies several processes that are to be measured and assessed that are usually practitioner specific, including: –medical assessment and treatment of patients –use of medications –use of blood and blood components –use of operatives and other procedures –efficiency of clinical patterns –significant departures from established patterns of clinical practice • NCQA does not require that recredential files contain actual quality review documents. A checklist that includes an affirmative statement related to review of information is acceptable. • If members are assigned by group rather than individual physician, quality data by practice may be used at time of recredentialing.

Training—Professional and Postgraduate School

PURPOSE/DESCRIPTION	
To verify the medical, dental, or other postgraduate training (following four-year undergraduate degree) of practice credentials, e.g., MD (medical doctor), DO, (doctor of osteopathy), DDS (doctor of dental science), DMD (doctor of medical dentistry), DC (doctor of chiropractic), and DPM (doctor of podiatry medicine).	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• Directly from the medical or professional school or degree-granting institution (letter of confirmation, phone verification acceptable) • For foreign medical graduates, ECFMG confirmation of certificate for those licensed after 1986 • AMA Physician Masterfile • AOA Physician Masterfile (NCQA residency) • Confirmation from state licensing agency if managed care organization provides recent evidence that the state agency conducts primary source verification of residency training (NCQA)	• The Joint Commission requires primary source verification of medical or professional school or degree-granting institution. • NCQA requires primary source verification of highest educational level attained per NCQA guidelines for each practitioner category. If MD, DO, DDS, or DMD is not boarded or residency trained, this is required.

FREQUENCY	APPLICABLE FOR
• At initial review/appointment	• Medical staff, other LIPs and/or AHPs according to bylaws, policies • Physicians and other licensed, certified, or registered independent practitioners (managed care)

ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES

- This verification is considered a "static" credential, so there are no time limits for verification. Once verified, this information can be used again for future verifications on the same individual (e.g., by a CVO that processes a practitioner multiple times for different clients).
- ECFMG is an acceptable primary source verification for foreign medical graduates. The ECFMG number given by the physician must be verified by ECFMG, which assesses the readiness of graduates of foreign medical schools to enter residency or fellowship programs in the United States that are accredited by the Accreditation Council for Graduate Medical Education (ACGME).

  A foreign medical graduate, as defined by ECFMG, is a physician whose basic medical degree or qualification was conferred by a medical school outside the United States, Canada, and Puerto Rico. The medical school must be listed in the *World Directory of Medical Schools* published by the World Health Organization. U.S. citizens who have completed their medical education in schools outside the United States, Canada, and Puerto Rico are considered foreign medical graduates. Foreign nationals who have graduated from medical schools in the United States, Canada, and Puerto Rico are not. ECFMG certification is also a prerequisite required by most states for licensure to practice medicine in the United States. Eligibility for certification requires passing the medical school application, passing the ECFMG English test, and documenting the completion of all educational requirements to practice medicine in the country in which the medical education is received.

  To verify an ECFMG certificate, include physician name, date of birth, and ECFMG number. Faxed requests and telephone inquiries are not accepted. Responses take approximately two weeks.
- Sometimes it can be difficult, even impossible, to verify education, especially for foreign medical graduates. With NCQA, there are other options, such as verification of the board or residency programs. The Joint Commission will accept a documented effort to obtain information. Also, it accepts the verification from ECFMG for a medical school without further verification.

Training—Internship, Fellowship, Residency, Postdoctoral

PURPOSE/DESCRIPTION	
To verify training beyond medical school that may include a rotating internship followed by specialty training.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• Directly from the training program (letter of confirmation or evaluation form, phone verification acceptable) • AMA Physician Masterfile (NCQA, Joint Commission) • AOA Physician Masterfile (NCQA residency) • ADA Masterfile (NCQA residency) • Confirmation from state licensing agency if the managed care organization provides recent evidence that the state agency conducts primary verification of residency training (NCQA residency)	• The Joint Commission requires primary source verification of all relevant training or experience from the primary source whenever feasible. • NCQA requires primary source verification of medical school or highest level attained (residency or board certification) (MD, DO); dental school or residency (DDS, DMO); or podiatry medical school or residency (DPM). If boarded in a podiatry specialty, board must provide evidence that the certifying board conducts primary source verification of podiatry school graduation and/or completion of residency.
FREQUENCY	**APPLICABLE FOR**
• At initial review/appointment	• Medical staff (hospitals) • LIPs and/or AHPs according to bylaws, policies (hospitals) • Physicians (managed care)
ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES	
• NCQA refers to medical school, residency, and/or board certification only in its education and training section. It does not acknowledge confirmation of internship or fellowship. • If recently out of a training program, hospitals should send a copy of the requested privilege delineation with the verification request and ask if the privileges requested relate to the training received. It is also a good idea to ask if the program was completed and if not, why not. Confirm the month as well as the year of program length to assist in identifying any gaps in time. • This verification is considered a "static" credential, so there are no NCQA time limits for verification.	

Utilization Management

PURPOSE/DESCRIPTION	
At time of recredentialing, information from utilization management activities may be considered as part of the decision-making process.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• Practitioner-specific information identified as part of utilization review activities	• The Joint Commission requires collection of data related to the appropriateness of admissions and hospital stays but does not specify that data must be used as part of the credentialing process. • NCQA requires the managed care organization to use performance monitoring information when credentialing PCPs. Use of three of six sources of information, one of which is utilization management data, is required.
FREQUENCY	**APPLICABLE FOR**
• At reappointment, recredential, or reapproval	• Admitting practitioners (hospitals) (managed care) • PCPs only
ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES	
• Documentation of review of objective criteria may be used regardless of whether any problems or issues are identified.	

Work History/Experience

PURPOSE/DESCRIPTION	
To be aware of gaps in reported work history and/or to gather additional information through references.	
SOURCES FOR VERIFICATION/INFORMATION	**ACCREDITATION**
• Information included on the application form (NCQA) • Curriculum vitae (NCQA) • Telephone verification of gaps (must be documented) (NCQA) • Letter of reference (hospitals)	• NCQA requires a minimum five-year work history, but no verifications are required from primary source. • Joint Commission standards do not address work history.

FREQUENCY	APPLICABLE FOR
• At initial review	• Physicians and other LIPs (managed care; hospitals optional)

ADDITIONAL COMMENTS, CONSIDERATIONS, AND ISSUES

- NCQA standards indicate that any gaps longer than six months be investigated; oral verification is acceptable.
- Some managed care organizations use this information to determine the private practice or employment in which the practitioner has been involved in order to match experience with needs of the organization.
- Even though the Joint Commission does not require any work history, hospital application forms may ask for any group affiliations and choose to solicit professional references from these groups or individuals named. Reference letters ask for any comments relative to communication and working relationships with others.

RESOURCES

Table 5–2 lists resources that the credentialing professional will find helpful with the activities of verification and information-gathering activities.

Exhibit 5–10 lists contact information for ABMS.

DEA office addresses can be found in Exhibit 5–11.

Table 5–2 Verification and Information-Gathering Resources

Resource	*Information or Service Provided*	*Contact Information*
Directory of American Medical Education (Association of American Medical Colleges [AAMC])	Listing of medical schools	AAMC 1 DuPont Circle, N.W. Washington, DC 20036
Association for Certification of Nurse Midwives (ACNM) Certification Council	Certification of nurse midwives	ACNM 8401 Corporate Drive, Suite 470 Landover, MD 20705 Phone 301-459-1321
Allied Health Education Directory (American Medical Assocation [AMA])	Occupational descriptions Educational program information	AMA Medical Education Group 515 North State Street Chicago, IL 60610 Phone 312-464-4956

continues

Table 5–2 continued

Resource	*Information or Service Provided*	*Contact Information*
AMA Masterfile	Verification source for MD and DO of * board certification * internship/residency * licensure status (most states) * medical school * sanctions	AMA 515 North State Street Chicago, IL 60610 Phone 800-665-2882 http://www.ama-assn.org
American Association of Nurse Anesthetists (AANA)	Certification of nurse anesthetists	AANA 222 South Prospect Avenue Park Ridge, IL 60069-6968 Phone 847-692-7050
American Board of Medical Specialties Reference Handbook (American Board of Medical Specialties [ABMS])	Purpose of ABMS Listing of ABMS boards with addresses Certification/recertification requirements	ABMS 1007 Church Street, Suite 404 Evanston, IL 60201 Phone 708-491-9091
ABMS Compendium (ABMS)	Verification source for board certification	Published by Marquis Who's Who 121 Chanlon Road New Providence, NJ 07974 Phone 800-521-8110
American Hospital Association (AHA) *Guide to the Health Care Field*	Information and addresses for: * hospitals in the United States * national organizations	AHA 1 North Franklin Chicago, IL 60606-3401 www.aha.org
American Nurses Credentialing Center (ANCC)	Verification for nurse practitioners	ANCC 600 Maryland Avenue, S.W. Suite 100W Washington, DC 20024-2571 Phone 202-554-4444
American Osteopathic Association (AOA), Credentials Services	Verification source for * board certification of osteopathic physicians * AOA-accredited continuing medical education	AOA 142 E. Ontario Street Chicago, IL 60611-2864 Phone 312-280-5800 or 800-621-1773
American Podiatric Medical Association (APMA) Masterfile	Verification source for podiatrists of * podiatry school and residency * board certification if primary source verification by certifying board	APMA 9312 Old Georgetown Road Bethesda, MD 20814 Phone 301-571-9200
Cumulative Sanction Report	Exclusion actions and monthly updates in the form of lists from the *Federal Register*	Website through the Office of Enforcement and Compliance of the HHS Office of the Inspector General at www.Sbaonline.Sba.gov/ignet/internal/hhs/oec.html

continues

Table 5–2 continued

Resource	*Information or Service Provided*	*Contact Information*
Directory of Medical Schools Worldwide, 5th ed.	International institutions that teach (the art and science of) medicine	U.S. Directory Services 655 N.W. 128th Street Miami, FL 33168 Phone 305-769-1700
Education Commission for Foreign Medical Graduates (ECFMG)	Provides confirmation for international medical graduates licensed after 1986	ECFMG 3624 Market Street Philadelphia, PA 19104 Phone 215-386-5910
Federation Credentials Verification Service (FCVS)	Verifies "core" credentials in six categories: • identity • medical education • postgraduate training • examination history • ECFMG certification • board action history	Federation of State Medical Boards Federation Place 400 Fuller Wiser Road, Suite 300 Euless, TX 76039-3855
Federation of Chiropractor Licensing Boards (CINBAD) Chiropractor Information Network/Board Action Database	Information source for chiropractors on • sanctions • licensure restrictions • limitations of scope of practice	CINBAD 901 54th Avenue, Suite 101 Greeley, CO 80634 Phone 970-356-3500
Federation of Podiatric Medical Boards (FPMB)	Information source for podiatrists on • sanctions • licensure restrictions • limitation on scope of practice	Federation of Podiatric Medical Boards 1729 Gladstonberry Road Potomac, MD 20854 Phone 301-424-1001
Federation of State Medical Boards (FSMB)	Information source for physicians on • sanctions • licensure restrictions • limitation on scope of practice	FSMB 6000 Western Place Fort Worth, TX 76107-4618 Phone 817-868-4000 http://www/usmle.org/boards.htm
Medicare/Medicaid Sanctions and Reinstatements Report—not available to general public. Cumulative Sanctions Report may be available.	Information source related to Medicare/Medicaid sanctions	Office of Inspector General Office of Enforcement and Compliance N2-01-26 7500 Security Blvd. Baltimore, MD 21244-1850 http://www.sbaonline.sba.gov/ignet/internal/hhs/invlis.htrml

continues

Table 5–2 continued

Resource	*Information or Service Provided*	*Contact Information*
National Commission for the Certification of Acupuncturists (NCCA)	Organization that certifies acupuncturists	NCCA 1424 16th Street, N.W., Suite 501 Washington, DC 20036 Phone 202-232-1404
National Board of Medical Examiners		http//www/nbme.org
National Commission of Certification of Physician Assistants (NCCPA)	Organization that certifies physician assistants	NCCPA 6849 B2 Peachtree Bunwoody Road Atlanta, GA 30328 Phone 770-399-9971
National Practitioner Data Bank (NPDB)	Required query for hospitals; other eligible entities may query	NPDB P.O. Box 10832 Chantilly, VA 20151 Helpline 800-767-6732
National Register of Health Service Providers in Psychology	Verification of * license * doctoral degree in psychology * supervised, experienced	National Register for Psychologists 1120 G Street, N.W., Suite 330 Washington, DC 20005 Phone 202-783-7663
National Technical Information Service (NTIS)	Verification of DEA	NTIS 5285 Port Royal Road Springfield, VA 22161 Order—703-487-4650 Other—703-487-4808

Exhibit 5–10 ABMS Contact Information

American Board of Allergy and Immunology
University City of Science Center
3624 Market Street
Philadelphia, PA 19104-2675
(215) 349-9466
http://www.abai.org

American Board of Anesthesiology
The Summit, Suite 510
4101 Lake Boone Trail
Raleigh, NC 27607-7506
(919) 881-2570

American Board of Colon and Rectal Surgery
20600 Eureka Road, Suite 713
Taylor, MI 48180
(313) 282-9400

American Board of Dermatology
Henry Ford Hospital
1 Ford Place
Detroit, MI 48202-3450
(313) 874-1088

continues

Exhibit 5–10 continued

American Board of Emergency Medicine
3000 Coolidge Road
East Lansing, MI 48823
http://www.abem.org

American Board of Family Practice
2228 Young Drive
Lexington, KY 40505-4294
(606) 269-5626
www.abfp.org

American Board of Internal Medicine
University City Science Center
3624 Market Street
Philadelphia, PA 19104-2675
(215) 243-1500 (800) 441-ABIM
http://www.abim.org

American Board of Medical Genetics
9650 Rockville Pike
Bethesda, MD 20814-3998
(301) 571-1825
http://www.faseb.org/genetics/abmg/abmgmenu.htm

American Board of Medical Specialties
1007 Church Street, Suite 404
Evanston, IL 60201-5913

American Board of Neurological Surgery
Smith Tower, Suite 2139
6550 Fannin Street
Houston, TX 77030-2701
(713) 790-6015
http://www.abns.org

American Board of Nuclear Medicine
900 Veteran Avenue, Room 12-200
Los Angeles, CA 90024-1786
(310) 825-6787

American Board of Obstetrics and Gynecology
2915 Vine Street
Dallas, TX 75204
(214) 871-1619
http://www.metronet.com/rhino

American Board of Ophthalmology
111 Presidential Blvd., Suite 241
Bala Cynwyd, PA 19004
(610) 664-1175
http://www.abop.org

American Board of Orthopaedic Surgery
400 Silver Cedar Court
Chapel Hill, NC 27514
(919) 929-7103

American Board of Pathology
P.O. Box 25915
Tampa, FL 33622-5915
(813) 286-2444
http://www.abpath.org

American Board of Pediatrics
111 Silver Cedar Court
Chapel Hill, NC 27514-1651
(919) 929-0461
http://www.abp.org

American Board of Physical Medicine and Rehabilitation
Suite 674, Norwest Center
21 First Street, S.W.
Rochester, MN 55902
(507) 282-1776

American Board of Plastic Surgery
Seven Penn Center, Suite 400
1635 Market Street
Philadelphia, PA 19103-2204
(215) 587-9322

American Board of Preventive Medicine
9950 W Lawrence Ave., Suite 106
Schiller Park, IL 60176
(847) 671-1750

American Board of Psychiatry and Neurology
500 Lake Cook Rd., Suite 335
Deerfield, IL 60015
(847) 945-7900
http://www.abpn.com

American Board of Radiology
5255 E Williams Circle, Suite 6800
Tucson, AZ 85711
(520) 790-2900

continues

Exhibit 5–10 continued

American Board of Surgery www.absurgery.org	(847) 475-1520 abts_evanston@msn.com
American Board of Thoracic Surgery 1 Rotary Center, Suite 803 1560 Sherman Ave Evanston, IL 60201	American Board of Urology 31700 Telegraph Road, Suite 150 Bingham Farms, MI 48025 (810) 646-9720

Exhibit 5–11 DEA Offices

ATLANTA DIVISION OFFICE
Attn: Registration
75 Spring St, SW, Room 740
Atlanta, GA 30303

Georgia	(404) 763-5908
North Carolina	(404) 763-5909
South Carolina	(404) 763-5909
Tennessee	(404) 763-5908

BOSTON DIVISION OFFICE
JFK Federal Building Room E-400
15 New Sudbury Street
Boston, MA 02203-0131

Connecticut	(617) 557-2200
Maine	(617) 557-2200
Massachusetts	(617) 557-2200
New Hampshire	(617) 557-2200
Rhode Island	(617) 557-2200
Vermont	(617) 557-2200

CARIBBEAN DIVISION OFFICE
2432 Loiza Street
Santurce, PR 00914

Puerto Rico	(787) 253-4230
Virgin Islands	(787) 253-4230

CHICAGO DIVISION OFFICE
230 S. Dearborn Street, Suite 1200
Chicago, IL 60604

Illinois	(313) 353-1234
Indiana	(313) 353-1236
Minnesota	(313) 253-1236
North Dakota	(313) 253-1234
Wisconsin	(313) 253-1236

DALLAS DIVISION OFFICE
1880 Regal Row
Dallas, TX 75235

Oklahoma	(214) 640-0849
Texas	(214) 640-0849

DENVER DIVISION OFFICE
115 Inverness Drive East
Englewood, CO 80112

Colorado	(303) 705-7323
New Mexico or Utah	(800) 326-6900
Wyoming	

DETROIT DIVISION OFFICE
431 Howard Street
Detroit, MI 48226

Kentucky	(313) 234-4302
Michigan	(313) 234-4302
Ohio	(313) 234-4302

HOUSTON DIVISION OFFICE
1433 West Loop South, Suite 600
Houston, TX 77027

Texas	(713) 793-3660

LOS ANGELES DIVISION OFFICE
255 E. Temple Street, 20th Floor
Los Angeles, CA 90012

California (South Central)	(888) 415-9822
Hawaii	(888) 415-9822
Nevada	(888) 415-9822
Trust Territory	(888) 415-9822

continues

Exhibit 5-11 continued

MIAMI DIVISION OFFICE
8400 N.W. 53rd Street
Miami, FL 33166

Florida	(305) 590-4880

NEW ORLEANS DIVISION OFFICE
Three Lake Way
3838 N. Causeway Blvd., Suite 1800
Metairie, LA 70002

Alabama	(504) 840-1063
Arkansas	(504) 840-1063
Louisiana	(504) 840-1063
Mississippi	(504) 840-1063

NEW YORK DIVISION OFFICE
99 Tenth Avenue
New York, NY 10011

New York	(212) 337-1593

NEWARK DIVISION OFFICE
80 Mulberry Street
Newark, NJ 07102

New Jersey	(201) 645-3501

PHILADELPHIA DIVISION OFFICE
William J. Green Federal Building
600 Arch Street, Room 10224
Philadelphia, PA 19106

Delaware	(215) 597-9536
Pennsylvania	(215) 597-9536

PHOENIX DIVISION OFFICE
3010 N. 2nd Street, Suite 301
Phoenix, AZ 85012

Arizona	(602) 664-5831

SAN DIEGO DIVISION OFFICE
4560 Viewridge Avenue
San Diego, CA 92123-1672

California (Southern)	(619) 616-4542

SAN FRANCISCO DIVISION OFFICE
450 Golden Gate Avenue
P.O. Box 36035
San Francisco, CA 94102

California (Northern)	(415) 436-7905

SEATTLE DIVISION OFFICE
220 West Mercer Street, Suite 104
Seattle, WA 98119

Alaska	(206) 553-4040
Idaho	(206) 553-4040
Montana	(206) 553-4040
Oregon	(206) 553-4040
Washington	(206) 553-4040

ST. LOUIS DIVISION OFFICE
United Missouri Bank Building
7911 Forsyth Blvd., Suite 500
St. Louis, MO 63105

Iowa	(314) 425-3241
Kansas	(314) 425-3241
Missouri	(314) 425-3241
Nebraska	(314) 425-3241
South Dakota	(314) 425-3241

HEADQUARTERS
U.S. Department of Justice
Drug Enforcement Administration
Central Station, P.O. Box 28083
Washington, DC 20038-8083
(800) 882-9539

WASHINGTON, DC, DIVISION OFFICE
400 6th Street, S.W., Room 2558
Washington, DC 20024

District of Columbia	(202) 401-7360
Maryland	(202) 401-7360
Virginia	(202) 401-7360
West Virginia	(202) 401-7360

NOTES

1. *1998 Surveyor Guidelines* (Washington, DC: National Committee for Quality Assurance, 1997), 356.
2. *1998 Hospital Accreditation Standards* (Oakbrook Terrace: IL: Joint Commission on Accreditation of Healthcare Organizations), 298.
3. *AMA Primary Source Physician Information for Credentialing* (Chicago, IL).
4. *AMA Primary Source Physician Information for Credentialing*.
5. 42 U.S.C. §§ 11101-11152.
6. *NPDB News* (U.S. Department of Health and Human Services) (February 1998), 1-4.

The Credentialing Handbook

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DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

PRELIMINARY CLINICAL SAFETY REVIEW OF NDA

Brand Name:	**Xyrem**
Generic Name:	**Sodium Oxybate**
Sponsor:	**Orphan Medical, Inc.**
Indication:	**Narcolepsy**
NDA Number:	**21196**
Original Receipt Date:	**10/3/00**
Clinical Reviewer:	**Ranjit B. Mani, M.D.**
Review Author:	**Ranjit B. Mani, M.D.**
Review Completed:	**5/3/01**

Table of Contents

1. Review Sources

This submission contains an original New Drug Application for Xyrem® (sodium oxybate; γ-hydroxybutyrate) oral solution. The application is dated 9/30/2000 and was received by the Center for Drug Evaluation and Research of this Agency on 10/3/00.

In this review the words/phrases "γ-hydroxybutyrate (GHB)", "sodium oxybate", and "Xyrem®" have been used interchangeably.

Xyrem® has been developed by Orphan Medical, Inc. for the treatment of narcolepsy under IND # 49641 and Treatment IND # 57271. Data obtained from individual sponsor-investigator INDs #s 21654 (M. Scharf) and 19911 (L. Scrima) have also been used in support of this application.

Note that this is a preliminary, and not final review. Further editing of this review is possible.

1.1 Materials from NDA

In reviewing this application I have read the following volumes of the NDA submission of 9/30/00. These volumes have been read almost entirely in electronic format.
Volumes 1, 5, 25-34, 36-63, 100-104 and 114-122

I have also reviewed the following:

- A separate submission dated 12/16/00 containing the final reports for several clinical trials: OMC-SXB-16, OMC-SXB-20 and OMC-SXB-21
- The sponsor's responses to a number of requests for information from this reviewer
- A 120-Day Safety Update
- Risk management materials, comprising physician and patient information materials, supplied by the sponsor

1.2 Related Reviews, Consults

I have utilized the many reviews that I have done, since 1997, of submissions under IND # 49641 and Treatment IND # 57271 for details about this drug.

Consults that were obtained from other Divisions within the Agency and have been reviewed by me include reports from

- The Controlled Substances Staff
- The Office of Post-Marketing Drug Risk Assessment

1.3 Other Reviews

I have reviewed publications submitted by the sponsor as part of the NDA and the following recently published article:
Zvosec DL et al. Adverse Events, Including Death, Associated With The Use Of 1,4-Butanediol. N Engl J Med 2001;344:87-94

2. Background

2.1 Indication

The sponsor wishes to pursue the following claim:

"Xyrem® (sodium oxybate) oral solution is indicated to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy."

Narcolepsy is a chronic neurological disorder characterized by excessive daytime sleepiness, disturbed nocturnal sleep, cataplexy, sleep paralysis and hypnagogic hallucinations. The prevalence of this condition in the United States, as per a publication cited by the sponsor, is between 0.02% and 0.07%. According to the sponsor, current treatments for this condition are limited in effectiveness and have frequent undesirable adverse events.

2.2 Important Information from pharmacologically related agents

None.

2.3 Administrative History

This drug has been developed by Orphan Medical, Inc. for the treatment of narcolepsy under IND # 49641 and Treatment IND # 57271. Data obtained from individual sponsor-investigator INDs #s 21654 (M. Scharf) and 19911 (L. Scrima) have also been used in support of this application.

This drug product has been the subject of numerous meeting and items of correspondence involving the following: the current sponsor; this Division; the Controlled Substances Staff; the Division of Anesthetic, Critical Care and Addiction Drug Products; the Division of Orphan Drug Products; and other bodies. These contacts are too numerous to summarize in this review

2.4 Proposed Labeling

The proposed labeling for this drug is reviewed separately

2.5 Foreign Marketing

Currently, this drug product has not been marketed in any country. However, according to the sponsor

- Gamma-OH® an injectable oxybate preparation is marketed as an adjuvant anesthetic and sedative in France
- Somsanit® an injectable oxybate preparation is marketed as a sedative in Germany
- Alcover® an oxybate containing oral solution (175 mg/mL) is marketed in Italy for the treatment of alcohol withdrawal
- A powdered form of GHB is sold by Biogenesis Laboratories of South Africa via the Internet, but **NOT** in the following countries: Australia, New Zealand, Norway, South Africa and the United States

For may years GHB was distributed in this country as a health food product under a variety of trade names. However, in 1990 it was removed from the market after a number of reports of adverse reactions.

2.6 Miscellaneous Background Information

In the popular media there have been many reports over the last few years of instances of overdose with illegally-manufactured GHB. A number of anecdotal single case reports/case series of a similar nature have also been published in the medical literature. There have also been similar reports linked to the use of related compounds such as gammabutyrolactone and 1,4-butanediol.

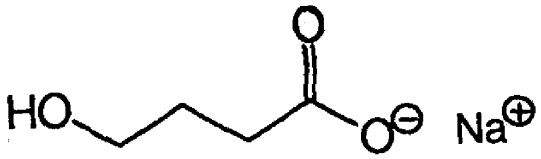
According to the sponsor, GHB users in this country derive the drug from the following sources

- Purchase from illegal vendors, including those selling the drug over the Internet
- By home manufacture: both recipes and starting materials are easily available

Public Law 106-172 (passed by the United State Congress) has allowed for the designation of GHB as a Schedule I agent, with exemption from the security requirements for the GHB drug product studied under an FDA-approved IND. Upon marketing approval from the FDA being received, the GHB drug product would become a Schedule III agent with Schedule I penalties for illicit use. All other GHB containing products would remain Schedule I agents

3. Chemistry, Manufacturing and Controls

Gamma-hydroxybutyrate is a short chain fatty acid normally found in a variety of mammalian tissues, including the human brain, where it is a metabolite of gamma-aminobutyric acid. The chemical structure of the sodium salt of this compound is as depicted below:



The drug product is a 500 mg/mL solution. It is composed of sodium oxybate, purified water, DL-malic acid, and sodium hydroxide.

The drug product is supplied in a 240 mL PET amber bottle, sealed with a child-resistant camp. Additional items supplied with the bottle include

- A Press-In-Bottle Adapter (PIBA Well)
- A dispenser (Exacta-Med®)
- 2 child-resistant dosing cups

The PIBA Well will be placed into the solution by the pharmacist dispensing the drug. The drug product, PIBA Well, dispenser and dosing cups will be packaged in a carton when supplied to the patient

4. Toxicology

Salient items that I have derived from a summary provided by the sponsor are below:

- The sponsor did not conduct any acute toxicity studies but has cited literature reports of such studies instead. The sponsor has conducted repeated-dose toxicity studies in rats and dogs, reproductive toxicity studies in rats and rabbits, and mutagenicity studies. A 104-week carcinogenicity study in rats is ongoing.
- Effects of GHB in toxicology studies included reduced activity, prostration, ataxia, emesis, reduced food consumption and weight loss/weight gain. No evidence of organ toxicity was seen based on laboratory tests, and gross as well as microscopic pathological examination.
- GHB had no evidence of reproductive toxicity or mutagenicity
- In regard to carcinogenicity
  - The carcinogenicity of gammabutyrolactone (GBL), a precursor of GHB, has been studied under the National Toxicology Program. According to the sponsor "equivocal" evidence of carcinogenicity was demonstrated in male, but not female, mice based on increased adrenal medulla hyperplasia and increases in benign and malignant pheochromocytomas at a dose of 262 mg/kg/day
  - In bridging studies with GBL in the same strain of mice studied under the National Toxicology Program the sponsor has measured plasma levels of both GHB and GBL. Based on these plasma levels the sponsor has concluded that systemic exposure to GHB is similar whether GBL or GHB is administered, and that the National Toxicology Program studies are therefore valid as an appropriate evaluation of GHB. These studies were discussed with the Agency
  - A 104-week rat carcinogenicity study is currently ongoing

5. Clinical Data Sources

5.1 Sources Of All Data In Integrated Summary of Safety

5.1.1 Study Type

A total of 15 clinical trials are included in the Integrated Summary of Safety. The sponsor has grouped these studies into 4 separate pools which are outlined below. Safety data for each of these pools are described separately by the sponsor. Note that the sponsor has not included controlled clinical trials under a separate heading

5.1.1.1 Integrated Clinical Trials

A total of 402 patients participated in these trials; some of these patients participated in more than one trial. 3/402 patients received placebo only.

Study #	Design	Number of Patients	Duration
OMC-GHB-2	Randomized, double-blind, placebo-controlled, parallel-arm	136 patients	4 weeks

OMC-GHB-3	Open-label, uncontrolled, extension study	118 patients	Up to 24 months
OMC-SXB-6	Open-label uncontrolled study	185 patients	6 months
OMC-SXB-7	Open-label uncontrolled study	145 patients	Up to 24 months
Scrima	Randomized, double-blind, placebo-controlled, cross-over	20 patients	4 weeks*

*GHB and placebo were each used for 4 weeks

Further details about the above extension studies are below

Study #	Comments
OMC-GHB-3	Extension to OMC-GHB-2.
OMC-SXB-6	Treatment naïve patients (except for a single patient previously in OMC-GHB-2 and OMC-GHB-3)
OMC-SXB-7	Extension to OMC-GHB-3 (52 patients) OMC-SXB-6 (30 patients) Scharf Study (63 patients) The numbers in parentheses in this cell refer to the number of patients entering OMC-SXB-7 from each study

5.1.1.2 Lammers Trial

25 patients participated in this randomized, double-blind, placebo-controlled, cross-over trial of 4 weeks' duration (GHB and placebo were each used for 4 weeks).

5.1.1.3 Long-Term Clinical Trial (Scharf)

This long-term open-label study involved 143 patients and has lasted about 16 years

5.1.1.4 Integrated Pharmacokinetic Trials

A total of 144 subjects/patients have been enrolled in these trials which are listed in the table below. All were single dose-studies. With the exception of those enrolled in Studies OMC-GHB-4 and OMC-SXB-10 (total of 19 narcoleptic patients) all were healthy volunteers (total of 125 subjects)

Study #	Number of subjects/patients
OMC-GHB-4	6*
OMC-SXB-8	36
OMC-SXB-9	13
OMC-SXB-10	13**
OMC-SXB-11	36
OMC-SXB-12	15
OMC-SXB-14	12
OMC-SXB-17	13

*The 6 narcoleptic patients participating in this study also enrolled in the Scharf study
**The 13 narcoleptic patients participating in this study also enrolled in OMC-SXB-6

5.1.2 Number Of Unique Narcoleptic Patients And Healthy Subjects In Integrated Summary Of Safety

I had obtained a clarification from the sponsor regarding the numbers of unique patients and healthy subjects in the Integrated Summary of Safety. The details are below

5.1.2.1 Unique Narcoleptic Patients

The number of unique narcoleptic patients participating in clinical trials of GHB is listed in the table below

Study Grouping	Number of Patients
OMC-GHB-2/OMC-GHB-3	133
OMC-SXB-6/OMC-SXB-7	183
Scrima	20
Lammers Trial	25
Scharf Trial	143
TOTAL	**504**

NOTE: The narcoleptic patients who participated in the pharmacokinetic trials OMC-GHB-4 (6 patients) and OMC-SXB-10 (13 patients) also participated in the Scharf and OMC-SXB-6 trials. These patients are counted in the above table under the Scharf and OMC-SXB-6 trials

5.1.2.2 Unique Healthy Subjects

The number of unique healthy subjects participating in clinical trials of GHB are in the following table. All these trials were pharmacokinetic.

Study #	Number of subjects/patients
OMC-SXB-8	36
OMC-SXB-9	13
OMC-SXB-11	36
OMC-SXB-12	15
OMC-SXB-14	12
OMC-SXB-17	13
TOTAL	**125**

5.1.3 Demographics

Demographics are summarized according to the study pools used by the sponsor in this summary

5.1.3.1 Integrated Clinical Trials

Demographics for all Xyrem®-treated patients are summarized below. The table is derived from one supplied by the sponsor

Variable	Number	Mean	Standard Deviation	Range
Age (years)	402	46.1	15.22	13.9-81.1
Weight (kg)	397	83.9	20.22	47.0-175.0
Height (cm)	396	170.3	10.33	129.0-206.0
Gender	402	Males 43% /Females 57%		

Demographics for the 3 patients treated exclusively with placebo are summarized below

Variable	Number	Mean	Standard Deviation	Range
Age (years)	3	37.5	14.43	26.1-53.7
Weight (kg)	3	90.0	15.72	76.0-107.0
Height (cm)	3	168.3	4.62	163.0-171.0
Gender	3	Females 100%		

5.1.3.2 Lammers Trial

The following table illustrates the demographics for all 25 patients in the study. The table is derived from one supplied by the sponsor

Variable	Number	Mean	Standard Deviation	Range
Age (years)	25	40	14	16-65
Weight (kg)	24	79	10	63-92
Height (cm)	24	175	7	157-187

Gender	25	Males 52% /Females 48%

5.1.3.3 Scharf Trial

The following table illustrates the demographics for all 143 patients in this study. The table is derived from one supplied by the sponsor

Variable	Number	Mean	Standard Deviation	Range
Age (years)	143	45.3	14.5	13.0-75.0
Gender	143	Males 55.9% /Females 44.1%		
Race	143	Caucasian 88.8%/Afro-American 1.4%/ Unavailable 9.8%		

5.1.3.4 Integrated Pharmacokinetic Trials

The following table illustrates the demographics for all 144 subjects in these 8 studies. The table is derived from one supplied by the sponsor

Variable	Number	Mean	Standard Deviation	Range
Age (years)	144	32.3	12.24	18.0-62.0
Weight (kg)	144	73.0	11.28	50.8-114.0
Height (cm)	138	169.3	7.92	152.4-190.5
Gender	144	Males 40% /Females 60%		

5.1.4 Extent of Exposures

Total exposure and exposure by study pool (Integrated Clinical Trials, Lammers Trial, Scharf Trial and Integrated Pharmacokinetic Trials) is described below.

In all trials listed in the Integrated Summary of Safety, the number of patients and healthy subjects exposed to GHB for specified periods is illustrated in the table below

Period of Exposure to Xyrem	Number of Patients with Narcolepsy	Number of Healthy Controls
Any Exposure	504	125
≥ 6 months	354	0
≥ 1 year	179	0
≥ 2 years	127	0
≥ 5 years	79	0
≥ 10 years	46	0

Total exposure in patient-years in each of the study pools (except the pharmacokinetic trials) is listed in the next table

Pool	**Exposure to Xyrem® (Patient-Years)**
Integrated Clinical Trials	266.83
Lammers Trial	2.08
Scharf Trial	996.15
Total	**1265.06**

5.1.4.1 Integrated Clinical Trials

The cumulative duration of exposure by last dose for this group of trials is illustrated in the following table. The duration of exposure was calculated based on the 28-day month. Note that the “Any Exposure” row lists all patients who have been exposed to specific doses at any time, not just as the last dose.

Duration of Exposure	Total	Xyrem® last dose g/day				
		3.0	4.5	6.0	7.5	9.0
Any Exposure	399	94	266	290	116	118
≥ 6 months	233	5	43	88	37	60
≥ 1 year	75	3	8	25	13	26
≥ 2 years	37	1	3	12	7	14

5.1.4.2 Lammers Trial

25 patients were exposed to a mean Xyrem® dose of 4.75 g/day (range 3.78 to 5.52 g/day) for 28 days

5.1.4.3 Scharf Trial

The cumulative duration by the Xyrem® dose administered for the longest duration is in the following table

Duration of Exposure	Total	Longest-used dose of Xyrem® (g/day)				
		3.0	4.5	6.0	7.5	9.0
Any Exposure	143	5	49	62	18	9
> 6 months	121	3	41	54	14	9
> 1 year	104	2	37	45	12	8
> 2 years	90	1	32	38	12	7
> 5 years	74	1	27	30	10	6
> 10 years	46	1	12	23	7	3

Note that 63 patients in the Scharf trial were subsequently also enrolled in OMC-SXB-7

5.1.4.4 Integrated Pharmacokinetic Trials

Exposure data for these studies was not calculated as these were all single dose studies. As noted earlier 144 patients/subjects were exposed to Xyrem® in these studies.

The dose(s) used in each these single-dose studies is indicated in the following table

Study #	GHB Total Dose	Number of subjects/patients
OMC-GHB-4	6.0 g	6*
OMC-SXB-8	4.5 g	36
OMC-SXB-9	4.5 g or 9.0 g	13
OMC-SXB-10	4.5 g	13**
OMC-SXB-11	4.5 g	36
OMC-SXB-12	3.0 g	15
OMC-SXB-14	4.5 g	12
OMC-SXB-17	4.5 g	13

*Narcoleptic patients
Note that the total dose of GHB was administered either as a true single-dose or 2 divided doses 4 hours apart

5.2 Cut-Off Date For Data In Integrated Summary Of Safety

- The only ongoing trial in the Integrated Summary Of Safety is OMC-SXB-7. The cut-off date for data in this trial is 12/31/99
- All other clinical trials in the Integrated Summary Of Safety are complete as are the safety data submitted with the NDA.

5.3 Primary Data Sources

These are studies conducted by Orphan Medical, Inc. They include the following

5.3.1 Efficacy And Long-Term Safety Studies

These are listed in the following table

Study #	Design	Number of Patients	Duration
OMC-GHB-2	Randomized, double-blind, placebo-controlled, parallel-arm	136 patients	4 weeks
OMC-GHB-3	Open-label, uncontrolled,	118 patients	Up to 24 months

Study #	Design	Number of Patients	Duration
	extension study		
OMC-SXB-6	Open-label uncontrolled study	185 patients	6 months
OMC-SXB-7	Open-label uncontrolled study	145 patients	Up to 24 months

5.3.2 Pharmacokinetic Studies

These are listed in the following table

Study #	Number of subjects
OMC-GHB-4	6
OMC-SXB-8	36
OMC-SXB-9	13
OMC-SXB-10	13
OMC-SXB-11	36
OMC-SXB-12	15
OMC-SXB-14	12
OMC-SXB-17	13

5.4 Secondary Data Sources

These are studies that have not been conducted by the sponsor and consist of efficacy and long-term safety studies only.

Study #	Design	Number of Patients	Duration
Scrima	Randomized, double-blind, placebo-controlled, cross-over	20 patients	4 weeks*
Lammers	Randomized, double-blind, placebo-controlled, cross-over	25 patients	4 weeks*
Scharf	Open-label extension study	143 patients	< 16 years

*GHB and placebo were each used for 4 weeks

5.5 Other Data Sources

The sponsor has also used 3 published reports of open-label studies of Xyrem® in narcolepsy to support the efficacy and safety of Xyrem®.

The outlines of these studies, including adverse event data, are summarized below. As these were open-label, uncontrolled studies, I have not summarized the efficacy data that was derived from them

Study	Scharf (1985)*	Broughton (1979)**	Broughton (1980)***
Design	Open-label, uncontrolled study	Open-label, uncontrolled study	Open-label, uncontrolled study
Maximum duration of treatment	30 weeks	20 months	7-10 days
Number of patients	30	16	14
Total nightly dose of Xyrem®	5-7 g	50 mg/kg	3.75 to 6.25 g
Adverse events	Protracted sleep paralysis (3 patients) Enuresis (1 patient) Increased sexual drive (1 patient)	"Hangover", urinary urgency, enuresis, dream-like confusional state prior to sleeping, abdominal pain, muscular weakness, left arm dysesthesia	"No serious toxic side-effects"

*Scharf MB et al. The effects and effectiveness of gamma-hydroxybutyrate in patients with narcolepsy. J Clin Psychiatry. 1985;:222-5. (Note that the patients reported in this publication are a subset of those included in the interim Scharf study report under this IND).
**Broughton R, Mamelak M. The treatment of narcolepsy-cataplexy with nocturnal gamma-hydroxybutyrate. Can J Neurol Sci. 1979;6:1-6.

***Broughton R, Mamelak M. Effects of nocturnal gamma-hydroxybutyrate on sleep/waking patterns in narcolepsy-cataplexy. Can J Neurol Sci. 1980;7:23-31.

5.6 Adequacy of Human Experience

- Xyrem® has been designated as an orphan drug product
- Based on the total number of narcoleptic patients exposed to Xyrem® in clinical trials derived from primary and secondary data sources (see Sections 5.3 and 5.4) and their duration of exposure (see Section 5.1.4)
  - The total number of unique patients exposed to this drug is below ICH guidelines
  - On the other hand the number of unique patients exposed to GHB for 6 month and 1 year periods is sufficient to meet these guidelines
- A separate review of the efficacy of Xyrem® indicates that the effective dose may range from 4.5 to 9 g/day, with the most conclusive evidence for efficacy at 9 g/day. The number of unique narcoleptic patients exposed to that dose range, and the duration for which they were exposed to that dose, is difficult to determine from the submission especially since a number of patients participated in more than one study grouping (e.g., Integrated Clinical Trials and Scharf study) and were exposed to several different doses
- The extent of human experience with this drug would not be considered adequate under ordinary circumstances, as per the ICH guidelines. However given that Xyrem® has been designated as an orphan drug, and that the narcoleptic population in this country is relatively small, a smaller safety database may be acceptable.

5.7 Data Quality and Completeness

The quality of the data available in this submission appears to be quite variable. The extent to which monitoring and data collection were systematic and accurate in the Secondary Data Source (see Section 5.4) studies is unclear.

6. Human Pharmacokinetics

The following pharmacokinetic summary is based on a summary supplied by the sponsor in this submission.

Orally administered GHB is rapidly absorbed with a t_{max} of 30 - 75 minutes and to a similar degree in narcoleptic and other patient populations; absorption characteristics are similar in males and females and are not altered by chronic dosing; t_{max} is delayed, at higher doses (suggesting a limited absorption capacity) and by the administration of food. C_{max} and AUC_{α} are reduced by the administration of the drug with food. The absolute bioavailability of the drug is < 30%.

The apparent volume of distribution divided by absolute bioavailability (V_2/F) ranges between 190 and 384 mL/kg. Inter-subject variability in the volume of distribution is high as indicated by the coefficient of variation which ranges between 16% and 84%. The drug readily crosses the placental and blood-brain barriers. Protein binding has been estimated at about 1%.

Less than 5% of an oral dose of GHB is excreted unchanged in the urine. Based on a review of the scientific literature the sponsor states that the end-product of metabolism, regardless of biotransformation pathway, is carbon dioxide. 2 main biotransformation pathways have been identified:

- A β-oxidation pathway

- A pathway involving the entry of succinic acid into the tricarboxylic acid cycle, through the initial formation of succinic semialdehyde

First-pass metabolism occurs with orally administered GHB, probably through the β-oxidation pathway, resulting in an oral bioavailability of < 30%. Intermediate compounds in the metabolic pathways for GHB do not appear to be pharmacologically active

The pharmacokinetics of GHB are non-linear. Plasma clearance is dose-dependent across the therapeutic range: following a total dose of 9 g (2 doses of 4.5 g each administered 4 hours apart) the apparent elimination half-life of GHB was 0.83 hours, which was approximately 40% longer than the mean elimination half-life following a total dose of 4.5 g (2 doses of 2.25 g each administered 4 hours apart). Chronic dosing with GHB did not alter its pharmacokinetics in a clinically significant manner: treatment with this drug for 8 weeks resulted in 13% and 16% increases in $AUC_{infinity}$ and C_{max}, respectively; these increases were not considered clinically significant.

There are no significant gender differences in the pharmacokinetics of GHB. Neither are there significant differences in pharmacokinetics between healthy subjects and narcoleptic patients, and between healthy patients and those who are alcohol-dependent. Oral clearance of GHB is altered in the presence of cirrhosis with or without ascites. Renal disease is not expected to alter the pharmacokinetics of GHB; studies in that setting have therefore not been carried out.

Formal studies indicated that GHB had no interactions with protryptiline, zolpidem and modafinil. In-vitro pooled human liver microsomal studies showed that GHB did not significantly inhibit or enhance the activities of human CYP450 isoenzymes.

7. Tabular Summary Of Key Efficacy Studies

4 studies have been used in this submission to support the efficacy of Xyrem® in the treatment of narcolepsy. These are summarized in tabular form below. For full details please refer to the NDA Efficacy Review

7.1 Study OMC-GHB-2

Study #	OMC-GHB-02 Orphan Medical			
Design	Randomized, double-blind, placebo-controlled, parallel-arm			
Duration	4 weeks			
Dosage	9 g	6 g	3 g	Placebo
Number randomized	35	33	34	34
Number completed	28	29	30	33
Main inclusion criteria	Narcolepsy for at least 6 months with both excessive daytime sleepiness and cataplexy			
Primary outcome measures	Total number of cataplexy attacks			
Main efficacy analysis (statistically significant results)	9 g dose superior to placebo, based on ANCOVA (p = 0.0008)			

7.2 Scrima Study

Study #	Scrima	
Design	Randomized, double-blind, placebo-controlled, cross-over	
Duration	4 weeks	
Dosage	50 mg/kg/day	Placebo
Number randomized	20	20
Number completed		
Main inclusion criteria	Excessive daytime sleepiness, a history of cataplexy with ≥ 10 cataplexy attacks over the 2 week baseline period and ≥ 2 REM onsets and a sleepiness index of ≥ 75 on the a multiple sleep latency test	
Primary outcome measures	Total number of cataplexy attacks per day	
Main efficacy analysis (statistically significant results)	GHB superior to placebo (p = 0.013)	

7.3 Lammers Study

Study #	N -1 (R 55 667 082) Lammers et al	
Design	Randomized, double-blind, placebo-controlled, cross-over	
Duration	4 weeks	
Dosage	4.75 g *	Placebo
Number randomized	25	25
Number completed	25 **	25 **
Main inclusion criteria	Excessive daytime sleepiness and at least one of the following: cataplexy, hypnagogic hallucinations, and sleep paralysis	
Primary outcome measures	Total number of cataplexy attacks Global therapeutic impression (patient) Global clinical impression (clinician)	
Main efficacy analysis (statistically significant results)	GHB superior to placebo on first two of above measures, numbered as above p = 0.002 (ANCOVA)*** p = 0.001 (McNemar's test) Not measured	

*This dose is the mean of the protocol-specified dose of 60 mg/kg/day (range 3.78 to 5.52 g/day)
** The number included in the efficacy analysis was 24 for reasons which are described below in a more detailed review of the study
***This was not the protocol specified analysis. The ANCOVA was performed by the current sponsor several years after the study blind was broken and after the initial report of this study was published. The protocol-specified analysis (which was cited in the publication) was the Wilcoxon Signed Rank Test which yielded a p-value of 0.42, but which may have been an inappropriate analysis.

7.4 Study OMC-SXB-21

Study #	OMC-SXB-21 Orphan Medical	
Design	Randomized, double-blind, placebo-controlled, parallel-arm, RANDOMIZED WITHDRAWAL study after long-term open label treatment	
Duration	2 weeks (withdrawal phase)	
Study Arms	GHB	Placebo
Number receiving study drug	26	29
Number completed	26	29
Main inclusion criteria	Continuous treatment with GHB for narcolepsy for 6 months to 3.5 years	
Primary outcome measures	Total number of cataplexy attacks	
Main efficacy analysis (statistically significant results)	GHB superior to placebo, based on ANCOVA ($p < 0.001$)	

8. Integrated Review of Safety

8.1 Background and Methodology

The 15 clinical trials included in the Integrated Summary of Safety consist of the following groupings which I have already tabulated in greater detail in Section 5.1.1, but which are also listed in the table below

Study Grouping	Number of Patients/Subjects
Integrated Clinical Trials	402
Lammers Trial	25
Scharf Trial	143
Integrated Pharmacokinetic Trials	144

The patients/subjects participating in these trials comprised

- 504 unique patients with narcolepsy
- 125 unique healthy subjects

2 separate integrated analyses were performed: one for the Integrated Clinical Trials and the second for the Integrated Pharmacokinetic Trials.

Additional analyses were performed separately on the Lammers and Scharf trials for the following reasons, as stated by the sponsor

- The Scharf study was not included on account of its design and history
- The Lammers study had a "simplified method of data collection"

8.2 Deaths

8.2.1 Tabular Summary Of Deaths

11 deaths occurred, all in the Scharf study. These are tabulated below: the table was provided by the sponsor.

Pt #	Age	Sex	Cause of Death	Prior History	Time on Drug (yrs)	Last Dose of Test Drug	Date of Death
001	51	M	Colon Carcinoma	None	5.7	7/31/89	9/89
009	68	M	Cardiovascular disease and diabetes	Cardiovascular disease and diabetes	10.0	11/30/94	1/2/95
014*	49	M	Cardiac arrhythmia	Coronary atherosclerosis	8.6	10/31/95	11/26/95
017*	68	M	Cardiopulmonary arrest	Atherosclerotic heart disease	6.1	2/28/95	3/6/95
032*	74	F	Lung cancer	Persistent cold symptoms	10.2	10/19/94	10/26/94
053	57	M	Heart attack	Hypertension, left ventricular hypertrophy	10.4	7/31/94	10/10/94
200*	71	M	Metastatic carcinoma	Lung cancer	5.4	9/30/90	1990
202	56	M	Boating accident	None	1.2	3/8/86	7/10/86
232*	69	M	Bladder carcinoma	Bladder carcinoma (1981)	4.8	3/13/92	3/14/92
241	59	M	Lung cancer (small cell)	None	3.9	1/31/89	5/26/89
243	63	M	Heart Attack	Left branch block, left ventricular dysfunction	4.7	3/1/89	7/89

*Death occurred within 30 days of last dose of study drug

As the table above indicates only 5/11 deaths are listed by the sponsor as having occurred within 30 days of the last dose of study drug. In the case of one death (patient # 200) the exact date of death is not stated in the Case Report Form and presumably other source documents were used to document that the patient's death occurred within 30 days of the last dose of study drug

8.2.2 Conclusions Regarding Deaths

The listed cause of death (and a detailed review by me of patient narratives, and of Case Report Forms when needed), for all 11 patients do not suggest that their deaths could be causally related to use of GHB. Intercurrent unrelated illnesses and, in one instance, an accident appear to have been responsible

8.3 Serious Adverse Events

A total of 72 patients experienced serious adverse events. Their distribution by study grouping is as follows.

Study Grouping	Total number of patients/subjects in grouping	Number (%) of patients/subjects with serious adverse events
Integrated Clinical Trials	402	18 (4.5%)
Scharf Study	143	54 (37.8%)
Lammers Study	25	0
Integrated Pharmacokinetic Trials	144	0

These serious adverse events are further discussed under the 2 study groupings in which they occurred

8.3.1 Serious Adverse Events In Integrated Clinical Trials

As noted above 18 patients had serious adverse events in the Integrated Clinical Trials. These are tabulated below using investigator terms.

Patient ID Initials Study #	Gender Age (years)	GHB Dose At Onset Of Adverse Event (g/day)	Study Day When Adverse Event Began	Study Day When Adverse Event Ended	Adverse Event	Action Taken	Outcome Of Serious Adverse Event
0123 (b) OMC-GHB-2	F 22.1	3.0	30	31	Removal of left ovarian cyst and ovary	Study drug temporarily stopped	Resolved
0181 (b) OMC-GHB-2	F 60.1	0	-30	-29	Somniloquy	None	Resolved
O207 (b) OMC-GHB-2	F 53.2	6.0	7	9	Acute confusional state	Study drug permanently discontinued	Resolved
0214 (b) OMC-SXB-7	M 42.9	9.0	877	None	Abnormal liver function tests	Study drug permanently discontinued	Unresolved
0231 (b) OMC-SXB-6	M 67.9	9.0	119	119	Dizziness, confusion, nausea, vomiting, vertigo, weakness	Study drug permanently discontinued	Resolved
0238 (b) OMC-SXB-6	M 64.3	4.5	170	171	Altered mental status, unresponsive, respiratory failure	Study drug permanently discontinued	Resolved
0801 (b) (6)----GHB-3	M 40.6	9.0 Carry-forward dose	181	186	Myocardial infarction	None	Resolved
0814 (b) (6)------HB-3	M 55.7	4.5	172	255	Breast carcinoma	None	Resolved
0932 (b) (6)----SXB-6	F 24.4	6.0	84	99	Auditory hallucinations	None	Resolved
0936 (b) (6)----SXB-6	F 50.9	6.0	79	83	Kidney stone	None	Resolved
1030 (b) OMC-SXB-6	F 34.8	6.0	32	None	Arthralgia	Study drug temporarily stopped	Unresolved
1032 (b) OMC-SXB-6	F 41.7	None	-7	-6	Injury to toe	No change	Resolved
1305 (b) OMC-GHB-3	F 73.6	9.0 Carry-forward dose	670	679	Agitation	Study drug temporarily stopped	Resolved
1433 (b) OMC-SXB-6	F 57.0	6.0	18	18	Body aches after automobile accident	Study drug temporarily stopped	Resolved
1509 (b) (6)----SXB-7	M 70.6	6.0	748	749	Gastroenteritis	Study drug temporarily stopped	Resolved
1630 (b) OMC-SXB-6	M 59.7	6.0	54	57	Lower back pain	Study drug temporarily stopped	Resolved
1735 (b)	F 26.8	6.0	108	108	Miscarriage	Study drug permanently	Resolved

Patient ID Initials Study #	Gender Age (years)	GHB Dose At Onset Of Adverse Event (g/day)	Study Day When Adverse Event Began	Study Day When Adverse Event Ended	Adverse Event	Action Taken	Outcome Of Serious Adverse Event
OMC-SXB-6						discontinued 6 weeks prior to adverse event	
(b)(6)---OMC-SXB-6	F 65.3	6.0	160	163	Pancreatitis Cholelithiasis	Study drug permanently discontinued	Resolved

In regard to the above list the sponsor has drawn attention to the following:

- 2 patients (#s 0181 and 1032) had serious adverse events prior to beginning GHB
- In 2 patients (#s 0181 and 0123) their "serious adverse events" were subsequently considered not to have been serious

Note that no serious adverse events occurred in placebo-treated patients in this grouping.

I have read the narratives, and where necessary the Case Report Forms, for the above patients. A further description is warranted in the following patients

8.3.1.1 Patient 0238 (Initials(b)(6

This 65 year old man, participating in OMC-SXB-6, had been taking Xyrem® 4.5 g daily for 5 months. He had a background history of hypertension.

Immediately after his wife heard a loud noise, he was found comatose, flaccid, incontinent, bradycardic and hypoventilating. No convulsive movements had been witnessed. He required intubation and artificial ventilation. However the same day he awoke, was extubated and returned home. An EEG was normal; an echocardiogram showed ventricular hypertrophy with posterolateral wall hypokinesia, but with a satisfactory ejection fraction. A "cardiac event" was proposed as a cause for his symptoms by the hospital staff caring for him. However the Principal Investigator, after reviewing his hospital records considered the possibility that an inadvertent overdose with GHB was responsible for the episode was responsible for the episode. Study medication was permanently discontinued. Further information is not available.

8.3.1.2 Patient 0207 (Initials(b)(6

This 53 year old woman participating in OMC-GHB-2 received Xyrem® 6 g daily. On Day 4 of treatment she developed nausea. Beginning Day 5 she became very talkative with pressured speech, and the next day was noted to be disoriented, agitated and to sleep poorly. Xyrem® was discontinued, the patient was treated with haloperidol and by the next day her confusion had resolved. An EEG was normal and a CT scan of the head showed minor temporal lobe asymmetry. The study drug was permanently discontinued.

8.3.1.3 Patient 0932 (Initials(b)(6

This 24 year old woman who participated in OMC-SXB-6 had a history of depression dating back to 1994. Her dose of Xyrem® was increased from 4.5 g daily to 6 g daily. On Day 84 she experienced auditory hallucinations for which she was hospitalized and treated with olanzapine. Her dose of Xyrem® was then reduced to 4.5 g daily. Her hallucinations resolved and she was discharged after 14 days continuing with GHB for

the remainder of the trial. Hospital discharge records indicated to her investigator that for the previous 5 years she had experienced repeated auditory hallucinations and had 2 psychiatric hospitalizations

8.3.1.4 Patient 1030 (Initials(b)(6

This 34 year old woman participating in OMC-SXB-6 had a preceding history of lower back and knee pain for which she received acetaminophen. Her back pain was believed to be related to herniated intervertebral discs; further descriptions of her back and knee pain are unavailable. She was begun on Xyrem® in a dose of 4.5 g/day. On Day 4 of the study she complained of knee pain and on Day 31 reported generalized joint pain. At that point Xyrem® was stopped temporarily (it is uncertain for how long) but was then resumed in a dose of 6 g/day. On Day 68 on account of continued generalized joint pain, she was referred to a rheumatologist (details of this consultation are unavailable); treatment with diclofenac 100 mg/day was begun. On Day 131 the patient was stated to have patello-femoral syndrome (presumably she had knee pain at that point). Study medication was then stopped for 3 days, resumed and continued until Day 185. Her generalized arthralgia and knee pain were apparently continuing at her last visit.

8.3.1.5 Patient 1735 (Initials(b)(6

This 26 year old woman participating in OMC-SXB-6 initially took Xyrem® 4.5 g/day for 13 days, followed by 6 g/day for 52 days. On Day 66 she was discontinued from the study on account of her becoming pregnant, a protocol violation. She had a miscarriage on Day 108.

8.3.1.6 Patient 0214 (Initials (b)(

This 42 year old man participating in OMC-SXB-7, was noted to have abnormal liver function tests at the Month 6 (Day 196) visit; he was taking 9 g/day of Xyrem® at that time. At that time he had a tremor and diaphoresis. His concomitant medications at that time included ascorbic acid, multivitamins, methylphenidate, acetaminophen and pseudoephedrine; earlier he had also taken a butalbital-aspirin combination, zolpidem, tramadol, alprazolam, fluoxetine and paroxetine for unknown periods of time, and modafinil for about 5 months. At that time (Day 196) his liver function studies were as follows: total protein 7.3 g/dl; albumin 4.2 g/dl; total bilirubin 0.6 mg/dl; alkaline phosphatase 135 U/L AST 189 IU/L; ALT 362 IU/L. A further 9 days later (Day 205) his liver functions were: total protein 7.0 g/dl; albumin 4.1 g/dl; total bilirubin 0.4 mg/dl; alkaline phosphatase 112 U/L; AST 141 IU/L; ALT 271 IU/L.

His past medical history was remarkable for migraine, hay fever, a right nephrectomy and known hepatitis C infection.

At the time of his entry into the OMC-SXB-7 study his serum liver function tests were as follows: total protein 7.2 g/dl; albumin 4.2 g/dl; total bilirubin 0.4 mg/dl; alkaline phosphatase 63 U/L AST 27 IU/L; ALT 41 IU/L (all well within normal limits)

On Study Day 205 Xyrem® was permanently discontinued. Results of follow-up liver functions, if any, are not available. It is unclear based on the Case Report Form, if his abnormal liver functions were associated with any symptoms.

8.3.1.7 Patient 0231 (Initials (b)(

This 67 year old man participating in Study OMC-SXB-6 took Xyrem® in a dose of 4.5 g/day for 12 days and 9 g/day for 106 days. He was reported to experience nausea,

vomiting, dizziness, confusion and generalized weakness. His past medical history was remarkable for a stomach ulcer, gastroesophageal reflux disease, and a cholecystectomy. Concomitant medications included clomipramine, methylphenidate, paroxetine, imipramine and modafinil.

Xyrem® was permanently discontinued. Within 24 hours the adverse event had resolved.

8.3.1.8 Patient 1305 (Initials (b))

This 73 year old woman participating in Study OMC-GHB-3 became agitated, frightened and restless after taking GHB for 670 days. Her dose of Xyrem® at that time was not recorded; her last recorded dose was 9 g/day and this dose was carried forward. Xyrem® was temporarily stopped, and she was treated at an emergency room with diphenhydramine and lorazepam injections. She was discharged home having apparently recovered, and was able to complete the study (study medication was resumed but it is unclear for how long and in what dose it was administered).

8.3.2 Serious Adverse Events In Scharf Study

54 patients had serious adverse events in the Scharf study. 51 of these patients had serious adverse events that occurred after they started to receive study drug: these adverse events are tabulated below.

	Number Of Patients	Percentage of Patients Participating In Study
Total Number With Serious Adverse Events	51	35.7
Asthenia	5	3.5
Cellulitis	3	2.1
Fever	1	0.7
Headache	1	0.7
Infection	2	1.4
Accidental injury	7	4.9
Neoplasm	1	0.7
Overdose	2	1.4
Pain	6	4.2
Abdominal pain	7	4.9
Back pain	3	2.1
Chest pain	10	7.0
Substernal chest pain	1	0.7
Unevaluated reaction	11	7.7
Angina pectoris	1	0.7
Vascular anomaly	2	1.4
Arrhythmia	1	0.7
Cerebrovascular accident	1	0.7
Coronary artery disease	1	0.7
Right-sided heart failure	1	0.7
Hypertension	1	0.7
Hypotension	1	0.7
Myocardial infarction	3	2.1
Ventricular tachycardia	1	0.7
Anorexia	1	0.7
Gastrointestinal carcinoma	1	0.7
Cholecystitis	3	2.1
Cholelithiasis	2	1.4
Diarrhea	2	1.4
Gastroenteritis	1	0.7
Gastrointestinal hemorrhage	1	0.7
Rectal hemorrhage	1	0.7
Melena	1	0.7
Nausea	2	1.4
Rectal disorder	1	0.7
Duodenal ulcer	1	0.7

Vomiting	3	2.1
Diabetes mellitus	2	1.4
Anemia	1	0.7
Leukocytosis	1	0.7
Rheumatoid arthritis	1	0.7
Anxiety	1	0.7
Coma	1	0.7
Confusion	1	0.7
Convulsion	1	0.7
Depression	1	0.7
Dizziness	2	1.4
Hypesthesia	1	0.7
Stupor	2	1.4
Apnea	3	2.1
Asthma	1	0.7
Lung carcinoma	2	1.4
Dyspnea	9	6.3
Pulmonary embolism	1	0.7
Hemoptysis	1	0.7
Hypoventilation	1	0.7
Lung disease	2	1.4
Pharyngitis	3	2.1
Pneumonia	2	1.4
Respiratory diseases	2	1.4
Skin carcinoma	4	2.8
Melanoma of skin	1	0.7
Skin disease	1	0.7
Skin disorder	3	2.1
Sweating	3	2.1
Bladder calculus	1	0.7
Carcinoma bladder	1	0.7
Carcinoma breast	1	0.7
Urinary incontinence	2	1.4
Unintended pregnancy	1	0.7
Prostate disorder	1	0.7
Urinary frequency	1	0.7
Enlarged uterine fibroid	1	0.7

I have read through the narratives, and Case Report Forms where needed, for the above patients. Serious adverse events that warrant further description are listed below.

8.3.2.1 Patient 012 (Initials (b)(

This man was 74 years old at the time of study entry. He had a past history of cardiomyopathy, left bundle branch block and sleep apnea. About 2 years after beginning GHB and while taking a dose of 7.5 g daily he had an episode of disorientation, stupor and weakness that necessitated hospitalization and a reduction in dose of GHB to 6 g daily for one day. The episode resolved and did not recur despite the patient continuing to take 7.5 g daily.

8.3.2.2 Patient 017 (Initials (b)

This 63 year old man had a history of narcolepsy and sleep apnea. as well as hypertension. Initial physical examination is reported to have shown a “mild-to-moderate degree of oropharyngeal compromise.”

He began taking GHB in a dose of 4.5 g daily. About 11 months after enrolling in an incident attributed to possible sleepwalking he ingested an additional estimated 9 g of GHB in addition to his first nightly 3 g dose of the drug. He drove himself to an emergency room, where he was administered ipecac and slept for 2 hours

Approximately 1 ½ years after enrolling in the study he was hospitalized after an overdose of GHB 18 g, again attributed to sleepwalking. At the time of hospitalization he was comatose and unresponsive. He needed intubation and artificial ventilation, and awoke 6 hours later. He continued in the study.

Other significant items of information regarding this patient are as follows

- He had many episodes of sleep walking and multiple episodes of urinary incontinence.
- In 2 instances episodes of sleep walking and urinary incontinence are listed in the Case Report Form as occurring on the same day although there is no evidence presented that they occurred at the same time.
- On the days when both incontinence and sleep walking are listed as having occurred, the patient's prescribed dose was 7.5 g/day
- As noted above this had multiple episodes of sleep walking that did not occur on the same days as his episodes of incontinence.
- He also reported muscle jerks over the front of his trunk over a period of several years while taking GHB. These were stated to be most prominent when lying in bed in the morning as the last dose of GHB was wearing off; they could be controlled voluntarily and would disappear with ambulation, returning when at rest.
- He developed congestive heart failure during the study and died about 5 years after study entry. While participating in the study he underwent a thoracotomy for a right lung nodule that was confirmed to be a squamous cell carcinoma.

8.3.2.3 Patient 019 (Initials (b)(

This 41 year old man with a past history of depression and suicidal ideation was begun on treatment with GHB in a dose of 5.3 g/day. 6 months later he was hospitalized for treatment of depression at a time when he was taking GHB in a dose of 6 g/day; that medication was interrupted for a day and then resumed at 9 g/day. About 2 years after first beginning the drug he was hospitalized after a suicide attempt that consisted of taking an overdose of GHB. At that time he was dropped from the study

8.3.2.4 Patient 257 (Initials (b)(

This 32 year old man with a past history of a whiplash injury with numbness and paresthesia in his hands was begun on treatment with GHB 4.5 g daily while concomitantly taking protryptiline. About 3 months later he was seen at a hospital emergency room on account of complaints of chills, sweating, blurred vision, memory loss, and shaking as well as vibrating sensations. A further 6 months later shaking and vibrating sensations occurred again at which time he was also recorded as having attacks of cataplexy at least one of which resulted in a fall. 2 further years later he was hospitalized overnight after an unspecified adverse reaction that was attributed to ingesting too much GHB.

After an additional 2 years on GHB the patient fell on a long butcher knife, and perforated his colon. During the peri-operative period GHB was stopped for 10 days. About 2 months after surgery he was hospitalized on account of hypoxemia and required intubation and mechanical ventilation. Further details are unavailable. GHB was apparently not stopped at the time.

8.4 Dropouts and "Other Significant Adverse Events"

A total of 63 GHB-treated patients permanently discontinued treatment on account of adverse events. Their distribution by study grouping, according to the sponsor, is as follows.

Study Grouping	Total number of patients/subjects in grouping	Number (%) of patients/subjects with adverse events leading to discontinuation
Integrated Clinical Trials	402	44 (10.9%)
Scharf Study	143	19 (13.3%)*
Lammers Study	25	0
Integrated Pharmacokinetic Trials	144	2 (1.4%)

*Note that the sponsor has counted 7 deaths as discontinuations due to adverse events. The actual adverse event discontinuation rate is 12/143 or 8.4%.

A single placebo-treated patient (# 0818; initials(b)(6 participating in OMC-GHB-2 discontinued treatment 1 month after study entry on account of insomnia (see Section 8.4.1)

These adverse event discontinuations are further discussed under the 3 study groupings in which they occurred.

8.4.1 Adverse Event Discontinuations In Integrated Clinical Trials

44 patients discontinued treatment on account of adverse events in this grouping

Of the 44 patients who discontinued treatment in the Integrated Clinical Trials Grouping, 10 discontinued treatment in the 3 controlled clinical trials; all 10 participated in OMC-GHB-2. The adverse events that led to treatment discontinuation in OMC-GHB-2 (n = 136) were as follows

Nausea 2.9%
Somnolence 2.2%
Confusion 1.5%
Amnesia, asthenia, chest pain, dizziness, dyspnea, hyperkinesia, fecal incontinence, insomnia, paranoid reaction, thinking abnormal, vertigo, and vomiting each 0.7%.

A listing of patients who discontinued treatment in OMC-GHB-2 is as follows; as the table indicates these adverse events were dose-related. Also note, however, that individual doses were not titrated in this study.

Patient Number	Preferred term [investigator term]
Placebo	
818	Insomnia [insomnia]
3g GHB	
901	Nausea [nausea], somnolence [lethargy], pain chest [chest pressure]
6g GHB	
207	Confusion [acute confusional state]
509	Hyperkinesia [restless leg increased], headache [headache]
9g GHB	
221	Somnolence [increased sleepiness], dizziness [dizzy], nausea [nauseated], and asthenia [weakness (had difficulty standing)]
605	Somnolence [daytime sedation feeling; "drugged feeling"], thinking abnormal [poor concentration]
702	Confusion [confusion], hallucinations [hallucinations], amnesia [forgetfulness], nausea [nausea], paranoid reaction [paranoia]
824	Dyspnea [difficulty breathing]
1201	Incontinence fecal [patient lost bowel control while asleep]
1504	Nausea [nausea], vertigo [vertigo], vomit [vomiting]

The following table, supplied by the sponsor, provides a summary for 38 out of 44 patients who discontinued treatment on account of an adverse event in the entire Integrated Clinical Trials grouping. In these 38 patients discontinuation was considered to be treatment-related by the investigator.

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day*		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0204	OMC-GHB-3	6.0	33	51	Insomnia	Insomnia	No	Moderate
0207	OMC-GHB-2	6.0	7	9	Acute confusional state	Confusion	Yes	Severe
0213	OMC-GHB-3	9.0	98	105	Depressed mood	Depression	No	Moderate
		9.0	96	105	Excessive tiredness	Asthenia	No	Moderate
0221	OMC-GHB-2	9.0	13	15	Dizzy	Dizziness	No	Moderate
		9.0	13	15	Increased sleepiness	Somnolence	No	Moderate
		9.0	13	15	Nauseated	Nausea	No	Moderate
		9.0	13	15	Weakness (had trouble standing)	Asthenia	No	Moderate
	OMC-GHB-3	7.0	36	106	Lethargic all day	Somnolence	No	Mild
0231	OMC-SXB-6	9.0	118	119	Dizziness	Dizziness	Yes	Severe
		9.0	119	119	Confusion	Confusion	Yes	Severe
		9.0	118	119	Nausea	Nausea	Yes	Severe
		9.0	119	119	Vomiting	Vomiting	Yes	Severe
		9.0	119	119	Vertigo	Vertigo	Yes	Severe
		9.0	116	119	Weakness	Asthenia	Yes	Severe
0238	OMC-SXB-6	4.5	170	170	Respiratory failure	Apnea	Yes	Severe
		4.5	170	170	Non-responsive	Coma	Yes	Severe
0239	OMC-GHB-3	9.0	61		Weight loss	Weight loss	No	Mild
0509	OMC-GHB-2	6.0	1	2	Restless leg syndrome increased	Hyperkinesia	No	Severe
0511	OMC-SXB-6	4.5	10		Swelling in legs	Peripheral edema	No	Severe
0605*	OMC-GHB-2	9.0	9	10	Daytime sedation feeling; "drugged feeling"	Somnolence	No	Mild
		9.0	9	12	Poor concentration	Thinking abnormal	No	Mild
0617	OMC-SXB-6	7.5	83*		Restless legs	Hyperkinesia	No	Moderate
		7.5	85*		Anxiety	Anxiety	No	Moderate

(continued)

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day*		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0701	OMC-GHB-3	6.0*	33		Decreased sexual libido	Libido decreased	No	Moderate
		6.0*	32		Decreased initiative to start any activity by gradual progression	Apathy	No	Mild
0702	OMC-GHB-2	9.0	29	28	Confusion	Confusion	No	Moderate
		9.0	30	25	Forgetfulness	Amnesia	No	Moderate
		9.0	30	33	Hallucinations	Hallucinations	No	Moderate
		9.0	21	21	Nausea	Nausea	No	Mild
		9.0	22	24	Paranoia	Paranoid reaction	No	Mild
0801	OMC-GHB-3	9.0	147	178	Chest pain, patient on drug, no hospitalization, no concomitant medication	Chest pain	No	Moderate
0802	OMC-GHB-3	9.0	49	55	Nervousness	Nervousness	No	Moderate
		9.0	49	51	Metallic taste	Taste perversion	No	Mild
		9.0	49	51	Upset stomach	Dyspepsia	No	Moderate
0809	OMC-GHB-2	3.0	332	333	Inability to control body 3 h after taking medicine	Incoordination	No	Mild
0810	OMC-GHB-2	Placebo	35		Insomnia	Insomnia	No	Moderate
0821	OMC-GHB-3	6.0	39	55	Headaches	Headache	No	Moderate
		6.0	40	52	Irritable	Nervousness	No	Moderate
0822	OMC-GHB-2	9.0*	5	5	Difficulty breathing	Dyspnea	No	Severe
	OMC-GHB-3	3.0	25	29	Difficulty breathing	Dyspnea	No	Moderate
0836*	OMC-SXB-6	4.5	1		Headache	Headache	No	Moderate
0843	OMC-SXB-6	6.0	1	42	Nausea	Nausea	No	Moderate
		6.0	1	42	Vomiting	Vomiting	No	Moderate
		6.0	1	42	Headaches	Headache	No	Severe

(continued)

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
0601	GHB-SXB-3	3.0	2	16	Lethargy	Somnolence	No	Mild
		3.0	2	18	Nausea	Nausea	No	Moderate
		3.0	2	18	Chest pressure	Chest pain	No	Mild
1101[b]	GHB-SXB-3	3.0	156		Acute psychosis[c]	Psychosis	No	Moderate
1114	GHB-SXB-6	3.0	3		Urinary incontinence	Urinary incontinence	No	Moderate
1142	GHB-SXB-6	7.5	31	38	Left eye exposure keratitis	Keratitis	No	Mild
1201	GHB-SHB-2	9.0	5	5	Patient lost bowel control while asleep	Incontinence, fecal	No	Moderate
1504	GHB-SXB-2	9.0	2	2	Nausea	Nausea	No	Severe
		9.0	2	2	Vertigo	Vertigo	No	Severe
		9.0	2	2	Vomiting	Vomiting	No	Severe
1631	GHB-SXB-6	6.0	23	58	Sleepwalking	Sleep disorder	No	Moderate
		4.5	44	50	Fragmented sleep	Sleep disorder	No	Severe
		4.5	44	50	Involuntary limb movements in sleep	Sleep disorder	No	Moderate
1715[d]	GHB-SXB-6	6.0	108[e]	108[e]	Miscarriage	Abortion	Yes	Mild
2512[f]	GHB-SXB-6	3.0	16	63	Sleepwalking	Sleep disorder	No	Mild
		4.5	16	43	Dizziness	Dizziness	No	Mild
		4.5	39	43	Arms and legs numb	Paresthesia	No	Mild
2533[f]	GHB-SXB-6	4.5	25	81	Nausea	Nausea	No	Moderate
		6.0	78	81	Morning grogginess	Somnolence	No	Moderate
2537[f]	GHB-SXB-6	4.5	12		Increased headaches	Headache	No	Moderate
2633	GHB-SXB-6	4.5	2	4	Increased awakenings	Sleep disorder	No	Mild
		4.5	2	4	Tongue paresthesia	Paresthesia	No	Mild
2933	GHB-SXB-6	4.5	29		"Phlegm/knot" in throat	Pharyngitis	No	Moderate
3231	GHB-SXB-6	6.0	58		Exacerbation of colitis (Crohn's disease)	Colitis	No	Moderate

(continued)

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[a]		Investigator Term	COSTART Preferred Term	Serious	Severity
			Start	Stop				
3835	GHB-SXB-6	7.5	52	52	Nausea	Nausea	No	Moderate
		7.5	56	56	Vomiting	Vomiting	No	Moderate
3931	GHB-SXB-6	3.0	12	24	Itching and swelling of extremities	Pruritus	No	Moderate
		3.0	12	24	Itching and swelling of extremities	Edema	No	Moderate
3935	GHB-SXB-6	6.0	2	3	Sleep paralysis	Sleep disorder	No	Moderate

[a] Day relative to start of treatment.
[b] Patient 0638 was not listed as discontinued on the end-of-trial page of the case report form, but had an AE action of "permanently discontinued" on the AE page.
[c] Whole or partial data imputed from start of trial medication.
[d] Dosage carried forward.
[e] Patients 0836, 2512, 2533, and 2537 were listed as discontinuing due to a lack of efficacy on the end-of-trial page of the case report form, but had an AE action of "permanently discontinued" on the AE page.
[f] After subsequent analysis by the principal investigator, the AE of psychosis for patient 1101 was determined to be not related to trial medication.
[g] Patient 1715 discontinued trial medication on Day 66, due to a presumed protocol violation (pregnancy).

Of the patients listed in the table above, short narratives have already been provided under the discussion of Serious Adverse Events above for the following: #s 0207, 0231, 0238 and 1735. Brief narratives are provided for the following additional patients. Narratives for more patients do not appear to be needed based on a review of the data provided by the sponsor.

8.4.1.1 Patient 0221 (Initials (b)(

This 57 year old woman was enrolled in the OMC-GHB-2 trial and was begun on GHB in a dose of 9 g/day. 12 days later she complained of increased sleepiness along with dizziness, nausea and weakness (with difficulty maintaining an upright posture). GHB was discontinued and her symptoms resolved. She was next enrolled in OMC-GHB-3 during which her most common dose of GHB was 6 g/day; while taking a dose of 3 g/day, her initial dose, she reported excessive somnolence from the first day in the trial onward. After about 1.5 months of participation in OMC-GHB-3, the study drug was stopped permanently with resolution of this adverse event

8.4.1.2 Patient 3831 (Initials(b)(6

This 31 year old woman with a previous history of eczema was enrolled in OMC-SXB-6. She took Xyrem® 4.5 g/day for 10 days followed by 3 g/day for 2 days; she then experienced itching and swelling of her extremities leading to discontinuation of GHB on Day 13. By Day 24 both itching and extremity swelling had resolved.

The 6 remaining patients who discontinued study drug permanently on account of adverse events and are not listed above are summarized in the table below. In these patients the adverse events that lead to treatment discontinuation were not considered to be drug-related

Patient ID Initials Study #	Gender Age (years)	GHB Dose At Onset Of Adverse Event (g/day)	Study Day When Adverse Event Began	Study Day When Adverse Event Ended	Adverse Event	Outcome After Study Drug Discontinuation
0123 (b) (6)------HB-2	F 22.1	6.0	42	None	Unintended pregnancy	"Unresolved"
0208 (b) OMC-GHB-3	M 26.7	9.0	43	525	Twitching	Resolved
(b)(6)---- ----------HB-3	F 44.4	60	30	352	Memory loss	Resolved
0214 (b) OMC-SXB-7	M 42.9	9.0	877	None	Abnormal liver function tests	Unresolved
(b)(6)--- ---------XB-6	F 51.2	4.5	38	None	Sinusitis Generalized edema	Unresolved
(b)(6)-- ---------XB-6	M 52.6	9.0	86	None	Apnea (sleep apnea)	Unresolved

A narrative for Patient # 0214 has already been provided under the discussion of Serious Adverse Events. Narratives are provided below for 2 additional patients

8.4.1.3 Patient 0504 (Initials(b)(6

This 45 year old woman participated first in OMC-GHB-2 and then in OMC-GHB-3 for a total period in these trials of 10 months. While taking Xyrem® in a dose of 6 g/day in

OMC-GHB-3 she was reported to have lapses of memory each afternoon. Xyrem® was stopped and this adverse event resolved.

8.4.1.4 Patient 3533 (Initials(b)(6

This 52 year old man participating in OMC-SXB-6 had no significant past medical history. At entry into the study he was begun on GHB in a dose of 4.5 g/day. This dose was gradually increased in steps to 9 g/day. After 4 days on the last dose and after 86 days of treatment with GHB he was noted to have sleep apnea which was judged to be severe and lead to Xyrem® being stopped. The adverse event did not resolve after the study drug was stopped

8.4.2 Adverse Event Discontinuations In Scharf Trial

According to the sponsor, 19 patients withdrew from this study because of adverse events. They are listed in the following table which I have copied from the submission. Note that of the 19 patients listed, 7 patients were "withdrawn" because of death; ordinarily such patients would not be considered as having withdrawn due to adverse events. **An eighth patient (# 064; Initials (b)(is incorrectly listed in this table as having died**

Pt No.:	Age[1]	Sex	Duration of Exposure (yr)[1]	Reason for patient withdrawal (as provided by the site)
001[2]	51	M	5.7	Death due to metastatic colon carcinoma
005	53	F	4.7	Increased difficulty sleeping, hospital admission to assess suspected psychiatric problem
009[2]	68	M	10.0	Died (2/95) last recorded dose gamma was 11/94. Death due to arteriosclerotic cardiovascular disease
014[2]	48	M	8.6	Death due to cardiac arrhythmia
019	43	M	2.0	Patient attempted suicide (unsuccessfully)
030[2]	74	F	10.2	Death due to lung cancer
053[2]	57	M	10.4	Died 10-10-94, heart attack
064[2]	15	F	1.8	Increased seizure activity
066	50	F	6.1	Repeated high ANA tests (antinuclear antibodies)
200[2]	71	M	5.4	Patient expired from lung cancer
232[2]	69	M	4.8	Death due to bladder cancer, CAD, and cardiac arrest
238	47	M	1.9	Decrease in short term memory
243[2]	63	M	4.7	Weight loss
244	56	F	0.9	Elevated ANA, possible Lupus Syndrome
247	34	F	0.8	Seizure
254	63	F	1.2	Interstitial infiltrate possible, pulmonary toxicity
259	41	F	0.1	Complains of feeling like zombie, stiffness in legs
271	46	M	0.5	Swelling
273	60	F	0.9	Weight loss

[1]Age and duration of exposure were based on the time of the last change in the dosage of study medication.

[2] Patients (n = 8) who died after withdrawing from the study. See Table 15 – Deaths.

After reading through the sponsor-supplied narratives, and Case Report Forms (when needed) for the above patients further details are provided for the following patients. Patient # 019 has already been described in the discussion of Serious Adverse Events.

8.4.2.1 Patient 005 (Initials (b)(

This 53 year old woman was reported to have developed anger, hostility and suspiciousness, while taking dextroamphetamine and other stimulants, prior to study entry. She was begun on GHB in a dose of 5.3 g/day; concomitant medications include clomipramine as well as caffeine tablets. After taking GHB for 4.7 years that drug was discontinued when the patient had difficulty sleeping and "psychiatric problems" that were considered similar to those that occurred when she was taking stimulants. She required a psychiatric hospitalization, the outcome of which and her subsequent course are unknown.

8.4.2.2 Patient 064 (Initials (b)(

This 15 year old girl had a previous history of a left frontal lobe lesion, previous burr hole placement after a "concussion" and headaches. Concomitant medications at study entry included protriptyline and methylphenidate. She received treatment with GHB for 1.8 years at a mean dose of 6 g/day. While on treatment she was reported to have "increased seizure activity" (no details of the seizures are provided; it is not clearly stated that she had seizures prior to study entry), increased urinary frequency, headache, vomiting, dyslexia, an increased appetite and shortness of breath. The increased seizures reportedly led to hospitalization and to discontinuation from the study, although the last date of medication administration is listed as being unknown. No further details are provided.

8.4.2.3 Patient 066 (Initials(b)(6

This 50 year old woman had a past medical history of hypertension, occasional chest pain, a dry skin rash, penicillin allergy, a hysterectomy and weight gain of 45 kg over 9 years. Concomitant medications at study entry included triamterene-hydrochlorthiazide, clorazepate and methylphenidate. She took GHB for a total of about 6 years, most commonly in a dose of 7.5 g/day. After a little less than 6 years of treatment she was noted to have an anti-nuclear antibody titer of 1:640 (this test was not performed earlier in the study). Over the next 3 months successive antinuclear antibody titers were 1:1280 and >1:2560, respectively. GHB was stopped; over the next 11 months follow-up antinuclear antibody titers were always > 1:160 (in a range of 1:160 to 1:1280). A diagnosis of drug-induced lupus was apparently considered. Antihistone antibody testing was not done.

The above summary is based on information obtained from the Case Report Form and sponsor narrative. However the sponsor has also supplied the following documents

- An abstract published by Dr Scharf in 1993 indicated that the same patient (whose identity was confirmed separately by Dr Scharf) developed "clinical symptoms suggestive of arthritis" after having received GHB for 68 months
- A letter to the sponsor from Dr Scharf dated 7/24/98, had been on GHB for 72 months at which time she was diagnosed to have rheumatoid arthritis was diagnosed

This diagnosis appears to have been made a few months before her first, positive antinuclear antibody test. Further clinical details are unavailable.

Also see “Elevated Antinuclear Antibodies” in Section

8.4.2.4 Patient 238 (Initials(b)(6

About 6 months after this 47-year old man began taking GHB he was first reported to have impaired short-term memory. Over the next 1.5 years further such reports occurred leading to the dose of drug being reduced from 9 g/day, the most commonly used dose, to 3.75 g/day and to the drug’s discontinuation a short while later after a total of about 2 years of treatment. Concomitant medications included methylphenidate and methamphetamine. No information is provided about his clinical course after study drug discontinuation.

8.4.2.5 Patient 244 (Initials (b)(

This 56-year old women had taken GHB for 1 year when the drug was discontinued on account of an antinuclear antibody titer of 1:80; there is no record of a similar test having been done previously or subsequently. The test was requested on account of back and leg pain. Antihistone antibody testing was not done. Her records indicate that she had consulted an orthopedic surgeon on account of back pain even prior to beginning GHB, and was recommended a spinal fusion. Prior included protriptyline, dextroamphetamine and meclofenamate. Her course after GHB was discontinued is unclear

Also see “Elevated Antinuclear Antibodies” in Section 8.5.5.2

8.4.2.6 Patient 247 (Initials(b)(6

This 34-year old woman had taken GHB for about 9 months in a dose of 6 g/day when she had a seizure that reportedly consisted of “continuous jerking all over her body”. At that time GHB was discontinued. Her narcolepsy was diagnosed 4 years before she entered this trial. Her previous medical history was also remarkable for incontinence, obesity and an unspecified psychiatric illness. Her only concomitant medication was fluoxetine. Prior medications for narcolepsy included L-tyrosine, methylphenidate, protriptyline, dextroamphetamine, imipramine, temazepam and alprazolam. No further details are available

8.4.2.7 Patient 254 (Initials(b)(

This 61 year old woman had been diagnosed with narcolepsy at age 34. Her medical history was also remarkable for “Hashimoto goiter”, and episodes of sleep apnea. Previous medications for narcolepsy included dextroamphetamine, methylphenidate, and imipramine. Concomitant medications included natural thyroid 2 g/day and calcium supplementation. 11 months after beginning GHB in a dose of 3.8 g/day she was hospitalized with shortness of breath, fever and cyanosis. Chest x-ray revealed evidence of an interstitial pneumonia and she was treated with oxygen. GHB was discontinued at that time: her last dose was 4.5 g/day. These symptoms appear to have resolved based on a letter from the patient to the study center written 5 months after the event, but no further details are available; earlier in the study she was reported to have ankle swelling.

8.4.2.8 Patient 259 (Initials(b)(6

This 41-year old woman was diagnosed to have narcolepsy 4 years prior to study entry. Her medical history was otherwise unremarkable. Concomitant medications included methylphenidate and estrogen. GHB was begun in a dose of 5.3 g/day. 3 days later the patient reported that she felt like a zombie, and had stiffness in her legs and chest together with excessive crying. Her dose of GHB was reduced to 3 g/day that day, to 1.5 g/day the next day, was omitted once a further day later and was then resumed at 1.5

g/day. A further 8 days later the dose was reduced to 0.8 g/day. As her symptoms had not resolved a month later the drug was stopped. No additional information is available; it is unclear if her symptoms eventually resolved.

8.4.3 Adverse Event Discontinuations In Integrated Pharmacokinetic Trials

2 subjects discontinued study participation on account of adverse events. They are summarized in the table below:

Subject ID Initials Study #	Gender Age (years)	GHB Dose At Onset Of Adverse Event (g/day)	Study Day When Adverse Event Began	Study Day When Adverse Event Ended	Adverse Event	Outcome After Study Drug Discontinuation
ID # 012 (b) (6)------XB-9	F 30	4.5*	After initial dose	Unclear	Headache, nausea and diarrhea	Adverse events resolved
ID # 003 (b) OMC-SXB-11	F 39	4.5**	After initial dose	5 hours after onset	Dizziness, nausea, vomiting, apneic episodes and fecal incontinence***	Adverse events resolved

*Administered in 2 divided doses of 2.25 g each, 4 hours apart
**Administered in a single dose of 4.5 g

***2 hours after her initial and only dose of GHB this subject began experiencing dizziness, nausea and vomiting. At the same time or shortly afterward the patient also experienced a single 2-minute period of apnea, a generally depressed depth of respiration and fecal incontinence. She was treated by rolling her over on her side, and administering oxygen by mask for several minutes on 2 occasions. All adverse events resolved over a period of about 5 hours after they first began. This summary is based on a review of the sponsor-supplied narrative and Case Report Form

In a further communication dated 2/23/01 the sponsor had, at my request, submitted further information about subject # 003 (initials:(b)(6)-participating in Study # OMC-SXB-11. The information is as follows:

- This p----------eighed 137 lbs (62.3 kg) and was 63 inches in height
- She received a single 4.5 g dose of GHB after a 10 hour fast
- 30 minutes after dosing she reported dizziness
- One hour after dosing and while asleep in the supine position she had labored, “decreased” respiration with inspiratory stridor. She did not improve with repositioning and was then apneic briefly before the episode resolved on stimulation and application of an oxygen mask
- After stimulation she awoke and vomited once.
- She then fell asleep again. 1 further hour later, and 2 hours after dosing her she vomited twice and then had a further episode of stridor (when lying on her side) and a brief pause in spontaneous respiration that again responded to stimulation and the use of an oxygen mask. At the same time she was fecally incontinent, but had her eyes open, could respond to verbal commands and was not observed to have any “seizure-like movements”
- 2 further hours later she was able to consume most of the offered lunch.
- Pulse and blood pressure remained normal throughout

The sponsor further stated that this food-effect pharmacokinetic study confirmed that exposure (based on C_{max} and AUC) was significantly increased, and t_{max} delayed, in the fasted state

8.5 Adverse Events Incidence Tables

8.5.1 Approach to Eliciting Adverse Events

Approaches used differed based on the clinical trial grouping, as discussed below.

8.5.1.1 Integrated Clinical Trials

In this clinical study grouping the following approach was used.

- Adverse events that occurred during the trial and up to 10 days after the last dose of study medication were recorded in detail on the appropriate page of the Case Report Form
- The frequency, severity, seriousness and relationship to study medication was recorded. A serious adverse event was defined using standard criteria. Serious adverse events were not recorded in the Scrima trial

- Medication dosage at which the adverse event began was also recorded

8.5.1.2 Lammers Trial

Only the incidence of adverse events was recorded. Serious adverse events were not recorded.

8.5.1.3 Integrated Pharmacokinetic Trials

The frequency, severity, seriousness and relationship to study medication were each recorded in a variable number of studies

8.5.1.4 Scharf Trial

The following is stated

- Adverse events were recorded retrospectively on Case Report Forms from information recorded by patients in daily diaries and from investigator-maintained medical records.
- The seriousness, severity and relationship to study medication of these adverse events was also recorded.
- A serious adverse event was defined using standard criteria

8.5.2 Adverse Events Categorization and Preferred Terms

Adverse events were initially entered in Case Report Forms using investigator terms, but were tabulated in the Integrated Summary of Safety and in the majority of study reports using

8.5.3 Key Adverse Events Tables

Key adverse event tables are grouped as follows

8.5.3.1 Controlled Clinical Trials

The following table, copied from the Integrated Summary of Safety, presents the number of adverse events that occurred in ≥ 5% of patients in each treatment group in the following controlled clinical trials, combined: OMC-GHB-2, Lammers and Scrima.

Body System COSTART Preferred Term	Total[a]	Placebo	Sodium Oxybate
Number of patients	226 (100%)	79 (100%)	147 (100%)
Patients with ≥ 1 AE	130 (58%)	39 (49%)	101 (69%)
Body as a Whole	79 (35%)	24 (30%)	60 (41%)
Headache	39 (17%)	12 (15%)	29 (20%)
Infection	11 (5%)	1 (1%)	10 (7%)
Pain	19 (8%)	3 (4%)	17 (12%)
Cardiovascular System	11 (5%)	2 (3%)	9 (6%)
Digestive System	46 (20%)	9 (11%)	37 (25%)
Dyspepsia	14 (6%)	5 (6%)	9 (6%)
Nausea	28 (12%)	4 (5%)	24 (16%)
Vomiting	13 (4%)	1 (1%)	9 (6%)
Musculoskeletal System	9 (4%)	1 (1%)	8 (5%)
Nervous System	80 (35%)	17 (22%)	66 (45%)
Confusion	12 (5%)	1 (1%)	11 (7%)
Dizziness	36 (16%)	2 (3%)	34 (23%)
Nervousness	12 (5%)	6 (8%)	7 (5%)
Sleep disorder	15 (7%)	2 (3%)	13 (9%)
Somnolence	24 (11%)	7 (9%)	17 (12%)
Respiratory System	20 (9%)	6 (8%)	14 (10%)
Skin	15 (7%)	4 (5%)	11 (7%)
Special Senses	10 (4%)	3 (4%)	7 (5%)
Urogenital System	24 (11%)	7 (9%)	18 (12%)
Incontinence, urine	8 (4%)	0	8 (5%)

[a] Two of the trials (Scrima and Lammers) were crossover trials, with patients in both the placebo and sodium oxybate groups.

As the above table indicates

- The proportion of patients with adverse events was higher in those treated with GHB than in those treated with placebo
- The most common adverse events in those treated with GHB were headache, nausea and dizziness. All 3 were more common in those treated with GHB than in those treated with placebo; nausea and dizziness were > 3-fold more common in the GHB group

8.5.3.2 Integrated Clinical Trials

The following table, copied from the Integrated Summary of Safety, presents the number of adverse events that occurred in ≥ 5% of patients in each treatment group in all studies in the Integrated Clinical Trials grouping. The dose listed is that at onset of the adverse event.

Body System COSTART Preferred Term	Total^	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total^	3.0	4.5	6.0	7.5	9.0
Number of patients	502 (100%)	92 (100%)	305 (100%)	94 (100%)	104 (100%)	100 (100%)	116 (100%)	118 (100%)
Body as a Whole	256 (50%)	25 (46%)	196 (64%)	55 (60%)	76 (73%)	84 (84%)	38 (94%)	87 (80%)
Abdominal pain	75 (15%)	5 (5%)	22 (7%)	4 (4%)	6 (6%)	8 (8%)	3 (3%)	3 (3%)
Accidental injury	27 (5%)	0	27 (9%)	4 (4%)	5 (5%)	15 (15%)	5 (5%)	4 (3%)
Asthenia	31 (6%)	1 (2%)	30 (10%)	4 (4%)	5 (5%)	16 (16%)	4 (3%)	8 (7%)
Back pain	27 (5%)	2 (4%)	25 (8%)	2 (2%)	5 (5%)	15 (15%)	5 (4%)	8 (7%)
Chest pain	18 (4%)	0	18 (6%)	2 (2%)	3 (3%)	7 (7%)	3 (3%)	4 (3%)
Flu syndrome	34 (8%)	3 (5%)	32 (6%)	4 (4%)	7 (7%)	13 (13%)	7 (6%)	5 (4%)
Headache	107 (20%)	13 (22%)	103 (34%)	37 (39%)	39 (38%)	28 (28%)	11 (9%)	21 (18%)
Infection	35 (5%)	3 (2%)	28 (9%)	5 (5%)	3 (3%)	10 (10%)	3 (3%)	5 (4%)
Malaise	8 (2%)	1 (2%)	7 (2%)	1 (1%)	1 (1%)	1 (1%)	3 (3%)	2 (2%)
Pain	61 (12%)	4 (7%)	44 (14%)	11 (12%)	14 (13%)	11 (11%)	6 (5%)	14 (12%)
Viral infection	25 (5%)	0	25 (8%)	2 (2%)	4 (2%)	17 (17%)	5 (4%)	10 (8%)
Cardiovascular System	37 (7%)	2 (4%)	26 (8%)	6 (6%)	3 (3%)	13 (13%)	5 (4%)	9 (8%)
Digestive System	149 (30%)	9 (17%)	126 (41%)	25 (26%)	38 (36%)	40 (40%)	17 (15%)	37 (31%)
Diarrhea	29 (7%)	1 (2%)	28 (9%)	5 (5%)	5 (5%)	14 (14%)	5 (4%)	7 (6%)
Dyspepsia	31 (6%)	3 (6%)	25 (8%)	7 (7%)	6 (6%)	9 (9%)	3 (3%)	6 (5%)
Nausea	69 (22%)	4 (7%)	85 (21%)	9 (10%)	21 (20%)	30 (30%)	13 (11%)	27 (23%)
Vomiting	28 (7%)	1 (2%)	28 (9%)	5 (5%)	5 (5%)	12 (12%)	2 (2%)	9 (8%)
Metabolic and Nutritional System	45 (21%)	2 (4%)	46 (11%)	6 (6%)	8 (8%)	17 (17%)	10 (9%)	11 (9%)
Musculoskeletal System	63 (14%)	2 (4%)	61 (15%)	8 (9%)	14 (9%)	31 (11%)	4 (3%)	9 (8%)

(continued)

Body System COSTART Preferred Term	Total^	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total^	3.0	4.5	6.0	7.5	9.0
Number of patients	502 (100%)	92 (100%)	305 (100%)	94 (100%)	104 (100%)	100 (100%)	116 (100%)	118 (100%)
Nervous System	196 (39%)	17 (31%)	193 (63%)	31 (33%)	61 (23%)	58 (34%)	33 (28%)	54 (46%)
Abnormal Dreams	20 (5%)	0	20 (6%)	2 (2%)	3 (3%)	7 (7%)	4 (3%)	1 (1%)
Confusion	29 (7%)	1 (2%)	28 (9%)	4 (4%)	4 (2%)	10 (10%)	6 (5%)	3 (3%)
Depression	25 (6%)	1 (2%)	25 (8%)	4 (4%)	2 (1%)	15 (15%)	3 (3%)	5 (4%)
Dizziness	72 (19%)	2 (4%)	70 (18%)	16 (17%)	13 (9%)	12 (11%)	9 (8%)	20 (17%)
Emotional lability	13 (3%)	3 (6%)	10 (3%)	2 (2%)	2 (1%)	2 (1%)	3 (3%)	3 (3%)
Nervousness	35 (9%)	6 (11%)	31 (8%)	5 (5%)	8 (3%)	13 (11%)	2 (2%)	8 (7%)
Sleep disorder	46 (11%)	3 (6%)	44 (11%)	4 (4%)	15 (5%)	22 (9%)	4 (3%)	10 (8%)
Somnolence	95 (24%)	8 (15%)	90 (12%)	11 (12%)	13 (5%)	21 (7%)	3 (3%)	12 (10%)
Respiratory System	105 (26%)	6 (11%)	103 (26%)	15 (16%)	28 (21%)	54 (19%)	13 (11%)	14 (12%)
Cough Increased	24 (6%)	2 (4%)	22 (6%)	5 (5%)	6 (2%)	8 (3%)	3 (2%)	1 (1%)
Pharyngitis	42 (10%)	3 (6%)	41 (10%)	5 (5%)	7 (3%)	22 (8%)	7 (6%)	3 (3%)
Rhinitis	30 (7%)	1 (2%)	29 (7%)	4 (4%)	11 (4%)	15 (5%)	5 (4%)	2 (2%)
Sinusitis	21 (5%)	0	21 (5%)	4 (4%)	4 (2%)	11 (4%)	2 (2%)	3 (3%)
Skin	52 (13%)	4 (7%)	49 (12%)	4 (4%)	9 (3%)	23 (8%)	4 (3%)	14 (12%)
Sweating	17 (4%)	0	17 (4%)	2 (2%)	2 (1%)	6 (2%)	2 (2%)	5 (4%)
Special Senses	48 (12%)	3 (6%)	48 (12%)	8 (9%)	8 (3%)	15 (5%)	7 (6%)	8 (7%)
Urogenital System	78 (18%)	6 (11%)	74 (19%)	6 (6%)	16 (6%)	34 (12%)	8 (7%)	21 (18%)
Incontinence Urine	8 (2%)	0	8 (2%)	0	0	2 (1%)	0	6 (5%)
Urinary Incontinence	26 (6%)	0	24 (6%)	2 (2%)	7 (3%)	7 (2%)	6 (4%)	5 (4%)

^ Patients are counted only once in each category.

The above table confirms that

- The most common adverse events in those treated with GHB were headache, pain, nausea and dizziness.
- A dose response could be seen, at least in the case of the 9 g dose, in the case of nausea.

8.5.3.3 Lammers Trial

Only a few adverse events were seen in this study as summarized by the following table taken from the Lammers study report. Note that

- Only 3 patients had adverse events while taking GHB
- Adverse events seen in this study have also been included in the Controlled Clinical Trials grouping above

Patient number	Treatment	Investigator term
8	GHB	terrible dreaming dry mouth paralysis in legs and arms anxious insecure
15	Placebo	kidney problems urination problems (stranguria)
2	GHB	severe perspiration influenza (common cold), sore throat headache frequent micturition
5	GHB	infection bladder sore throat flickering in the eyes
9	Wash out	frequent headache
17	Wash out	severe dreaming

8.5.3.4 Integrated Pharmacokinetic Trials

The following table, copied from the Integrated Summary of Safety, presents the number of adverse events that occurred in ≥ 5% of subjects in the Integrated Pharmacokinetic Trials Grouping

Body System COSTART Preferred Term	Sodium Oxybate*
Number of Subjects	144 (100%)
Body as Whole	21 (15%)
Headache	18 (13%)
Digestive System	44 (31%)
Nausea	37 (26%)
Vomiting	27 (19%)
Nervous System	40 (28%)
Confusion	7 (5%)
Dizziness	26 (18%)

* Subjects are counted only once in each category.

As the above table indicates the most common adverse events in this grouping as well are headache, nausea, vomiting and dizziness.

8.5.3.5 Scharf Trial

Given the duration of this study, adverse events were common and at least 1 adverse event was experienced by 95.1% of those participating in this trial. Adverse events that occurred in ≥ 5 % of patients in the study are in the following table

Adverse Event (COSTART)	Number of patients	% of Patients
Allergic reaction	13	9.1
Asthenia	32	22.4
Chills	19	13.3
Fever	38	26.6
Flu syndrome	55	38.5
Headache	75	52.4
Infection	16	11.2
Infection viral	81	56.6
Injury accidental	60	42.0
Malaise	33	22.1
Neoplasm	12	8.4
Pain	69	48.3
Pain abdominal	38	26.6
Pain back	29	20.3
Pain chest	33	20.1
Pain neck	15	10.5
Reaction unevaluable	33	23.1
Arrhythmia	15	10.5
Ventricular extrasystoles	10	7.0
Hypertension	21	14.7
Tachycardia	11	7.7
Vasodilatation	11	7.7
Periodontal abscess	8	5.6
Colitis	6	4.2
Constipation	8	5.6
Diarrhea	40	28.0
Dry mouth	12	8.4
Dyspepsia	36	25.2
Gastroenteritis	20	14.0
Nausea	58	40.6
Tooth disease	18	12.6
Vomiting	29	12.3
Peripheral edema	18	12.6
Arthralgia	16	11.2
Arthritis	26	18.2
Leg cramps	11	7.7
Joint disease	15	10.5
Myalgia	15	10.1
Anxiety	10	7.0
Ataxia	9	6.3
Confusion	9	6.3
Convulsion	8	5.6
Depression	19	13.3
Dizziness	39	27.3
Emotional lability	8	5.6
Hypertonia	13	9.1
Hypesthesia	12	8.4
Insomnia	10	7.0
Nervousness	20	14.0
Neuralgia	8	5.6
Paresthesia	17	11.9
Sleep disorder	45	31.5
Somnolence	15	10.5
Tremor	9	6.3
Apnea	19	13.3
Bronchitis	32	22.4
Increased cough	49	34.3
Dyspnea	27	18.9
Epistaxis	10	7.0
Lung disease	13	9.1
Pharyngitis	54	37.8
Pneumonia	9	6.3
Rhinitis	52	36.4
Sinusitis	38	26.6

Pruritus	13	9.1
Rash	13	9.1
"Sweat"?	26	18.2
Amblyopia	13	9.1
Conjunctivitis	19	13.3
Otitis media	10	7.0
Ear pain	14	9.8
Eye pain	13	9.1
Abnormal vision	9	6.3
Urinary incontinence	33	23.1

The most common adverse events in this study, at least some of which were due to intercurrent illnesses, included (in descending order of frequency) viral infection, headache, pain, accidental injury, nausea, flu syndrome, pharyngitis, rhinitis, increased cough, sleep disorder, diarrhea, dizziness, fever, abdominal pain, sinusitis and dyspepsia.

The most common adverse events considered to be drug-related by the investigator, and occurring in the first 6 months (in descending order of frequency) of GHB use were sleep walking, dizziness, nausea, pain, dyspepsia, abdominal pain, viral infection and headache. The most frequent adverse events (whether considered related to GHB or not) during that period were headache, viral infection, pain, nausea and dizziness: tables for all adverse events in this time period have been provided by the sponsor

The most common adverse events occurring after the first 6 months of treatment were viral infection, pain, headache and accidental injury. Tables for all adverse events in this time period have been provided by the sponsor.

8.5.4 Common and Drug-Related Side Effects

I have used 2 sets of studies in defining these

- Controlled clinical trials
- All clinical trials

8.5.4.1 Controlled Clinical Trials

In the controlled clinical trials group I have selected those adverse events that have been listed as occurring in ≥ 5% of Xyrem®-exposed patients and at least twice as frequently as those exposed to placebo. The following adverse events, listed using COSTART terms, fit these criteria:

Infection (5%), pain (8%), nausea (12%), vomiting (4%), confusion (5%), dizziness (16%), sleep disorder (7%) and urinary incontinence (4%)

8.5.4.2 All Clinical Trials

The 3 most common adverse events in GHB-treated patients across the 2 main clinical trial subsets (Integrated Clinical Trials, Integrated Pharmacokinetic Trials and Scharf Study) were:

Headache, nausea and dizziness.

The next table indicates their incidence in each of the clinical trial groupings

Adverse Event	Integrated Clinical Trials (%)	Integrated Pharmacokinetic Trials (%)	Scharf Trial (%)
Headache	26	13	52
Nausea	21	26	41
Dizziness	18	18	27

8.5.5 Additional Analyses and Explorations

Special analyses were performed by the sponsor for the following adverse events

- Urinary incontinence (and its relationship to seizures)
- Elevated anti-nuclear antibodies

Further analyses explored the relationship of adverse events to dose, duration of treatment, concomitant medication use, age, and gender

These items are discussed in greater detail below

8.5.5.1 Urinary Incontinence And Its Relationship To Seizures

8.5.5.1.1 BACKGROUND

Animal studies have shown a relationship between the use of high doses of GHB, and symptomatology as well as EEG changes that resemble those of absence seizures in humans. An experimental animal model for absence seizures has in fact been developed using sodium oxybate. Myoclonic jerks have also been seen in patients (outside the United States) in whom anesthesia has been induced with GHB.

In our original review of Treatment IND # 57271, this Division had noted that several GHB treated patients were noted to have nocturnal urinary incontinence There was a concern as to whether unrecognized seizures were responsible for the episodes of incontinence in these patients.

Based on the above a more detailed analysis of urinary incontinence in clinical trials of GHB, and its possible relationship to hitherto-unrecognized seizures was requested by this Division

8.5.5.1.2 METHODS

The sponsor conducted an analysis of urinary incontinence using the following methods

- Adverse events suggestive of urinary incontinence were searched for in the databases for both trials
- Adverse events that appeared to be of central nervous system origin were also looked for.
- A questionnaire was distributed to all investigators whose patients had reported urinary incontinence in Studies OMC-GHB-2 and OMC-GHB-3. The questionnaire asked investigators to list any additional nocturnal observations that would suggest the presence of seizures, ascertain the patient's urological

history prior to beginning GHB treatment and to note any new neurological symptoms

- Patients who had both central nervous system adverse events and urinary incontinence were identified as were patients who had urinary incontinence and central nervous system adverse events contemporaneously
- Overnight EEG recordings were made prospectively in 6 patients who had a prior history of incontinence during sodium oxybate treatment at a dose of 9 g/day. Note that only 4/6 patients had recordings done with what was believed to be an adequate number of scalp electrodes to reliably detect electrical seizure activity (the EEG recorded during polysomnography does not typically use enough scalp electrodes to reliably detect seizure patterns). In addition polysomnogram EEG recordings were looked at retrospectively in 2 additional patients who had urinary incontinence
- The data were reviewed by an independent expert in epilepsy, Dr Nathan Crone, who was asked to render an opinion as to whether the episodes of incontinence that have occurred during clinical trials of GHB could have been due to seizures.
- Other experts were also consulted by the sponsor regarding whether GHB could cause seizures.
- The medical literature was also reviewed.

8.5.5.1.3 RESULTS

8.5.5.1.3.1 Incontinence In Studies OMC-GHB-2 And OMC-GHB-3

- In OMC-GHB-2, 15 events of enuresis/urinary incontinence occurred in 8 of the 136 patients participating in that trial. 5 of these patients had at least one episode occurring at night; in the remaining 3 there is insufficient information to indicated that the incontinence occurred at night. The distribution of these events based on the daily dose of GHB taken at the time of incontinence is in the following table (note that patients were randomized equally to the placebo, 3 g/day, 6 g/day and 9 g/day doses in this study)

GHB Dose (g/day)	Number of events of incontinence
6	3
9	11
0*	1

*Not taking study drug or placebo

- In OMC-GHB-3, 51 events of enuresis/urinary incontinence occurred in 13 of the 188 patients who participated in this study. A single patient accounted for 15 events. 20/51 events were considered related to GHB by the investigator. Only a few of these events are specifically documented as having occurred at night. The distribution of these events based on the daily dose of GHB taken at the time of incontinence is in the following table

GHB Dose (g/day)	Number of events of incontinence
2.3	1
3	1
4.5	5
6	27
7.5	1
9	16

- One additional patient in each trial (OMC-GHB-2 and OMC-GHB-3) experienced fecal incontinence. The doses of GHB at the time of incontinence were 9 g/day and 6 g/day, in the OMC-GHB-2 and OMC-GHB-3 trials respectively. The patient participating in the OMC-GHB-2 trial had a single episode of fecal incontinence after which the study drug was stopped. The patient participating in the OMC-GHB-3 trial had multiple episodes of fecal incontinence, a previous history of milk allergy with diarrhea, and a negative sigmoidoscopy.
- The central nervous system adverse events that occurred in patients who had urinary incontinence included the following
  Tremor, disorientation, confusion, impaired concentration, tingling in head, tingling/numbness in face, numbness of left hand, face and leg, abnormal muscle sensations, muscle jerks/spasms, "drunkenness", and poor balance/unstable gait/poor equilibrium/impaired coordination
- 2 patients in OMC-GHB-2 and 2 patients in OMC-GHB-3 had central nervous system adverse events contemporaneously with urinary incontinence. These adverse events were disorientation, confusion and muscle jerks. Narratives have been provided for these 4 patients and do not provide any strong evidence that these patients had seizures of any kind, although one of these adverse events (muscle jerks) could conceivably have represented myoclonic jerks. Unfortunately, descriptions of the events are lacking. These 4 patients are summarized in the following table.

Study	Patient ID #	Age/Gender	GHB Dose At Time Of Incontinence	Contemporaneous Central Nervous System Adverse Event
OMC-GHB-2	0702	59/F	9 g/day	Confusion
OMC-GHB-2	0124	57/M	9 g/day	Confusion
OMC-GHB-3	0219	65/F	9 g/day	Disorientation
OMC-GHB-3	0819	57/M	3 g/day	Muscle jerks*

*This patient had a single episode of incontinence which occurred at the same time as his muscle jerks began. However the muscle jerks persisted long after his episode of incontinence ended

8.5.5.1.3.2 Incontinence In Other Clinical Trial Groupings

- In the 5 integrated clinical trials 32 of the 402 patients experienced urinary incontinence; 2 patients had fecal incontinence.
- In the 8 integrated pharmacokinetic trials 2 of 144 subjects experienced urinary incontinence and 1 subject experienced fecal incontinence. None of these individuals was observed to have seizures
- No patients in the Lammers or Scrima studies experienced incontinence.

8.5.5.1.3.3 EEG Studies

- In the prospective overnight EEG recordings in 6 patients, only one had urinary incontinence during the recording. No electrical seizure activity was apparent in any of the 6 patients. Note that the patient who had incontinence (Initials:(b)(had what was believed to be an adequate number of scalp electrodes for the recordings.
- No electrical seizure activity was seen on either of the 2 retrospectively reviewed polysomnogram EEG recordings although one recording was stated to be of poor quality.

- The sponsor believes that the EEG data described here represent a reasonable attempt to show that GHB does not cause clinically subtle seizures, and that enuresis associated with GHB is not caused by seizures.

8.5.5.1.3.4 Animal Data In Literature

The sponsor has summarized the animal data in the medical literature as follows.

- As noted above GHB is used to induce absence seizures in an experimental animal (monkey) model developed by O. Carter Snead. In that model, following an IV dose of 400mg/kg GHB, the EEG and behavioral effects in the monkey consist of an initial low-voltage slowing of brain rhythms combined with drowsiness from which the animal can be easily aroused. This state then progresses to paroxysmal rhythmic 2.5 to 3 per second high-voltage slowing, punctuated by spikes, during which the animal exhibits starring, occasional rhythmic eye movement, dilated pupils, unresponsiveness to any stimuli, and myoclonic movements. Such paroxysms are frequently precipitated by auditory stimuli. The doses and serum concentrations at which these phenomena occur depend on the age of the animal and the elapsed time between administration of the dose and drawing of the blood sample
- Higher doses can also cause generalized tonic-clonic seizures.
- Epileptiform abnormalities on EEG typically appear at GHB serum levels greater than 300 μg/ml, corresponding to a dosage threshold of 200 mg/kg. Myoclonic seizures occur at levels greater than 500 μg/ml.
- In contrast, a pharmacokinetic study of GHB in six patients with narcolepsy showed that after a typical 3 g oral dose the peak serum level of GHB did not exceed 125 μg/ml.

8.5.5.1.3.5 Clinical Data In Literature

These data are summarized below

- There are many anecdotal case reports and case series of intoxication with GHB reported in the medical literature, and related to illicit use of that drug
  - Many of these incidents include reports of tonic-clonic seizures. In most of these it is not clear how much GHB was ingested, and adverse reactions were often associated with concomitant alcohol consumption.
  - In one of the rare instances where the dose of GHB ingested could be estimated a 40-year-old man had a “tonic-clonic major motor seizure without a previous history of epilepsy” about 20 minutes after taking about 115 mg/kg of GHB.
  - GHB has been used in Europe as an anesthetic, and as a sedative in intensive care units, at doses of about 50 mg/kg.
  - This dose of GHB has not been associated with seizures.
  - A German study examined the effect of GHB on the EEG of 31 patients after abdominal surgery. After injection of 50 mg/kg intravenously, no seizure-like electrical activity was observed in the EEG

8.5.5.1.3.6 Expert Opinions

- According to Dr Martin Scharf, one of the experts consulted by the sponsor, no bed-partners of patients taking GHB had reported phenomena that might be considered seizure-like. Dr Scharf reportedly stated that there were about 750 patient-years of exposure to GHB (he was presumably referring to

studies in which he was the principal investigator) and that the majority of these patients had bed partners. Since urinary incontinence that results from seizures is most commonly associated with the generalized tonic-clonic variety such seizures might have been expected to awaken a bed partner, at least in some patients.

- Another expert, Dr Mortimer Mamelak, stated that despite a long history of GHB use for a variety of indications there were no reports of seizures occurring in association with use of the drug.
- Dr Nathan Crone's analysis included a review of OMC-GHB-2 and OMC-GHB-3 clinical trial data, data from a recently completed pharmacokinetic trial (OMC-SXB-11), the discussions with Drs Scharf and Mamelak, the prospectively collected EEG data described above, and relevant literature. His conclusions have been summarized by the sponsor as follows:

"After review of the clinical and research literature on the epileptogenic properties of GHB it is Dr. Crone's opinion that GHB does have the potential to cause seizures in humans, but this probably requires higher doses than those planned for the clinical treatment of narcolepsy. The doses used to induce absence and generalized tonic-clonic seizures in animals are probably higher than those used for clinical purposes in humans. There are a handful of reports of seizures due to GHB abuse. Some have occurred with doses that appear to be similar to clinically useful dosages, but the actual amount ingested could not be readily verified. Clinical studies of GHB in patients with narcolepsy have not reported any seizures in association with GHB. EEG recorded during polysomnography may not be sufficient to detect subclinical, electrographic seizure activity. Other than data collected by Dr. Scharf, only one study has been done on the effects of GHB on human EEG. Although this study did not detect any epileptiform changes, future evaluation of the utility of GHB for any clinical purpose should include EEG recordings during administration of GHB, as well as EEG during maneuvers that are known to provoke absence seizures, i.e. hyperventilation and stroboscopic photic stimulation."

8.5.5.1.4 SPONSOR'S CONCLUSIONS

Despite the appearance of absence-like seizure states in primates at intravenous GHB doses "far exceeding the human therapeutic dose", there is no support, in the clinical trials included in this Integrated Summary of Safety or in the literature reporting human experience in therapeutic dosages for a relationship between instances of incontinence reported with GHB and seizures

8.5.5.1.5 CONVULSIONS WITH XYREM® (REVIEWER'S SUMMARY)

"Convulsions" were reported as an adverse event in a number of GHB-treated patients in the NDA safety database. In practically every instance no additional qualitative descriptions of this adverse event are available, even in instances where narratives and Case Report Forms have been provided (i.e., in instances where convulsions have been listed as a serious adverse event or adverse event discontinuation). It is also unclear as to what extent the term "convulsions" truly referred to an epileptic phenomenon (e.g., it is unclear how frequently the term "convulsion" was used to describe an attack of cataplexy or whether tremor or myoclonus was referred to as "convulsion").

There were no patients in the entire safety database who had adverse events listed under any other preferred term that would strongly suggest that they had true convulsions.

I have summarized convulsions as recorded as an adverse effect of Xyrem® in the NDA safety database as follows.

- In the controlled clinical trials 2 (1.4% of) GHB-treated patients are listed as having convulsions whereas no placebo-treated patient had convulsions. In neither of these 2 patients was "convulsion" listed as a serious adverse event or as a reason for treatment discontinuation. Detailed descriptions of this adverse event are unavailable

- In the entire integrated clinical trials grouping 10 (2.5% of) GHB-treated patients are listed as having convulsions. In none of these instances was "convulsion" listed as a serious adverse event or as a reason for treatment discontinuation. Detailed descriptions of this adverse event are unavailable

- In the Scharf study, 9 (6.3% of) GHB-treated patients are listed as having convulsions: the sponsor believes that in 5 of those instances the events coded as "convulsions" more likely represented cataplexy; of the remaining 4 patients one had seizures prior to study entry. These patients are summarized in the table below

  Of the patients in the table below: 1 patient (# 064; see description in Section 8.4.2.2) was listed as discontinuing treatment on account of seizures and in another patient (# 257; see Section 8.3.2.4) the convulsion was listed as a serious adverse event.

  For all 9 patients detailed descriptions of the events called "convulsions" are lacking. Narratives and Case Report Forms are available for 2 patients (#s 064 and 257) but do not help clarify whether the events were true convulsions, epileptic phenomena of any other kind or neither.

Patient ID	COSTART Term	Verbatim Term	No. of Events	Dose (g)[1]
043	Convulsion	Excessive cataplexy	-	6.0
048[2]	Convulsion	Convulsive-like seizure	1	8.3
049	Convulsion	Fall, sudden cataplexy	-	6.0
051	Convulsion	Fell twice, with cataplexy	-	3.0
064	Convulsion	Seizure	1	7.5
		Seizure	1	6.0
		Seizure	1	6.0
		Seizure-morning	1	6.0
		Seizure-afternoon	1	6.0
		Seizure-morning	1	6.0
		(Total events)	6	
219	Convulsion	Cataplexy, twice	-	7.5
247	Convulsion	Seizures, continuous jerking	1	6.0
255[3]	Convulsion	Grand mal seizure	1	5.3
257	Convulsion	Violent shaking and vibrations	-	5.3
		Jerking during cataplexy	-	9.0
		Severe cataplexy	-	9.0
		Cataplexy	-	12.0
		Fall due to cataplexy. Patient suffered injury, resulting in increased catalepsy.	-	11.3

[1]Dose recorded is the dose at the onset of the adverse event.
[2]This event for patient 048 was judged a serious adverse event that was related to the study medication.
[3]Patient 255 had a history of seizures of unknown etiology at enrollment.

- Based on the narratives and Case Report Forms that have been supplied for some patients with convulsions (i.e., those in whom this adverse event was listed as serious or led to study drug discontinuation) it is difficult to determine
  - If they in fact had true convulsions or any epileptic phenomenon at all (clinical descriptions of the episodes were lacking)
  - If at least some patients treated with GHB did have true convulsions, it is not clear that GHB caused their convulsions; confounding factors included the use of concomitant medications such as stimulants or tricyclic antidepressants which are themselves reputed to have epileptogenic properties
  - One patient (# 255 in the above table) was documented as having a seizure disorder even prior to receiving GHB
  - Another patient recorded as having convulsions (see Section 8.4.2.2) during a GHB study may have had convulsions even prior to the study: she also had a history of a left frontal lobe lesion and burr hole surgery
- The sponsor has stated that absence-like seizure states occur in primates at intravenous GHB doses “far exceeding the human therapeutic dose”. In fact the safety margin between the highest human dose used in efficacy trials and that used in primate models to induce absence seizures, while it certainly exists, may not extremely wide as the following indicate
  - The highest human dose used in efficacy trials is 9 g/day. In a 60 kg individual this dose is equal to 150 mg/kg/day or 5550 mg/m^2/day

- Intravenous doses of 400 mg/kg in monkeys are sufficient to induce clinical absence seizures. Assuming that GHB has an oral bioavailability of 30% in monkeys this would be equivalent to an oral dose of 1333 mg/kg or 26660 mg/m^2
- Intravenous doses of 200 mg/kg in monkeys are sufficient to induce epileptiform abnormalities on an EEG. Again, assuming that GHB has an oral bioavailability of 30% in monkeys this would be equivalent to an oral dose of 667 mg/kg or 13340 mg/m^2
- Epileptiform abnormalities on EEG typically appear at GHB serum levels greater than 300 μg/ml, corresponding to a dosage threshold of 200 mg/kg. Myoclonic seizures occur at levels greater than 500 μg/ml.
- A pharmacokinetic study of GHB in six patients with narcolepsy showed that after a typical 3 g oral dose the peak serum level of GHB did not exceed 125 μg/ml.
- In an additional pharmacokinetic study in 13 healthy individuals, after 2 nightly doses of GHB of 9 g each the mean C_{max} was 142 μg/mL (coefficient of variation 35%)

8.5.5.1.6 REVIEWER'S COMMENTS

- In controlled clinical trials urinary incontinence was more frequent in those treated with GHB than in those treated with placebo (5% vs 0%) suggesting that, while not very common, urinary incontinence may be caused by that drug. Furthermore, urinary incontinence in GHB-treated patients may be dose-related.
- In controlled clinical trials fecal incontinence was seen in 1 GHB-treated patient (1%) but not in any placebo-treated patient. A number of other instances of fecal incontinence were seen in the entire database, but the overall incidence of this adverse event was much lower than that of urinary incontinence
- Based on the circumstantial evidence supplied above, there is no firm evidence that urinary incontinence in any patients treated with GHB was caused by seizures, whether generalized tonic-clonic or of another kind. However only one patient appears to have had an episode of incontinence while actually undergoing EEG monitoring; in that instance the EEG did not show any evidence of epileptiform activity; this patient did appear to have an adequate number of scalp electrodes and montages.
- In the open-label Scharf study which was not included in the sponsor's formal analysis of incontinence, 33 patients (23.1%) had urinary incontinence. 1 patient (0.7%) had fecal incontinence. There has been no formal attempt by the sponsor to determine if any of these instances could have been secondary to seizures. All that the sponsor has done is to provide a summary table for those with convulsions providing further details for the patients summarized under the previous bullet. This table is above.
- Overall, the evidence that urinary incontinence associated with therapeutic use of GHB is due to unrecognized seizures, or that GHB is epileptogenic at therapeutic doses, is not strong at present. However either possibility cannot be excluded based on the available information which is very limited: studies conducted to address this matter have also been very limited in scope so far and further studies to evaluate this issue may be warranted.

8.5.5.2 Elevated Antinuclear Antibodies

This analysis has been confined entirely to the Scharf study

8.5.5.2.1 BACKGROUND

After a patient in the Scharf trial developed elevated antinuclear antibodies in 1991, this phenomenon was further investigated in that study and was also discussed with this Agency

8.5.5.2.2 METHODS

These are described only very briefly in the submission.

After the index case of elevated antinuclear antibodies was noted, the same titers were checked for all "ongoing" patients in the trial; these checks appear to have been initially done on a total of 65 patients over the 2 years after the index case was identified. After discussions with this Agency Dr Scharf continued to check antinuclear antibody titers on all patients participating in this study; data are provided for until 5/31/99, the cut-off date for the Scharf study report. A total of 87 patients had at least one antinuclear antibody titer estimated.

In a proportion of those with positive antinuclear antibodies, antihistone antibody titers were checked.

An attempt was made to correlate the antibody titers with symptoms consistent with systemic lupus erythematosus, medication-induced lupus or any other rheumatic disease using a symptom questionnaire that was supplied to the initial 65 patients who had antibody titers determined.

In each patient in whom antinuclear antibody titers were positive on more than one occasion summaries were made of demographics, antinuclear antibody titers (with specific dates) and adverse events that developed during the course of the study (with specific dates)

The methods of sample collection, storage, analysis and interpretation were not standardized for the antinuclear antibody and antihistone antibody titer estimations: these tests were performed at a variety of laboratories. An antinuclear antibody titer of > 1:40 was considered positive.

The vast majority of patients who had the above antibody titers determined lacked baseline measurements. In the majority of instances (80%) these determinations were made after an extended period of treatment with GHB

8.5.5.2.3 RESULTS

The results of this analysis have been presented as

- Summary text
- Data listings for all patients who had antinuclear antibody and antihistone antibody testing: these listings include patient ID number, date of initial dose of GHB, date of testing, dose of GHB at time of testing and antibody titers
- A table listing all patients who had positive antinuclear antibody tests on at least a single occasion: the table included the patient number, the date treatment was started, the date of

the first antinuclear antibody, the result of the first antinuclear antibody, the total number of antinuclear antibody titer determinations, the number of positive antinuclear antibody determinations and the sequence of antinuclear antibody determinations

- Summaries of demographics, antinuclear antibody titers (with specific dates) and adverse events that developed during the course of the study (with specific dates) for all patients whose antibody titers were positive on more than one occasion

8.5.5.2.3.1 In the population of 65 patients who initially had antinuclear antibody testing done.

- 19/65 (29.2%) of patients had one or more antinuclear antibody elevations ranging from 1:40 to 1:2560
- No correlations were found between positive antinuclear antibody titers and duration of treatment, age or gender
- 15/19 patients who were antinuclear antibody-positive had antihistone antibodies done: these were negative in all but one patient who had a result that was termed "borderline positive" and who did not have symptoms characteristic of lupus
- The symptom questionnaire showed a low overall incidence of symptoms that could have been consistent with lupus with no differences between the subgroup of those with positive antinuclear antibody titers and those in whom these titers were negative

8.5.5.2.3.2 In the total population of 87 patients who had antinuclear antibody testing done

- 26/87 (29.9%) had at least one positive antinuclear antibody test. These patients are summarized in the next table which has been copied from the submission.

Table 30 Narcoleptic Patients with Positive ANA Results

PATIENT NO.	DATE RX STARTED	DATE 1ST ANA	RESULT 1ST ANA	TOTAL NO. ANA'S	NO. POSITIVE ANA'S	SEQUENCE OF ANA FINDINGS*
3	11/85	7/90	N	10	1	N-N-N-P-N-N-N-N-N-P
4	1/88	12/90	N	15	2	N-N-N-P-P-N-N-N-N-N-N-N-N-N-N
15	1/84	5/90	N	15	5	N-P-P-N-N-P-N-N-P-P
19	2/89	1/90	N	12	6	N-P-P-P-P-N-P-P-N-N-N-N
38	6/87	5/90	N	13	7	N-P-P-N-P-N-N-N-P-P-N-N-P-P
39	11/84	12/90	N	12	3	N-N-N-N-N-N-N-N-P-N-N-N
83	6/86	1/92	N	17	14	N-P-N-P-P-P-N-P-P-P-P-P-P-P-P-P
62	1/87	6/92	N	12	2	N-N-N-N-N-N-P-N-N-N-N-N
45	1/87	1/90	N	14	4	N-N-N-N-N-N-N-P-N-P-P-P-P
58	2/84	6/90	N	12	5	N-N-N-N-N-N-P-P-P-P-N
31	10/85	12/91	N	10	1	N-N-N-N-N-N-N-N-N-P
34	8/87	6/90	N	9	1	N-N-P-N-N-N-N-N-N
52	6/87	6/90	N	13	2	N-P-N-N-N-N-N-N-N-N-P-N
65	11/83	12/90	N	16	5	N-N-N-N-N-N-N-N-N-N-N-N-N-P-N
68	2/85	1/91	P	7	7	P-P-P-P-P-P-P
87	8/86	8/90	P	14	7	P-N-N-P-N-N-P-N-N-N-P-P-P-P
75	5/87	5/90	N	13	1	N-P-N-N-N-N-N-N-N-N-N-N-N
335	11/84	6/92	N	6	2	N-N-N-N-P-P
227	10/89	8/90	N	15	1	N-N-N-P-N-N-N-N-N-N-N-N-N-N-N
233	9/84	1/90	N	13	4	N-N-P-N-N-N-P-N-N-N-N-P
237	6/90	12/96	P	2	2	P-N
252	8/90	2/92	N	11	5	N-N-N-N-N-N-P-P-P-P-P-P
280	2/84	12/88	N	12	10	N-N-P-P-P-P-P-P-P-P-P-P
267	4/82	8/92	P	13	4	P-N-N-N-N-N-N-N-P-P-P-N
270	1/91	5/95	N	8	5	N-P-N-N-N-P-P-P-P
277	7/96	7/96	N	2	1	N-N-N-P

- In the above table, 9 patients had only a single positive result while the remaining 17 had multiple positive antinuclear antibody determinations
- In the above table 4 patients were positive on their first antinuclear antibody test, whereas the remaining 22 had at least one negative determination prior to a positive one

8.5.5.2.3.3 Among the 17 patients with 2 or more positive antinuclear antibody results

- There were 7 males and 10 females
- Their ages ranged from 15 to 66 years; all were Caucasian
- Daily doses of GHB ranged from 4.5 g to 11 g/day. The most frequent stable dose was 6 g/day
- When the sequence of antinuclear antibody testing was examined several different patterns of positivity/negativity were seen
- Adverse event data obtained from Case Report Forms (which I have examined) indicates the presence of very few rheumatological symptoms
- No patient was diagnosed to have either drug-induced lupus or systemic lupus erythematosus

8.5.5.2.4 SPONSOR'S CONCLUSIONS

- The incidence of positive antinuclear antibody tests in the population in this study appears to be higher than what might be expected in the general population
- Sodium oxybate-treated narcoleptic patients in the Scharf trial who had positive antinuclear antibody titers did not present with, or subsequently develop, symptoms suggestive of systemic lupus erythematosus, drug-induced lupus or any rheumatic disease.
- There is no evidence that chronic treatment with GHB results in an increase in occurrence of any rheumatic or immune-mediated disease.
- In medication-induced lupus, positive antinuclear antibody titers are accompanied in most cases (90%) by antihistone antibodies.
- Use of sodium oxybate may result in elevated antinuclear antibody titers without the corresponding increase in antihistone antibodies seen in patients with drug-induced lupus
- A review of the scientific literature published since 1966 failed to uncover any study that reported the incidence of antinuclear antibodies in narcolepsy. Thus it is impossible to determine if the increased incidence of positive antinuclear antibody tests is related to GHB or narcolepsy, or is unique to this dataset
- Dr Evelyn Hess, an expert in systemic lupus erythematosus and drug-induced lupus, whose opinion was sought by the sponsor, concurred with the sponsor's conclusions. According to her, the most that might be concluded was that sodium oxybate, like many other drugs, may be associated with low level increases in antinuclear antibody titer of no known clinical significance.

8.5.5.2.5 DISCONTINUATIONS DUE TO POSITIVE ANTINUCLEAR ANTIBODIES

2 patients discontinued from the Scharf study on account of positive antinuclear antibody tests. These patients are already described above (Sections 8.4.2.3 and 8.4.2.5)

8.5.5.2.6 REVIEWER'S COMMENTS

- There are clearly a number of readily-evident limitations to the sponsor's analysis. In addition
  - Full details of some analyses have not been supplied (e.g., the actual tables comparing the incidence of symptoms attributable to lupus in the antinuclear antibody-positive and negative groups)
  - Antinuclear antibody titers have been in only a subset of those participating in one study out of a number of studies in this NDA
- At least one patient is stated to have been diagnosed to have "rheumatoid arthritis" close to the time when she was first detected to have a positive antinuclear antibody test (1:640) and after she had received GHB for about 6 years. The test remained positive, sometimes in high titer, while she continued to receive GHB, and for 11 months thereafter. Antihistone antibodies were not checked in this patient. Unfortunately, few details are details are available regarding this patient's symptoms. However based on the information available for this patient, the following statement by the sponsor is not entirely correct
  "Sodium oxybate-treated narcoleptic patients in the Scharf trial who had positive antinuclear antibody titers did not present with or subsequently develop symptoms suggestive of systemic lupus erythematosus, drug-induced lupus or any rheumatic disease."
- There is no firm evidence that any patient treated with GHB developed drug-induced lupus.

8.5.5.3 Relationship Between Adverse Events And Dose

8.5.5.3.1 CONTROLLED CLINICAL TRIAL: OMC-GHB-2

This is the only trial in which randomized comparisons between multiple dose groups treated in parallel for the same period of time (1 month) is possible. The table below indicates that while the overall incidence of treatment-emergent adverse events were comparable across treatment groups, certain specific adverse events did show a dose-response and were most common in the 9 g/day dose group. These were: headache, pain, nausea, dizziness, sleep disorder, and incontinence of urine. Note, however, that in this trial patients were not titrated to their assigned doses

Adverse Event (COSTART term)	Treatment Group			
	Placebo (n =34)	GHB 3 g (n = 34)	GHB 6 g (n = 33)	GHB 9 g (n = 35)
Any	24 (70.6)	25 (73.5)	25 (75.8)	26 (74.3)
Headache	7 (20.6)	3 (8.8)	5 (15.2)	11 (31.4)
Infection	1 (2.9)	3 (8.8)	5 (15.2)	0
Infection Viral	1 (2.9)	1 (2.9)	3 (9.1)	0
Pain	2 (5.9)	3 (8.8)	4 (12.1)	7 (20.0)
Pain Back	2 (5.9)	0	2 (6.1)	0
Diarrhea	0	0	2 (6.1)	2 (5.7)
Dyspepsia	2 (5.9)	0	3 (9.1)	2 (5.7)
Nausea	2 (5.9)	2 (5.9)	5 (15.2)	12 (34.3)
Nausea Vomiting	0	0	2 (6.1)	2 (5.7)
Myalgia	0	2 (5.9)	0	0
Myasthenia	0	2 (5.9)	1 (3.0)	0
Amnesia	0	1 (2.9)	0	2 (5.7)
Anxiety	1 (2.9)	1 (2.9)	0	2 (5.7)
Confusion	1 (2.9)	3 (8.8)	1 (3.0)	5 (14.3)
Dizziness	2 (5.9)	8 (23.5)	10 (30.3)	12 (34.3)
Dream Abnormal	0	0	3 (9.1)	1 (2.9)
Hypertension	1 (2.9)	0	2 (6.1)	0
Hypesthesia	0	2 (5.9)	0	0
Sleep Disorder	1 (2.9)	2 (5.9)	4 (12.1)	5 (14.3)
Somnolence	4 (11.8)	5 (14.7)	4 (12.1)	5 (14.3)
Thinking Abnormal	0	1 (2.9)	0	2 (5.7)
Pharyngitis	3 (8.8)	0	3 (9.1)	1 (2.9)
Sweating	0	1 (2.9)	1 (3.0)	4 (11.4)
Amblyopia	1 (2.9)	2 (5.9)	0	0
Tinnitus	0	2 (5.9)	0	0
Dysmenorrhea	1 (2.9)	1 (2.9)	0	2 (5.7)
Incontinence of Urine	0	0	2 (6.1)	5 (14.3)

8.5.5.3.2 OTHER CLINICAL TRIAL GROUPINGS

The sponsor's analyses indicate the following

- In the Scharf trial no "strong" evidence of a dose-response relationship was seen
- In the Integrated Clinical Trials grouping, based on the dose at the time of onset of the adverse event, a higher incidence of adverse events was seen for the 9 g/day dose as compared with the other dose groups as follows
  - Those with at least one adverse event (74% for the 9 g/day dose group versus 45 to 61% for the other dose groups)
  - Discontinuations due to adverse events (12% for the 9 g/day group versus 3-5% for the other dose groups)
  - In the OMC-GHB-2 trial a dose-response effect was seen for nausea and viral infection that was statistically significant ($p < 0.05$)

Adverse events were not analyzed by dose for the Integrated Pharmacokinetic Trials.

8.5.5.4 Relationship Between Adverse Events And Duration Of Treatment

To determine this relationship the sponsor appears to have performed analyses of the OMC-GHB-3 (2-year) and Scharf trials

In the OMC-GHB-3 trial

- Almost all adverse events appeared within the first 12 months of treatment

- Only 15 additional COSTART terms were reported during the second twelve months: adverse events that occurred during the second 12 months in > 1 patient included gastrointestinal distress (3 patients), bilirubinemia (2 patients), and increased alkaline phosphatase (2 patients)

In the Scharf trial

- The profile of adverse events specifically associated with long-term use of GHB was consistent with the serious illnesses that could be expected in older adults
- The most frequent serious adverse events were related to cardiovascular disease and narcolepsy
- Factors that might contribute to this profile of adverse events included: the increasing age of patients during the trial, underlying cardiovascular abnormalities which were present in 20% of patients at baseline

Note that the only actual analyses that appear to have been performed by the sponsor consisted of separate tables of adverse events for the first 6 months of treatment versus those that appeared after the first 6 months of treatment. I have already discussed these tables in Section 8.5.3.5

8.5.5.5 Relationship Between Adverse Events And Concomitant Medications

No analyses were performed

8.5.5.6 Relationship Between Adverse Events And Age

In the 5 integrated clinical trials subset analyses based on age (< 65 years and ≥ 65 years) were performed for adverse events. The incidence of all adverse events, severe adverse events and discontinuations due to adverse events were similar between the 2 subsets. The incidence of serious adverse events was higher in the older subset, where the sample size was clearly much smaller. The results of these comparisons for GHB-treated patients are illustrated in the following table.

Adverse Events	Age < 65 years N = 356	Age ≥ 65 years N = 43
All adverse events	269 (76%)	29 (67%)
Serious adverse events	12 (3%)	4 (9%)
Severe adverse events	61 (17%)	8 (19%)
Adverse event discontinuations	38 (11%)	5 (12%)

The incidence of the following specific adverse events was also similar between the 2 subsets for GHB-treated patients: nausea, dizziness, headache, vomiting and urinary incontinence.

Adverse Events	Age < 65 years N = 356	Age ≥ 65 years N = 43
Nausea	21%	23%
Headache	26%	21%
Dizziness	17%	21%
Vomiting	7%	7%
Urinary incontinence	6	7%

No similar analyses were performed for the Scharf trial or any other trial grouping.

8.5.5.7 Relationship Between Adverse Events And Gender

In the 5 integrated clinical trials subset analyses were performed based on for adverse events. The analyses for GHB-treated patients showed the following

- The incidence of the total number of adverse events was higher in women (80%) than in men (69%)
- The incidence of serious and severe adverse events, and adverse event discontinuations was similar between the 2 dose groups

These data are illustrated in the following table

Adverse Events	Male N = 171	Female N = 228
All adverse events	116 (68%)	182 (80%)
Serious adverse events	7 (4%)	9 (4%)
Severe adverse events	26 (15%)	43 (19%)
Adverse event discontinuations	15 (9%)	28 (12%)

- The incidence of several specific adverse events in the 2 subsets was as indicated in the table below. As can be seen the incidence of headache, vomiting, nausea and dizziness was higher in women than in men

Adverse event	Women %	Men %
Headache	29	22
Nausea	29	11
Dizziness	24	9
Vomiting	10	3
Urinary incontinence	2	3

8.5.5.8 Relationship Between Adverse Events And Race

No analyses of this relationship were performed

8.6 Laboratory Findings

8.6.1 Extent of Laboratory Testing During Development

The data below refer only to post-treatment laboratory testing.

8.6.1.1 Integrated Clinical Trials

Laboratory parameters analyzed included those listed in the table below

Serum chemistry	Albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, calcium, creatinine, glucose, LDH, phosphorus, potassium, sodium, total bilirubin, and total protein
Hematology	Hematocrit, hemoglobin, total and differential WBC count, RBC count
Urinalysis	pH, specific gravity, glucose, ketones and protein

The frequency at which laboratory parameters were intended to be checked (as per protocol) in these studies is indicated in the following table

Study #	Frequency of safety laboratory testing
OMC-GHB-2	Screening, baseline and weekly during the 4 weeks of study drug administration
OMC-GHB-3	Baseline and every 6 months
OMC-SXB-6	Screening and Month 6
OMC-SXB-7	Baseline and every 6 months thereafter

Scrima	Beginning and end of each 30-day treatment period

Criteria for determining potentially clinically significant laboratory abnormalities have been specified in the study reports

8.6.1.2 Lammers Trial

There was no provision for checking laboratory parameters during this trial

8.6.1.3 Integrated Pharmacokinetic Trials

No post-treatment laboratory parameters were checked during these trials

8.6.1.4 Scharf Trial

Laboratory parameters analyzed included those listed in the table below

Serum chemistry	Albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, bicarbonate, calcium, creatinine, cholesterol, glucose, LDH, phosphorus, potassium, sodium, total bilirubin, total protein and uric acid
Hematology	Hematocrit, hemoglobin, total and differential WBC count, RBC count, platelet count
Urinalysis	pH and specific gravity

Laboratory parameters were to be checked prior to study entry and semi-annually thereafter. Criteria for determining clinically significant laboratory results have been specified in the study report

8.6.2 Selection of Studies for Overall Drug-Control Comparisons And Other Analyses

3 study groupings have been selected

- Controlled clinical trial: OMC-GHB-2 (this was the only controlled trial in which safety laboratory tests were checked after study drug administration)
- Integrated Clinical Trials
- Scharf trial

8.6.3 Standard Analyses and Explorations of Laboratory Data

8.6.3.1 Controlled Clinical Trial OMC-GHB-2

8.6.3.1.1 CHANGES IN LABORATORY RESULTS OVER TIME

The sponsor has provided 2 shift tables for changes in laboratory data from baseline to Visit 6 (the end of the period of double-blind treatment)

8.6.3.1.1.1 Categorical Change In Laboratory Values From Baseline To Week 6

The sponsor's table depicts the number of patients in each treatment group who exhibited a change in specific laboratory values from baseline to Visit 6 that fell into one of the following 3 categories: "normal to abnormal", "abnormal to normal" and "no change" (i.e., no categorical change).

The following table which I have derived from the sponsor's larger table depicts the number of patients who moved from normal to abnormal in each treatment group

Laboratory Parameter	Treatment Group (n = number randomized)			
	Placebo (n =34)	GHB 3 g (n = 34)	GHB 6 g (n = 33)	GHB 9 g (n = 35)
Albumin	1	1	1	1
Alkaline phosphatase	1	1	1	0
SGPT	0	0	1	0
SGOT	0	1	0	0
LDH	0	0	2	0
Phosphorus	2	1	1	0
Total bilirubin	4	3	1	2
Total protein	0	0	0	0
Sodium	1	0	0	0
Potassium	1	0	0	1
Hemoglobin	3	0	0	0
Hematocrit	2	2	0	1
White blood cell count	2	0	0	1
Red blood cell count	2	0	0	0
Neutrophils	2	1	1	2
Lymphocytes	3	2	1	2
Monocytes	1	0	0	1
Eosinophils	0	0	0	0
Basophils	2	3	2	5
Urinary pH	0	0	0	0
Urinary specific gravity	0	0	0	0
Urinary protein	4	2	6	4
Urine glucose	0	0	0	0
Urine ketones	0	1	1	1
Urine occult blood	1	2	2	1
Urine white blood cells	1	0	2	1
Urine red blood cells	2	1	0	0
Urine squamous epithelial cells	1	0	0	0
Urine hyaline casts	1	0	0	0
Urine crystals	0	0	0	0

As the above table indicates

- Very small numbers of patients in each treatment group showed normal to abnormal changes in individual laboratory parameters
- There were no striking differences between the individual GHB groups and the placebo group; neither was there a tendency to a dose response in each treatment group

Note: A maximum of 29 patients in each treatment group had records of individual laboratory parameters for both baseline and Week 6

8.6.3.1.1.2 Mean Change In Laboratory Values From Baseline To Week 6

This sponsor's table depicts the mean change (and standard deviation) from baseline to Week 6 for each laboratory parameter.

The following table which is extracted from the sponsor's table shows the mean change only for individual laboratory parameters in each treatment group

Laboratory Parameter	Treatment Group (n = number randomized)			
	Placebo (n =34)	GHB 3 g (n = 34)	GHB 6 g (n = 33)	GHB 9 g (n = 35)
Albumin	-0.10	-0.09	0.14	0.06
Alkaline phosphatase	0.07	-0.21	-4.52	-0.78
SGPT	0.62	-4.62	-4.14	-5.70
SGOT	-1.21	-3.03	-1.86	-1.15
LDH	-1.59	-10.0	4.0	-4.74
Phosphorus	0.25	-0.05	0.07	0.11
Total bilirubin	0.04	-0.07	-0.03	-0.06
Total protein	-0.02	-0.02	0.02	-0.07
Sodium	0.17	-0.07	0.24	-0.19
Potassium	-0.06	-0.09	-0.01	-0.12
Hemoglobin	-0.01	0.21	0.11	-0.15
Hematocrit	-0.42	0.50	0.79	-0.11
White blood cell count	0.20	-0.19	-0.40	-0.53
Red blood cell count	-0.04	0.04	0.05	-0.07
Neutrophils	1.19	-1.10	0.06	-3.55
Lymphocytes	-0.81	1.70	1.23	3.80
Monocytes	-0.08	-0.38	-0.36	-0.15
Eosinophils	-0.11	-0.11	-0.67	-0.11
Basophils	-0.28	-0.10	-0.32	-0.01
Urinary pH	-0.02	0.04	0.52	0.67
Urinary specific gravity	0.00	0.00	0.00	0.00
Urine white blood cells	11.36	-0.33	0.75	-0.04
Urine red blood cells	88.93	0.37	-0.75	-4.27
Urine squamous epithelial cells	0.46	0.41	0.50	0.38
Urine hyaline casts	-0.11	0.00	0.00	0.00

The above table indicates that

- Mean changes in individual treatment groups were minimal and clinically insignificant
- There were no prominent differences between the individual GHB groups and the placebo group; neither was there a tendency to a dose response in the GHB groups

Note: A maximum of 29 patients in each treatment group had records of individual laboratory parameters for both baseline and Week 6

8.6.3.1.2 LABORATORY ADVERSE EVENTS

Laboratory abnormalities that occurred in patients who eventually received study medication, and were determined by the investigator to be abnormal and clinically significant, were considered adverse events and are summarized in the following table. I have used the patient data listings in preparing this table. Note that the study drug was administered only between Visits 4 and 6

Patient ID #	Treatment Group	Laboratory Abnormality	Comments
512	Placebo	Leukocytosis in urine	Abnormality present only at Visit 5; normal at all other visits including Visit 6
1505	Placebo	Elevated alkaline phosphatase, blood glucose and total white blood cell count	Mild elevations present at all visits including screening visit
1509	Placebo	Trace occult blood in urine Mild increase in urine red cells	Trace occult blood present at Visits 2 and 5; increased urine red cells present only at Visit 5
1604	Placebo	Elevated serum potassium	Serum potassium 5.3 meq/L at Visit 5, normal by Visit 6
411	GHB 3 g	Anemia	Mild anemia (hematocrit 35.3 and 36.5 at Visits 3 and 4)
1610	GHB 3 g	Low serum potassium	Serum potassium 3.6, 3.4 , 3,3 and 3.4 meq/L at Visits 3, 4, 5 and 6, respectively
506	GHB 6 g	Proteinuria	Mild proteinuria at Visits 1 and 3; normal at other times
1204	GHB 6 g	Elevated ALT and AST	Mild elevations in ALT and AST (< 2 x upper limit of normal) at Visits 2 and 3 only
1502	GHB 6 g	Elevated uric acid and glucose	Mild elevation in blood glucose (123 - 129 mg/dl) at Visits 3 and 5. Mild elevation in uric acid (max 7.7 mg/dl) at Visits 3, 5 and 7
1302	GHB 9 g	Anemia Abnormal urinalysis	Mild anemia at Visit 1 Mild proteinuria and trace occult blood at Visits 2 and 6; hyaline casts at Visit 7

As the table indicates, in not a single instance could a laboratory abnormality in a patient who received GHB be attributed to the drug

8.6.3.2 Integrated Clinical Trials

8.6.3.2.1 CATEGORICAL CHANGES IN LABORATORY TESTS FROM BASELINE TO LAST OBSERVATION

The sponsor's table depicts the number of patients in each treatment group [placebo, and 5 Xyrem® dose groups based on last dose(3 g/day, 4.5 g/day, 6 g/day, 7.5 g/day and 9 g/day)] who exhibited a change in specific laboratory values from baseline to last observation that fell into one of the following 9 categories

Normal to normal	Low to normal	High to normal
Normal to high	Low to low	High to low
Normal to low	Low to high	High to high

For all laboratory parameters, the majority in each dose group (≥ 67%) was in the "normal to normal" category. The percentage with changes in all the other categories in each dose group was in the vast majority of instances very small. No dose-response was readily evident. Moreover, these comparisons are not randomized and vary in the duration of exposure to study drug; they therefore do not carry as much significance as those for a OMC-GHB-2. The significance of these comparisons is therefore small.

The only possibly noteworthy change was in serum calcium; a shift from normal to low was seen in 14/132 (10.6 %) of all patients who had this test done. The distribution of this change across dose groups is illustrated in the following table

Dose Group	Placebo	3 g/day	4.5 g/day	6 g/day	7.5 g/day	9 g/day	Total
Number With Change	0	4	2	3	0	5	14
Total number in dose group	3	16	11	45	14	43	132

None of these patients discontinued treatment on account of the change in serum calcium and there is no evidence that this change was correlated with any symptoms or clinical signs.

8.6.3.2.2 MEAN CHANGES IN LABORATORY VALUES FROM BASELINE TO LAST OBSERVATION

I have reviewed the sponsor's tables which compare the mean changes in hematology, chemistry and urinalysis parameters in Xyrem®-treated patients, based on last dose (5 dose groups: 3 g/day, 4.5 g/day, 6 g/day, 7.5 g/day and 9 g/day) with the corresponding mean changes in those treated with placebo. These changes were very small, clinically insignificant and comparable across treatment groups. No clear dose-response was seen with the comparisons. Since the treatment groups are not randomized and vary in their duration of exposure to study drug; the number in the placebo group represents those treated exclusively with placebo and is exceedingly small (n=3); drug-placebo comparisons are therefore not reasonable. Since the significance of these comparisons is minimal I have not reproduced the sponsor's tables

8.6.3.2.3 POTENTIALLY CLINICALLY SIGNIFICANT LABORATORY RESULTS

These are summarized in the next 2 tables which I have copied from the Integrated Summary of Safety. The following are noteworthy

- An increase in transaminases (SGOT and/or SGPT) in a small number of patients (all increases were < 10 x baseline). In only one of these patients (# 0214; see Section 8.3.1.6) was this increase considered a serious adverse event and/or a reason for GHB discontinuation
- None of the other potentially clinically significant laboratory changes seen below were considered serious adverse events or led to treatment discontinuation.
- There were no laboratory adverse events with a frequency of ≥ 5%

Note that there are no further details supplied or explanations offered for the potentially clinically significant laboratory abnormalities noted in the table below: these include several apparent instances of marked hypoglycemia.

Laboratory Parameter (clinically significant range)		Last Sodium Oxybate Dosage (g/d)	Baseline	Post-Baseline	
Patient Number	Trial[a]			Study Day[b]	Result
Hematology (N = 1)					
Hemoglobin (> 3 g/dL decrease and absolute values < 12.0 g/dL)					
0814	GHC-GHB-3	4.5	16.6	391	11.5
Clinical Chemistry (N = 26)					
ALT (SGPT) (≥ 100% increase and absolute values > 75 IU/L)					
0102	GHC-GXB-7	6.0	29	848	262
0214	GHC-GXB-6	9.0	60	877	368
0507	GHC-GHB-3	7.5	39	436	109
		7.5	39	716	88
	GHC-GXB-7	7.5	39	750	86
1610	GHC-GHB-3	9.0	86	398	248
1709	GHC-GHB-3	4.5	23	386	76
AST (SGOT) (≥ 100% increase and absolute values > 75 IU/L)					
0214	GHC-GXB-6	9.0	44	877	180
1610	GHC-GHB-3	9.0	38	398	76
Creatinine (≥ 66% increase and absolute values > 1.5 mg/dL)					
0127	GHC-GHB-3	9.0	0.8	241	1.6
0507	GHC-GHB-3	7.5	1	220	1.7
1501	GHC-GHB-3	6.0	1	720	1.6
	GHC-GXB-7	3.0	1	725	1.8
1505	GHC-GHB-3	6.0	0.8	880	1.7
	GHC-GXB-7	6.0	0.8	880	1.7
Glucose (≥ 33% decrease and absolute values < 70 mg/dL; ≥ 75% increase and absolute values > 200 mg/dL)					
0108	GHC-GHB-3	6.0	229	424	398
0115	GHC-GHB-3	9.0	104	618	217
0410	GHC-GHB-3	7.5	178	201	307
0504	GHC-GHB-3	4.5	86	273	52
0535	GHC-GXB-7	6.0	112	208	85
0603	GHC-GXB-6	6.0	68	210	56
0608	GHC-GHB-3	9.0	76	206	69

Laboratory Parameter (clinically significant range)		Last Sodium Oxybate Dosage (g/d)	Baseline	Post-Baseline	
Patient Number	Trial[a]			Study Day[b]	Result
Clinical Chemistry (N = 26) (continued)					
Glucose (continued)					
0809	OMC-GHB-3	3.0	92	222	54
0810	OMC-GHB-3	4.5	87	219	12
0814	OMC-GHB-3	4.5	101	205	34
		4.5	101	716	66
	OMC-SXB-7	4.5	101	716	66
		4.5	101	903	65
0815	OMC-GHB-2	3.0	87	33	28
0820	OMC-GHB-2	6.0	42	17	16
	OMC-GHB-3	6.0	42	331	15
0844	OMC-SXB-6	3.0	92	53	58
1509	OMC-GHB-3	6.0	168	278	226
		6.0	168	650	353
	OMC-SXB-7	6.0	168	650	409
1708	OMC-GHB-3	6.0	144	650	49
	OMC-SXB-7	6.0	144	650	48
2136	OMC-SXB-6	6.0	107	176	68
3841	OMC-SXB-6	9.0	124	169	60
Total bilirubin (≥ 100% increase and absolute values > 1.5 mg/dL)					
0208	OMC-GHB-3	9.0	1.1	213	3.5
0504	OMC-GHB-3	4.5	0.4	336	1.9
1503	OMC-GHB-2	6.0	0.3	15	2.1

[a] Trial during which post-baseline value was obtained.
[b] Day relative to start of treatment (trial duration).

8.6.3.3 Scharf Trial

8.6.3.3.1 MEAN CHANGES IN LABORATORY VALUES FROM BASELINE TO SPECIFIC TIMEPOINTS

The sponsor has provided tables containing descriptive statistics for absolute values and changes in laboratory parameters at specific successive timepoints. These values (absolute and change) are not categorized according to last dose.

On review of these tables it is apparent that across all laboratory parameters, both the mean absolute values and the mean changes are unremarkable.

8.6.3.3.2 PROPORTION OF PATIENTS WITH ABNORMAL TESTS AT SPECIFIC TIMEPOINTS

The sponsor has provided tables specifying the number and percentage of patients with clinically significant abnormalities of laboratory tests for a number of specific timepoints, as well as listings of the patients with abnormalities.

On review of the tables and listings it appears that

- The proportion of patients having clinically significant laboratory abnormalities at each time point is generally small (0 – 16.7% with the vast majority < 5%) except in the case of abnormal serum bicarbonate. The proportion of patients with an abnormal serum bicarbonate at specific timepoints is illustrated in the following table