#	Claims of the '059 Patent
	confirming receipt by the patient of the prescription drug; and generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.
2	The method of claim 1, wherein the exclusive central pharmacy controls the exclusive computer database.
3	The method of claim 1, comprising selectively blocking shipment of the prescription drug to a patient.
4	The method of claim 1, wherein an abuse pattern is associated with a patient, and shipment is blocked upon such association.
5	The method of claim 1, wherein the prescription drug comprises gamma hydroxy butyrate (GHB).
6	A computerized method of distributing a 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 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; 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; 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 received and/or read prior to providing the 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 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; confirming receipt by the patient of the prescription drug; and

#	Claims of the '059 Patent
	generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.
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.
8	The computerized method of claim 7, wherein the another pharmacy places controls on the distribution of the prescription drug, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of the prescription drug by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription drug, and limiting the prescription to a supply of limited duration.
9	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 received and/or 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.

#	Claims of the '059 Patent
10	The computerized method of claim 9, wherein providing GHB to the patient comprises the central pharmacy authorizing the prescription drug to be dispensed to the patient by another pharmacy.
11	The computerized method of claim 10, wherein the another pharmacy places controls on the distribution of GHB, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of GHB by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for GHB, flagging early requests to refill the GHB, and limiting the prescription to a supply of limited duration.
12	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 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 received and/or 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 or sending by courier 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.
13	A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:

#	Claims of the '059 Patent
	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 received and/or 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 or sending by courier 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.
14	A computerized method of distributing a 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 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; 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;

#	Claims of the '059 Patent
	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 received and/or read prior to providing the prescription drug to the patient; 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; 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 confirming receipt by the patient of the prescription drug.
15	The computerized method of claim 14, 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.
16	The computerized method of claim 15, wherein the another pharmacy places controls on the distribution of the prescription drug, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of the prescription drug by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription drug, and limiting the prescription to a supply of limited duration.

B. LEVEL OF SKILL IN THE ART OF THE '059 PATENT

The subject matter of the '059 patent falls within the field of designing computer systems. Depending on the claim, the person of ordinary skill in this field would be a programmer, or a systems analyst/programmer. Such an individual would have a Bachelor's Degree in Computer Science and several years of experience in the field. *E.I. DuPont de Nemours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), *aff'd* 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein and would have the capability to draw inferences from them.

C. CLAIM CONSTRUCTION OF THE '059 PATENT

One of ordinary skill in the art and a court would interpret the claims of the '059 patent according to their plain and ordinary meaning unless otherwise specified herein.

D. NONINFRINGEMENT OF THE '059 PATENT

Par does not directly infringe any claim of the '059 patent under 35 U.S.C. § 271(a) because Par does not perform the claimed method. Notably, independent claims 1, 6, and 14 describe "a computerized method of distributing a prescription drug " which requires that "an exclusive central pharmacy" receive "all prescription requests, for any and all patients being prescribed the prescription drug ." Independent claims 9, 12, and 13 are similar, describing "a computerized method of distributing gamma hydroxy butyrate (GHB)" which requires that "an exclusive central pharmacy" receive "prescription requests for GHB, for any and all patients being prescribed GHB." Par will not infringe these claims if granted approval for its generic product, because it will not control "an exclusive central pharmacy" that receives all of the prescriptions for the drug gamma hydroxyl butyrate or any other prescription drug.

Par further does not infringe claims 5, and 9-13, as they require the distribution of "gamma hydroxyl butyrate," whereas Par's proposed product contains sodium oxybate (sodium gamma-hydroxybutyrate).

Par also does not contributorily infringe under 35 U.S.C. § 271(c) because the claimed method has noninfringing uses. Furthermore, Par does not infringe claims 1-6 of the '107 patent under § 271(b) because the Par has a good faith belief that the '059 patent is invalid, which negates the requisite intent for induced infringement. *Commil USA, LLC v. Cisco Systems, Inc.*, 720 F.3d 1361, 1364 (Fed. Cir. Jun. 25, 2013) ("we find that Cisco's evidence of a good-faith belief of invalidity may negate the requisite intent for induced infringement.")

E. OBVIOUSNESS OF THE '059 PATENT

1. The Scope and Content of the Prior Art

The earliest possible effective U.S. filing date for the '059 patent is December 17, 2002, based on the filing date of U.S. Application 10/322,348 for the parent, '730 patent. The prior art is described in section X(E)(1), above.

2. Obviousness of the '059 Patent in Light of Borsand (Claim 1)

Claim 1 of the '059 patent is obvious over Borsand, which describes each of the elements of claim 1 in combination with other prior art references. Claim 1 is directed to a computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy. The claim essentially requires patients to obtain the prescription drug from a single, central pharmacy that maintains an exclusive computer database of information, thus allowing the pharmacy to perform checks of potential abuse before delivering the drug to the patient. The method of claim 1 controls distribution by subjecting the single, central pharmacy to a multitude of controls before the drug is delivered.

Claim 1 of the '059 Patent	Borsand
A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:	Borsand states that the "invention relates to a computer based system for tracking information related to pharmaceutical prescriptions." (Borsand ¶ 10.)

Claim 1 of the '059 Patent	Borsand
	Borsand further discloses a system that allows for "pharmaceutical information to be stored only once and in a centralized location accessible by the appropriate parties." (Borsand ¶ 3.)
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;	A computer system or a computer, as described in Borsand, inherently includes a computer processor for processing data. Borsand teaches an exclusive central computer system, which contains patient and doctor information. Borsand discloses a prescription subsystem where "prescriptions are only issued by a certain subset of health care providers, such as physicians ...." Processing a prescription requires inputting "patient record which includes patient information relevant to pharmaceutical selection." Each doctor must use a unique "UserID" and a patient is assigned a unique "PatientID." (Borsand ¶¶ 57-58; Figure 4b). Borsand addresses prior art deficiencies where "[i]t would be desirable for pharmaceutical information to be stored only once and in a **centralized location** accessible by the appropriate parties." (Borsand ¶ 3).
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;	Borsand teaches an exclusive computer database associated with an exclusive computer system. For example, Borsand discloses a system that allows for "pharmaceutical information to be stored only once and in a centralized location accessible by the appropriate parties." (Borsand ¶ 3). Borsand teaches that all relevant data is housed in a computer that "can be a single centralized computer or server, a single network ...." (Borsand ¶ 31.) According to Borsand, in the preferred embodiment, "all pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate regulations, policies, and guidelines." (Borsand ¶ 43.) Borsand also teaches that the relevant data must be entered in the system by the provider, *see, e.g.*, Borsand ¶¶ 58; 108, or the pharmacist. (*See* Borsand ¶ 86 ("If the pharmacist fills a pharmaceutical prescription, that information needs to be memorialized at 40.02 or its related pages.").)
processing with the computer processor all prescriptions for the prescription drug only by the exclusive central pharmacy using only the	Borsand teaches that the "invention relates to a computer based system for tracking information related to pharmaceutical prescriptions."

Claim 1 of the '059 Patent	Borsand
central database;	(Borsand ¶ 10). A computer inherently includes a computer processor for processing data. Borsand teaches that, in the preferred embodiment, "all pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate regulations, policies, and guidelines." (Borsand ¶ 43.)
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;	Borsand teaches that the "invention relates to a computer based system for tracking information related to pharmaceutical prescriptions." (Borsand ¶ 10). A computer inherently includes a computer processor for processing data. Borsand teaches a system that can "**check** of for unfavorable pharmaceutical interactions and allergic reactions, **prevent misuse of a prescription**, monitor the filling and re-filling of a prescription, as well as cancel a prescription after it has been issued by a provider." (Borsand Abstract.) According to Borsand's prescription subsystem, "prescriptions are only issued by a certain subset of health care providers, such as physicians ...." Processing a prescription requires inputting "patient record which includes patient information relevant to pharmaceutical selection." Each doctor must use a unique "UserID" and a patient is assigned a unique "PatientID." (*See* Borsand ¶¶ 57-58; Fig. 4b)
confirming with a patient that educational material has been received and/or read prior to shipping the prescription drug;	While Borsand does not explicitly require confirming that the patient has received and/or read the educational material "prior" to shipping the prescription drug, the FDA Safety Review (*See* obviousness analysis *supra*) and Califona cure this deficiency: Califano requires "confirming with the patient that educational material has been read prior to providing the drug to the patient." (*See* Califano ¶ 84; Examiner's Answer OA, dated 10/18/06.)
checking the exclusive computer database for potential abuse of the prescription drug;	The system of Borsand provides "functionality for tracking pharmaceutical, prescription and related information," where "tracking can be in a proactive and real-time manner, or in the form of reports and analysis ...." (Borsand ¶ 34). Any abuse or violation can be detected by the system which "can be configured to not allow the attempted conduct, or to allow the conduct,

Claim 1 of the '059 Patent	Borsand
	but generate a report relating to the undesired activity." *Id.* Further, Borsand discloses that the pharmaceutical subsystem (part of the overall exclusive central computer system) re-evaluates the prescription before the prescription is filled or sent to a payor, where "medical aspects of a prescription can also be reviewed, so that the appropriateness of the selected pharmaceutical can be confirmed as it relates to ... other patient attributes that could affect the desirability of filling a particular prescription." (Borsand ¶ 87). Borland discloses in multiple places that desirability of filling prescriptions may be tied to misuse of pharmaceuticals; for example, patient attributes includes patient's refill behavior. *Id.* at ¶ 53.
mailing or sending by courier 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;	Borsand discloses that in filling a prescription for a drug, an event can trigger a modification or cancellation of the prescription, where such an event includes "evidence of fraud, misuse, or redundancy on the part of a provider, pharmacist, or patient." (Borsand ¶ 120.) While Borsand does not explicitly disclose mailing or sending via courier the prescription drug, the Video, Briefing Booklet, FDA Safety Review, and Moradi disclose mailing or sending via courier the prescription drug if no abuse is found. (*See* obviousness analysis of the Video, Briefing Booklet, and the FDA Safety Review *infra*; Moradi ¶¶ 6, 43, 45; Examiner's Answer, OA dated 10/18/06.)
confirming receipt by the patient of the prescription drug; and	Borsand discloses that the system allows monitoring of whether or not a patient actually fills the prescription. (Borsand ¶ 56.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	Borsand discloses that "[i]f a patient 22, provider 30, pharmacist 40, or PBM 50 attempts an action that is not in accordance with the predefined rules 34 of the payor 60, the system 20 can be configured to not allow the attempted conduct, or to allow the conduct, but **generate a report** 42 relating to the undesirable activity." (Borsand ¶ 54.)

The examiner allowed claim 1 because the prior art considered by the examiner did not teach that all prescriptions will be received by an exclusive computer system/database.

> 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/sent only if no potential abuse is found by the patient to whom the prescription drug is prescribed *and* the doctor/authorized prescriber prescribing the prescription drug.

(Notice of Allowance, Dec. 21, 2010). The examiner, however, never considered Borsand. Instead, the examiner found that "the closest prior art of record" was Moradi (US 2004/0019794 A 1), Lilly et al. (US 2004/0176985 A1), Melker et al. (US 2002/0177232 A1), and Ukens ("Specialty Pharmacy"). Notably, the examiner found that all the elements of claim 1 are disclosed in combination in the prior art of record rendering the alleged invention obvious, except an exclusive central computer system/database that receives all prescriptions from all patients, controls the distribution of the prescriptions, and authorizes distribution of the prescriptions. Furthermore, Borsand, alone, also teaches an exclusive computer system/database that performs the functions recited in claim 1.

"[O]nce a challenger has presented a *prima facie* case of invalidity, the patentee has the burden of going forward with rebuttal evidence." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359–60 (Fed. Cir. 2007). It is the patentee's obligation to present evidence of secondary considerations, if any, to rebut a *prima facie* case of obviousness. The '059 patent provides no specific evidence of secondary considerations of non-obviousness. Secondary considerations of non-obviousness do not control the analysis where there is an otherwise strong case of obviousness, such as one based upon art not considered during prosecution. *Tokai Corp. v. Easton Enterprises, Inc.*, 632 F.3d 1358 (Fed. Cir. 2011) ("A strong case of prima facie obviousness, such as that presented here, cannot be overcome by a far weaker showing of objective indicia of nonobviousness."); *Sandt Tech. v. Resco Metal & Plastics*, 264 F.3d 1344, 1355 (Fed. Cir. 2001) ("We see no error in the district court's conclusion . . . that the secondary considerations cannot overcome the strong prima facie evidence of obviousness presented."). Any evidence of secondary considerations is insufficient to overcome the strong case of *prima facie* obviousness of the claimed subject matter.

3. Obviousness of the '059 Patent in Light of the Briefing Booklet (Claim 1)

Claim 1 of the '059 is obvious in light of the Briefing Booklet. See chart below for each disclosed element and analysis thereof.

Claim 1 of the '059 Patent	Briefing Booklet
A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:	The Briefing Booklet generally teaches use of a database using an exclusive specialty pharmacy. The reference to "real-time data" implies a computer processor managing the database. (Briefing Booklet at 20.)
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	In Orphan Medical's Briefing Booklet, it teaches use of a database using an exclusive specialty pharmacy. The reference to "real-time data" implies a computer processor managing the database.

Claim 1 of the '059 Patent	Briefing Booklet
information identifying patients, the prescription drug, and various credentials of the any and all medical doctors;	"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." (Briefing Booklet at 15). "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." (Briefing Booklet at 20.)
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;	The Briefing Booklet teaches data collection into the central database. The reference to "data collection" necessary includes entering the information into the central database. "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." (Briefing Booklet at 19.)
processing with the computer processor all prescriptions for the prescription drug only by the exclusive central pharmacy using only the central database;	The Briefing Booklet's reference to "real-time data" implies a computer processor processing the data.

Claim 1 of the '059 Patent	Briefing Booklet
	The Briefing Booklet teaches under the section entitled "Prescribing Options Selected" that the closed-loop distribution system controls distribution by controlling who prescribes Xyrem and controlling how it is prescribed. This, according to the Briefing Booklet, is achieved, in part, "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 of Xyrem. (Briefing Booklet at 14.)
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;	The Briefing Booklet discloses that "[t]he 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." The reference to real-time data implies a computer processor managing the data. (Briefing Booklet at 20.) The Briefing Booklet discloses that upon receipt of a prescription from the physician, the central pharmacy will "verify physician's eligibility by checking the AMA, DEA, or State Medical Board on-line databases" to ensure that "the prescription was written by a "real" physician with current privileges to prescribe controlled medications." (Briefing Booklet at 19.) The Briefing Booklet discloses that the collection of 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.**" (Briefing Booklet at 15).
confirming with a patient that educational material has been received and/or read prior to shipping the prescription drug;	The Briefing Booklet teaches that "[o]nce 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 point's in-between." (Briefing Booklet at 20.) While the Briefing Booklet does not explicitly require confirming that the patient has received and/or read the educational material "prior" to shipping the prescription drug, the FDA Safety Review (*See* obviousness analysis *infra*) and Califano cure this deficiency: Califano requires "confirming with the patient that educational

Claim 1 of the '059 Patent	Briefing Booklet
	material has been read prior to providing the drug to the patient." (*See* Califano ¶ 84; Examiner's Answer OA, dated 10/18/06.)
checking the exclusive computer database for potential abuse of the prescription drug;	The Briefing Booklet discloses that "[t]he 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." (Briefing Booklet at 20.)
mailing or sending by courier 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;	The Briefing Booklet discloses a distribution system that requires physician verification process "to catch any prescriptions written on stolen or counterfeit prescription pads" and entering patient information in a "patient registry which also aids in diversion prevention" before the Xyrem shipping process begins, where Xyrem is mailed via Federal Express. (Briefing Booklet at 19-20.)
confirming receipt by the patient of the prescription drug; and	The Briefing Booklet discloses a distribution system that requires the exclusive central pharmacy pharmacist to contact the patient to confirm receipt of the Xyrem prescription. (Briefing Booklet at 20.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	The Briefing Booklet teaches that "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." (Briefing Booklet at 16.) The Briefing Booklet further teaches that "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." (Briefing Booklet at 15.)

4. Obviousness of the '059 Patent in Light of the FDA Safety Review (Claim 1)

Claim 1 of the '059 is obvious in light of the Briefing Booklet. See chart below for each disclosed element and analysis thereof.

Claim 1 of the '059 Patent	FDA Safety Review

Claim 1 of the '059 Patent	FDA Safety Review
A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:	The FDA Safety Review teaches a method of distributing a prescription drug (Xyrem®) under exclusive control of an exclusive central pharmacy (or distributor). (FDA Safety Review at 108). Apparently, Orphan Medical proposed Nova Factor to be the central pharmacy.
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;	The FDA Safety Review describes a "closed-loop distribution system," wherein "Xyrem® will NOT be placed in retail pharmacy outlets," and instead, the document describes a "primary and exclusive distributor of Xyrem®." (*Id.* at 108). The FDA Safety Review teaches that every patient and physician allowed to prescribe the prescription drug (Xyrem®) will be registered into the exclusive central database. (FDA Safety Review at 110).
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;	The FDA Safety Review teaches that a single, sole, and secure database will store the relevant information. "Every patient and prescribing physician will be registered with [the exclusive distributor] in 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." (FDA Safety Review at 110.)
processing with the computer processor all prescriptions for the prescription drug only by the exclusive central pharmacy using only the central database;	FDA safety review teaches that the exclusive central pharmacy (or distributor) will control distribution by being the primary and exclusive distributor, maintaining inventory and distribution records, and maintaining patient registry. (FDA Safety Review 108-109.)
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;	The FDA Safety review teaches that the exclusive central pharmacy will verify that the physician is eligible to prescribe Xyrem®, including checking whether the physician has an active DEA number and whether any actions are pending against the physician. (FDA Safety Review at 109.)
confirming with a patient that educational material has been received and/or read prior to shipping the prescription drug;	The FDA Safety Review discloses that the Office of Post-Marketing Drug Risk assessment recommended that confirmation of whether the patient has read and fully understands the education material should be received by Nova

Claim 1 of the '059 Patent	FDA Safety Review
	Factor "**prior to the initial dispensing of the drug.**" (FDA Safety Review at 114-115.)
checking the exclusive computer database for potential abuse of the prescription drug;	The FDA Safety Review notes in several in several places checking for potential for abuse, misuse, or diversion: prescriptions refills before anticipation date will be questioned (FDA Safety Review at 110); lost, stolen, destroyed, or spilled prescription/supply will be documented, flagged, and monitored (*Id.*); noting prescribing frequency (*Id.*); among others.
mailing or sending by courier 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;	The FDA Safety Review discloses that "once approval has been established, (b)(4) [exclusive specialty pharmacy] will … arrange shipment though (b)(4) or a similar carrier." (FDA Safety Review at 109.) The approval process requires verification of eligibility to prevent potential abuse. (*Id.*)
confirming receipt by the patient of the prescription drug; and	The FDA Safety Review discloses that "[r]eceipt of the drug by the patient will be ensured through … a phone call by the pharmacy to the patient." (FDA Safety Review at 109.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	The FDA Safety Review notes in several places potential for abuse, misuse, or diversion: prescriptions refills before anticipation date will be questioned (FDA Safety Review at 110); lost, stolen, destroyed, or spilled prescription/supply will be documented, flagged, and monitored (*Id.*); noting prescribing frequency (*Id.*); among others. While the FDA Safety Review does not explicitly disclose generating periodic reports, the Video, Borsand, Briefing Booklet, and Lilly, among others, disclose generating periodic reports to evaluate potential diversion patterns. (*See* obviousness analysis of the Video, Briefing Booklet, and the FDA Safety Review; Lilly ¶¶ 11, 33, 54, 57, 58, 61, 69; Examiner's Answer, OA dated 06/19/06.)

5. Obviousness of the '059 Patent in Light of the Video (Claim 1)

Claim 1 of the '059 patent is obvious over the Video.

Claim 1 of the '059 Patent	Video
A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:	The Video shows a "shot of pharmacy employee picking up prescription fax and sitting down at a computer to verify physician's eligibility." (Video ¶ 21). The illustration of a computer in the Video teaches using a computer to control distribution.

Claim 1 of the '059 Patent	Video
	The Video discloses a single, centrally-located specialty pharmacy that controls distribution, documentation, and security through a closed-loop distribution system. (Video ¶¶ 3-5.)
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;	The Video teaches using a computer to process prescription requests. A computer inherently includes a computer processor. The Video discloses a single, centrally-located specialty pharmacy that controls distribution, documentation, and security through a closed-loop distribution system. The prescriptions are sent to the central pharmacy, which verifies that the "physician is an Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data ... to check if there are any pending or previous actions against the physician." (Video ¶¶ 14; 21.) The single, specialty pharmacy stores data about prescriptions by patients; thus, it follows that the prescription sent by the physician includes patient identifying information. (*See, e.g.*, Video ¶ 24.)
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;	The Video teaches that all "data about inventory, physicians, reimbursements, patients, and delivery" is stored in one efficient and quickly-accessible location [single, specialty pharmacy]." (Video ¶ 24.) Further, the Video teaches that the "closed-loop distribution system … will 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." (Video ¶ 14.)
processing with the computer processor all prescriptions for the prescription drug only by the exclusive central pharmacy using only the central database;	The Video discloses that the secure distribution system of Xyrem® is achieved through a specialty pharmacy, which "is a single centrally located facility that stores "all the data about inventory, physicians, reimbursement, patients, and delivery in one efficient and quickly-accessible location." (Video ¶ 24). The Video teaches that the single, specialty pharmacy uses a computer, which inherently includes a computer processor.
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;	The Video teaches using a computer to process the specialty pharmacy prescription requests. A computer inherently includes a computer processor.

Claim 1 of the '059 Patent	Video
	The Video discloses that the prescriptions are sent to the central pharmacy, which verifies that the "physician is an Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data ... to check if there are any pending or previous actions against the physician."
confirming with a patient that educational material has been received and/or read prior to shipping the prescription drug;	The Video teaches sending a patient educational material, "Patient Success Program." (Video ¶ 31.) While the Video does not explicitly require confirming that the patient has received and/or read the educational material "prior" to shipping the prescription drug, the FDA Safety Review (*See* obviousness analysis *supra*) and Califano cure this deficiency: Califano requires "confirming with the patient that educational material has been read prior to providing the drug to the patient." (*See* Califano ¶ 84; Examiner's Answer OA, dated 10/18/06.)
checking the exclusive computer database for potential abuse of the prescription drug;	The Video discloses that the central pharmacy staff 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." (Video ¶ 14). The Video also discloses that the specialty pharmacy will keep track of anomalous patient requests to fill their prescriptions. (*Id.* at 38.)
mailing or sending by courier 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;	The Video discloses that Xyrem® will be "shipped overnight by Federal express utilizing a tracking system designed specifically for the specialty pharmacy." (Video ¶ 30.) The Video teaches that during "the process of verification and documentation, if any data or behavior suggest the possibility that Xyrem® may be used inappropriately, the specialty pharmacy is empowered to contact the appropriate authorities." (Video ¶ 29.)
confirming receipt by the patient of the prescription drug; and	The Video teaches that receipt of Xyrem® and educational materials is verified by a telephone call placed to the patient where "the specialty pharmacy will confirm receipt of the Xyrem prescription and the Patient Success program." (Video ¶ 35.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	The Video discloses that the closed-loop distribution system "will be able to **generate data**, recording prescribers, patients and dosing that could provide information for any possible investigations and prosecutions for state and

Claim 1 of the '059 Patent	Video
	federal authorities." (Video ¶ 14).

6. Application of the Prior Art (Claims 2-16)

Claim 2 of the '059 patent is directed to the method of claim 1 "wherein the exclusive central pharmacy controls the exclusive central database." References not considered by the Examiner disclose that the exclusive central pharmacy controls the exclusive central database. For example, the FDA Safety Review discloses that a method of distributing a prescription drug (Xyrem®) is under exclusive control of an exclusive central pharmacy (or distributor). (FDA Safety Review at 108). Similarly, Borsand discloses that, in the preferred embodiment, "all pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate regulations, policies, and guidelines," where the prescription subsystem limits issuance of prescriptions to certain subset of health providers. (Borsand ¶¶ 3; 50.)

Claim 3 of the '059 is directed to the method of claim 1 "comprising selectively blocking shipment of the prescription drug to a patient." References not considered by the Examiner disclose that shipments of the prescription drug may be selectively blocked. For Example, the FDA Safety Review discloses that if a patient is unavailable to accept a shipment of Xyrem® and execute the required receipt, the package will be returned to the pharmacy. (FDA Safety Review at 109). Similarly, The Briefing Booklet discloses that "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." (Briefing Booklet at 20.)

Claim 4 is directed to the method of claim 1 "wherein an abuse pattern is associated with a patient, and shipment is blocked upon such association." References not considered by the Examiner disclose that prior to shipment of the prescription drug, the verification process will prevent shipment to patients associated with an abuse pattern. For example, the Video teaches that prior to shipping the patient's medication overnight by Federal Express, a process of verification and documentation will allow the specialty pharmacy to determine "if any of the data or behavior suggests the possibility that Xyrem may be used inappropriately." (Video ¶¶ 29-30). Similarly, the FDA Safety Review teaches that Xyrem® will only be shipped once approval has been established, where approval requires verifying eligibility of the physician to prescribe the prescription drug and obtaining a certificate of medical necessity. (FDA Safety Review at 109.)

Claim 5 is directed to the method of claim 1 "wherein the prescription drug comprises gamma hydroxyl butyrate (GHB)." At least the Briefing Booklet and the FDA Safety Review explicitly disclose that the prescription drug is GHB.

Claim 6 is an independent claim, but is similar to claim 1. The preamble in claim 6 recites under "control," instead of under "exclusive control." Claim 6 recites "authorized prescribers" instead of "medical doctors." Clause 2 of claim 6 does not include "requiring entering," but only includes "entering" and additionally recites "wherein the use of the exclusive computer database is required for distribution of the prescription drug." Clause 5 includes "requiring checking" instead of "checking" and additionally recites "potential abuse associated with the patient and the authorized prescriber." Clause 6 recites "providing" instead of "mailing

or sending by courier." However, these differences do not add any limitation that overcomes any of the references discussed above.

For example, an "authorized prescriber" is broader than a "medical doctor." Similarly, "entering" is broader than "requiring entering" and "control" is broader than "exclusive control." Likewise, "providing" is broader than "mailing or sending by courier." Thus, to the extent the references discussed above with respect to claim 1 disclosed the recited limitations, they would also encompass these terms recited in claim 6.

The recitation "wherein the use of the exclusive computer database is required for distribution of the prescription drug" does not add any limitation that overcomes the references discussed with respect to claim 1. For example, Borsand teaches that, in the preferred embodiment, "***all*** pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate regulations, policies, and guidelines." (Borsand ¶ 43).

The differences in Clause 5 do not any add limitation that overcomes the references discussed above with respect to claim 1. For example, the Video discloses that, upon receipt of the prescription, the specialty pharmacy must first verify that the prescribing physician is an Orphan Medical's list of targeted physicians, has an active DEA and State license, and does not have any pending or previous actions. (Video ¶ 21). Similarly, the Briefing Booklet requires that, upon receipt of the prescription, the specialty pharmacy will verify the physician's eligibility to ensure the prescription was written by a "real-physician" and also call the physician's office to obtain patient information for diversion prevention. (Briefing Booklet at 19.)

Claim 7 is directed to the 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." References not considered by the Examiner disclose this limitation. For example, the FDA Safety Review teaches that the specialty pharmacy may ship the prescription to another pharmacy for patient pick-up. (FDA Safety Review at 110).

Claim 8 is directed to the method of claim 7 "wherein the another pharmacy places controls on the distribution of the prescription drug, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of the prescription drug by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription drug, and limiting the prescription to a supply of limited duration." References not considered by the Examiner disclose this limitation. For example, the FDA Safety Review discloses that, where the prescription will be picked up by another pharmacy, the specialty pharmacy must verify that there is a mechanism for the second pharmacy to protect against diversion of the prescription drug. (FDA Safety Review at 110). Further, the FDA Safety Review discloses diversion prevention mechanisms, which include, at least, some of the controls recited in claim 8 to protect against diversion. For example, the FDA Safety Review discloses identifying "physician name, address, telephone and facsimile, DEA and state license numbers" (FDA Safety Review at 110);

verifying that "the physician is eligible to prescribe Xyrem [by checking] the National Practitioner Databank ... including confirming that the physician has an active DEA number and check on whether any actions are pending against the physician" (*Id.* at 109); among others.

Claim 9 is an independent claim and is similar to claim 6. The only difference between claim 9 and claim 6 is that claim 9 is directed to GHB instead of a prescription drug. At least, the Briefing Booklet and FDA Safety Review, disclose that the prescription drug may be GHB. (*See, e.g.*, Briefing Booklet at 18; FDA Safety Review at 7). Thus, for the same reasons claim 6 is rendered obvious, claim 9 is also rendered obvious by the same references.

Claim 10 is directed to the method of claim 9 "wherein providing GHB to the patient comprises the central pharmacy authorizing the prescription drug to be dispensed to the patient by another pharmacy." Claim 10 is similar to claim 7, but is directed to GHB. Thus, for the same reasons claim 7 is rendered obvious, claim 10 is also rendered obvious by the same references.

Claim 11 is directed to the method of claim 9 "wherein the another pharmacy places controls on the distribution of GHB, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of GHB by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription drug, and limiting the prescription to a supply of limited duration." Claim 11 is similar to claim 8, but is directed to GHB. Thus, for the same reasons claim 8 is rendered obvious, claim 11 is also rendered obvious by the same references.

Claim 12 is an independent claim, but is similar to claim 6. Claim 12 is directed to GHB instead of a prescription drug. Clause 5 of claim 12 is limited to the patient, whereas clause 5 of claim 6 is directed to the patient and the authorized prescriber, thus is narrower. Thus, for the same reasons claim 6 is rendered obvious, claim 12 is also rendered obvious by the same references.

Claim 13 is an independent claim, but is similar to claim 9. The differences between claim 13 and claim 9 are that claim 13 includes additional clauses "manufacturing GHB" and "providing manufactured GHB only to the exclusive central pharmacy." However, adding these additional clauses does not overcome the references discussed above. For example, the FDA Safety Review discloses manufacturing GHB and providing the GHB to the central pharmacy (the primary and exclusive distributor of Xyrem®). (FDA Safety Review at 108). Clause 8 of claim 13 recites "mailing or sending by courier," as recited in claim 1, instead of "providing." Thus, for the same reasons claims 1 and 9 are rendered obvious, claim 13 is also rendered obvious by the same references.

Claim 14 is an independent claim, but is similar to claim 6. The differences between claim 14 and 6 are that in clause 5, claim 14 recites "potential abuse by the patient" instead of "potential abuse associated with the patient." In addition, claim 14 does not include the clause "generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns," thus making claim 14 broader than claim 6. Thus, for the

same reasons claim 6 is rendered obvious, claim 14 is also rendered obvious by the same references.

Claim 15 is directed to the method of claim 14 "wherein providing the prescription drug comprises the central pharmacy authorizing the prescription drug to be dispensed to the patient by another pharmacy." Claim 15 is similar to claims 7 and 10. Thus, for the same reasons claims 7 and 10 are rendered obvious, claim 15 is also rendered obvious by the same references.

Claim 16 is directed to the method of claim 14 "wherein the another pharmacy places controls on the distribution of GHB, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of GHB by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription drug, and limiting the prescription to a supply of limited duration." Claim 16 is similar to claims 8 and 11. Thus, for the same reasons claims 8 and 11 are rendered obvious, claim 16 is also rendered obvious by the same references.

F. INELIGIBLE SUBJECT MATTER UNDER 35 U.S.C. § 101

The claims of the '059 patent are invalid under 35 U.S.C. § 101 because the claimed subject matter is not patentable. The claims of the '059 patent do not satisfy the machine-or-transformation test, and are directed to algorithms and abstract ideas *Bilski v. Kappos*, 130 S.Ct. 3218, 3229-30 (2010); *In re Bilski*, 545 F.3d 943, 962-63 (Fed. Cir. 2008).

In the '059 patent, the process is not tied to a particular machine or apparatus. Although the claims include terms like "computerized method" and "computer processor," there is nothing in the specification indicating that a computer is integral to implementing the process. Further, while some of the steps require use of a "computer processor," 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.*, '059 patent, col. 3, lines 10-14.)[37]

The '059 patent claims do not transform an article into a different state or thing. They merely claim a method of distributing sensitive drugs that does not transform or make the drugs any less sensitive. Although some claims require 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. Although the claimed methods refer to periodic reports that are generated to evaluate

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[37] 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).

potential diversion patterns or potential for abuse, misuse, or diversion, this is merely an addition of "non-essential post-solution activity." *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.*, '059 patent, col. 1, lines 6- 7.)

The Federal Circuit has determined that patent claims are abstract when the "steps can be performed in the human mind, or by a human using a pen and paper." *CyberSource*, 654 F.3d at 1372. In the '059 patent, the process is similar to a clearing house in that the method merely requires collecting and organizing data of doctors who are able to prescribe, and the patients who are able to receive, the medication, and organizing the data describing shipments of the medication, and associated marketing material. This process could equally be performed by pencil, paper, and a traditional filing cabinet system.

The steps of the claims in the '059 patent represent common ways that people have used to restrict allocation of materials, where a central controlling entity confirms with a validated third-party authority whether a substance should be delivered to an individual. Without meaningful limits, the claims effectively preempt the fundamental concept itself and foreclose a wide range of inventions that the patentee never conceived. For example, in *Dealertrack*, the Federal Circuit determined that the patentee's claimed process in its simplest form includes three steps: receiving data from one source (step A), selectively forwarding the data (step B, performed according to step D), and forwarding reply data to the first source (step C). *Dealertrack*, 674 F.3d at 1333. Because this claim "explain[s] the basic concept of processing information through a clearing-house . . . [t]he steps that constitute the method here do not impose meaningful limits on the claim's scope." *Id.* (citing *Bilski*, 130 S. Ct. at 3231; *Bilski*, 545 F.3d at 961-62) (quotations omitted). The Federal Circuit was "compelled to conclude that the claims are invalid as being directed to an abstract idea ***preemptive of a fundamental concept or idea*** that would foreclose innovation in this area." *Id.* at 1333 (emphasis added); *see also Mayo*, 132 S. Ct. at 1294 (the patent should not "risk disproportionately tying up the use of" the abstract idea in future discoveries). Similarly, here, the steps of the claims in the '059 patent are directed to a fundamental concept itself, thus are directed to an abstract idea.

In sum, the claims of the patent-in-suit fail to meet the requirements of § 101 because they: (1) fail the machine-or-transformation test and (2) are directed to the abstract idea of a centralized authorization center for prescriptions drugs , which is a fundamental principle that would be improperly preempted by the patent-in-suit. Here, the computer must be integral to the claimed invention, facilitating the process in a way that a person making calculations or computations could not." *Bancorp*, 687 F.3d at 1278. This method could be performed by someone using pencil, paper, and a standard records-keeping system. For these reasons, the claims of the '059 patent are invalid under 35 U.S.C. § 101.

G. CONCLUSION

For the reasons stated above, claims 1-16 of the '059 patent are obvious over the prior art, and claims 1-16 are not patentable under 35 U.S.C. § 101. Par reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these patents are invalid, unenforceable or not infringed.

XIV. THE '988 PATENT

A. OVERVIEW OF THE '988 PATENT

1. Specification of the '988 Patent

The '988 patent issued from U.S. Application 13/013,680, filed August 27, 2012, which is a divisional of U.S. Application 13/013,680 (filed January 25, 2011, and now abandoned), which is a continuation of U.S. Application 12/704,097, which itself issued as U.S. Patent No. 7,895,059, which is a continuation of U.S. Application 10/322,348, which itself issued as U.S. Patent No. 7,668,730. The '988 patent lists three inventors: Dayton Reardon, Patti Engel, and Bob Gagne. It is assigned to Jazz. The '988 patent is titled "Sensitive Drug Distribution System and Method."

The '988 patent is directed, *inter alia*, to therapeutic methods of treating a patient with a prescription drug that is effective for therapeutic purposes but has the potential to be abused, the method including control of distribution by a central computer system and the drug including sodium oxybate/gamma hydroxyl butyrate (GHB). According to the '988 patent, the "invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs." ('988 patent, col. 1, lines 18-35). The '988 patent indicates that there is a need for a distribution system to address abuse. ('988 patent, col. 1, lines 36-39).

The invention purports to provide a drug distribution system and method utilizing 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 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. ('988 patent, col. 1, line 44 to col. 2, line 21.)

2. Prosecution History of the '988 Patent

On August 27, 2012, the applicants filed U.S. Application No. 13/595,757 ("the '757 application") with 15 total claims, including 2 independent claims. While filing the '757 application, the applicants filed a non-publication request under 35 U.S.C. § 122(b) and requested a Track I Prioritized Examination.

On October 10, 2012, applicants filed an IDS, listing documents related to office actions, amendments, appeal briefs of related patents, and documents related to *Jazz Pharmaceuticals Inc. v. Roxane Laboratories Inc.*, No. 10-6108, D.I. 151 (D.N.J. Sept. 14, 2012), such as the complaint, answer, counterclaims, and Markman briefs, among others.

On January 17, 2013, the USPTO issued a non-final rejection. Claims 1-15 were rejected for nonstatutory obviousness-type double patenting over claims 1-11 of the '730 patent and over claims 1-16 of the '059 patent. The USPTO also rejected claims 1-15 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.

('988 patent application, Jan. 17, 2013, Non-Final Rejection.)

On March 05, 2013, the applicants filed an IDS, listing documents related to a lawsuit *Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, Jazz Pharmaceuticals Inc. v. Roxane Laboratories Inc.*, and other documents submitted to the FDA.

On March 07, 2013, the applicants filed an Amendment and Response. In response to the § 112 rejections, the applicants made the following amendment to claim 1:

> A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising:
>
> receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at ~~the~~ an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic 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, wherein the exclusive central pharmacy and the exclusive central database ~~are unique in that they~~ are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's 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 company's prescription drug;
>
> confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;
>
> checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the ~~uniqueness~~ of the exclusive central pharmacy and the exclusive central database facilitate[[s]] a determination of the potential abuse of the company's prescription drug;
>
> providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the

company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;

confirming receipt by the narcoleptic patient of the company's prescription drug; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

('988 patent application, Mar. 6, 2013, Response.)

In response to the § 112 rejections, the applicants made the following amendment to claim 5:

The method of claim 1, wherein the exclusive central pharmacy enters data into ~~controls~~ the exclusive computer database.

In response to the § 112 rejections, the applicants made the following amendment to claim 9:

A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising:

receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug inventory is owned by a company, only at ~~the~~ an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic 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, wherein the exclusive central pharmacy and the exclusive central database ~~are unique in that~~ are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's 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 company's prescription drug;

confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;

> checking the exclusive computer database for potential abuse of the company's prescription drug, wherein ~~the uniqueness of~~ the exclusive central pharmacy and the exclusive central database facilitate[[s]] a determination of the potential abuse of the company's prescription drug;
>
> providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;
>
> confirming receipt by the narcoleptic patient of the company's prescription drug; and
>
> generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

('988 patent application, Mar. 6, 2013, Response.)

In response to the § 112 rejections, the applicants made the following amendment to claim 13:

> The method of claim 9, wherein the exclusive central pharmacy enters data into ~~controls~~ the exclusive computer database.

('988 patent application, Mar. 6, 2013, Response.)

In regards to the nonstatutory obviousness-type double patenting rejection, the applicants filed two terminal disclaimers with the response filed on March 7, 2013.

On March 8, 2013, the USPTO approved the terminal disclaimers noted above.

On March 11, 2013, the applicants filed a supplemental IDS, filing a video entitled "Advisory Committee Video on Xyrem, Oral Solution."

On March 21, 2013, the USPTO issued a Notice of Allowance, allowing claims 1-15, and determining PTA to be 0 days. The USPTO also provided an initialed copy of an IDS listing non-patent literature.

On April 19, 2013, the USPTO initialed and returned the supplemental IDS filed on March 11, 2013.

On May 29, 2013, the applicants filed another supplemental IDS, listing additional documents related to the *Jazz v. Roxane* lawsuit.

On June 4, 2013, the '988 patent issued.

3. Claims of the '988 Patent

The '988 patent issued with the following claims:

#	Claims of the '988 Patent
1	A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising: receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic 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, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's 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 company's prescription drug; confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug; checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug; providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug; confirming receipt by the narcoleptic patient of the company's prescription drug; and generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.
2	The method of claim 1, wherein one or more of the exclusive central pharmacy and the exclusive central database are distributed over multiple computers, and wherein a query operates over all data in all the distributed databases relating to the prescriptions, the doctors, and the narcoleptic patients.
3	The method of claim 1, wherein the providing the company's prescription drug to the narcoleptic patient comprises the exclusive central pharmacy authorizing the company's prescription drug to be dispensed to the narcoleptic patient by another pharmacy.

#	Claims of the '988 Patent
4	The method of claim 1, comprising delivering the company's prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the company's prescription drug.
5	The method of claim 1, wherein the exclusive central pharmacy enters data into the exclusive computer database.
6	The method of claim 1, comprising selectively blocking shipment of the company's prescription drug to the narcoleptic patient.
7	The method of claim 1, wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the company's prescription drug is blocked based upon such association.
8	The computerized method of claim 1, wherein the company's prescription drug comprises a gamma hydroxyl butyrate (GHB) drug product.
9	A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising: receiving in a computer processor all prescription requests, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's 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 company's prescription drug; confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug; checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug; providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug; confirming receipt by the narcoleptic patient of the company's prescription drug; and generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.
10	The method of claim 9, wherein one or more of the exclusive central pharmacy and the exclusive central database are distributed over multiple computers, and wherein a

#	Claims of the '988 Patent
	query operates over all data in all the distributed databases relating to the prescriptions, the doctors, and the narcoleptic patients.
11	The method of claim 9, wherein the providing the company's prescription drug to the narcoleptic patient comprises the exclusive central pharmacy authorizing the company's prescription drug to be dispensed to the narcoleptic patient by another pharmacy.
12	The method of claim 9, comprising delivering the company's prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the company's prescription drug.
13	The method of claim 9, wherein the exclusive central pharmacy enters data into the exclusive computer database.
14	The method of claim 9, wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the company's prescription drug is blocked based upon such association.
15	The method of claim 9, wherein the company's prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

B. LEVEL OF SKILL IN THE ART OF THE '988 PATENT

The subject matter of the '988 patent falls within the field of designing computer systems. Depending on the claim, the person of ordinary skill in this field would be a programmer, or a systems analyst/programmer. Such an individual would have a Bachelor's Degree in Computer Science and several years of experience in the field. *E.I. DuPont de Nemours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), *aff'd* 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein and would have the capability to draw inferences from them.

C. CLAIM CONSTRUCTION OF THE '988 PATENT

One of ordinary skill in the art and a court would interpret the claims of the '988 patent according to their plain and ordinary meaning unless otherwise specified herein.

On September 14, 2012, the U.S. District Court for the District of New Jersey issued a claim construction order for terms in the '730 patent family, which includes distribution patents, '106, '107, and '059, in the case of *Jazz Pharmaceuticals Inc. v. Roxane Laboratories Inc.*, No. 10-6108, D.I. 151 (D.N.J. Sept. 14, 2012). While the '988 patent was not at issue at the time the court issued the claim construction order, the '988 patent stems from the same '730 distribution patent family, and shares many of the same terms. The district court's constructions for several relevant terms are briefly in sections X(D), XI(D), and XIII(D), above. Par includes these

constructions for informational purposes only and reserves its right to challenge these constructions.

D. NONINFRINGEMENT OF THE '988 PATENT

Par does not directly infringe any claim 1 of the '988 patent under 35 U.S.C. § 271(a) because Par does not perform the claimed method. Notably, independent claim 1 describes "a mtheod of treatment of a narcoleptic patient with a prescription drug while controlling potential misues, abuse or diversion" which requires that "an exclusive computer database" receive "all prescription requests, for any and all patients being prescribed the prescription drug ." Claims 2-8 are all dependant on claim 1. Par will not infringe these claims if granted approval for its generic product, because it will not control "an exclusive central pharmacy" that receives all of the prescriptions for sodium oxybate or any other prescription drug.

Par further does not infringe claims 8 or 15, as they require that the prescription drug comprises "a gamma hydroxyl butyrate (GHB) drug product," whereas Par's proposed product contains sodium oxybate (sodium gamma-hydroxybutyrate).

Par also does not contributorily infringe under 35 U.S.C. § 271(c) because the claimed method has noninfringing uses. Furthermore, Par does not infringe claims 1-6 of the '988 patent under § 271(b) because the Par has a good faith belief that the '988 patent is invalid, which negates the requisite intent for induced infringement. *Commil USA, LLC v. Cisco Systems, Inc.*, 720 F.3d 1361, 1364 (Fed. Cir. Jun. 25, 2013) ("we find that Cisco's evidence of a good-faith belief of invalidity may negate the requisite intent for induced infringement.")

E. OBVIOUSNESS OF THE '988 PATENT

1. The Scope and Content of the Prior Art

The earliest possible effective U.S. filing date for the '988 patent is December 17, 2002, based on the filing date of U.S. Application 10/322,348 for the grandparent, '730 patent. The prior art is described in section X(E)(1), above.

2. Obviousness in Light of Borsand (Claim 1)

Claim 1 of the '988 patent is obvious over Borsand, which describes each of the elements of claim 1 in combination with other prior art references. Claim 1 is directed to a method for treating patients with a prescription drug that has the potential to be abused, misused, or diverted. The claim essentially requires patients to obtain the prescription drug from a single, central pharmacy that maintains an exclusive computer database of information, thus allowing the pharmacy to perform checks of potential abuse before delivering the drug to the patient. The method of claim 1 controls distribution by subjecting the single, central pharmacy to a multitude of controls before the drug is delivered.

Claim 1 of the '988 Patent	Borsand
A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription	Borsand discloses that Borsand's system reduces fraud, redundancy, pharmaceutical abuse, pharmaceutical misuse, and errors, with respect to

Claim 1 of the '988 Patent	Borsand
drug, comprising:	prescription drugs. (Borsand ¶¶ 33; 38.)
receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic patients, the prescription drug, and various credentials of the any and all medical doctors;	A computer system or a computer, as described in Borsand, inherently includes a computer processor for processing data. Borsand teaches an exclusive central computer system, which contains patient and doctor information. Borsand discloses a prescription subsystem where "prescriptions are only issued by a certain subset of health care providers, such as physicians ...." Processing a prescription requires inputting "patient record which includes patient information relevant to pharmaceutical selection." Each doctor must use a unique "UserID" and a patient is assigned a unique "PatientID." (Borsand ¶¶ 57-58; Figure 4b). Borsand addresses prior art deficiencies where "[i]t would be desirable for pharmaceutical information to be stored only once and in a centralized location accessible by the appropriate parties." (Borsand ¶ 3). While Borsand may not explicitly teach that the prescription requests are for narcoleptic patients, the video, Briefing Booklet, and FDA Safety Review all disclose that the prescription drug is used to treat narcolepsy patients. Similarly, while Borsand may not explicitly teach distributing the prescription drug by a company that obtained approval, at least, the Briefing Booklet and FDA Safety Review cure this deficiency.
requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;	Borsand teaches an exclusive computer database associated with an exclusive computer system. For example, Borsand discloses a system that allows for "pharmaceutical information to be stored only once and in a centralized location accessible by the appropriate parties." (Borsand ¶ 3). Borsand teaches that all relevant data is housed in a computer that "can be a single centralized computer or server, a single network ...." (Borsand ¶ 31.) According to Borsand, in the preferred embodiment, "all pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate regulations, policies, and guidelines." (Borsand ¶ 43.) Borsand also teaches that the relevant data must be entered in the system by the provider, *see, e.g.*, Borsand ¶¶ 58; 108, or the pharmacist. (*See* Borsand ¶ 86 ("If the pharmacist fills a

Claim 1 of the '988 Patent	Borsand
	pharmaceutical prescription, that information needs to be memorialized at 40.02 or its related pages.").)
checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the company's prescription drug;	Borsand teaches that the "invention relates to a computer based system for tracking information related to pharmaceutical prescriptions." (Borsand ¶ 10). A computer inherently includes a computer processor for processing data. Borsand teaches a system that can "check of for unfavorable pharmaceutical interactions and allergic reactions, prevent misuse of a prescription, monitor the filling and re-filling of a prescription, as well as cancel a prescription after it has been issued by a provider." (Borsand Abstract.) According to Borsand's prescription subsystem, "prescriptions are only issued by a certain subset of health care providers, such as physicians ...." Processing a prescription requires inputting "patient record which includes patient information relevant to pharmaceutical selection." Each doctor must use a unique "UserID" and a patient is assigned a unique "Patient*ID*." (*See* Borsand ¶¶ 57-58; Fig. 4b)
confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;	While Borsand does not explicitly require confirming that the patient has received and/or read the educational material "prior" to shipping the prescription drug, the FDA Safety Review (*See* obviousness analysis supra) and Califona cure this deficiency: Califano requires "confirming with the patient that educational material has been read prior to providing the drug to the patient." (*See* Califano ¶ 84; Examiner's Answer OA, dated 10/18/06.) Further, as noted above, the video, FDA Safety Review, and Briefing Booklet disclose that the prescription drug is for a narcoleptic patient.
checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug;	The system of Borsand provides "functionality for tracking pharmaceutical, prescription and related information," where "tracking can be in a proactive and real-time manner, or in the form of reports and analysis ...." (Borsand ¶ 34). Any abuse or violation can be detected by the system which "can be configured to not allow the attempted conduct, or to allow the conduct, but generate a report relating to the undesired activity." *Id.* Further, Borsand discloses that the pharmaceutical subsystem (part of the overall exclusive central computer system) re-evaluates the prescription before the prescription is filled or sent to a payor,

Claim 1 of the '988 Patent	Borsand
	where "medical aspects of a prescription can also be reviewed, so that the appropriateness of the selected pharmaceutical can be confirmed as it relates to ... other patient attributes that could affect the desirability of filling a particular prescription." (Borsand ¶ 87). Borland discloses in multiple places that desirability of filling prescriptions may be tied to misuse of pharmaceuticals; for example, patient attributes includes patient's refill behavior. (*Id.* at ¶ 53.)
providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;	Borsand discloses that in filling a prescription for a drug, an event can trigger a modification or cancellation of the prescription, where such an event includes "evidence of fraud, misuse, or redundancy on the part of a provider, pharmacist, or patient." (Borsand ¶ 120.)
confirming receipt by the narcoleptic patient of the company's prescription drug; and	Borsand discloses that the system allows monitoring of whether or not a patient actually fills the prescription. (Borsand ¶ 56.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	Borsand discloses that "[i]f a patient 22, provider 30, pharmacist 40, or PBM 50 attempts an action that is not in accordance with the predefined rules 34 of the payor 60, the system 20 can be configured to not allow the attempted conduct, or to allow the conduct, but **generate a report** 42 relating to the undesirable activity." (Borsand ¶ 54.)

It is the patentee's obligation to present evidence of secondary considerations, if any, to rebut a *prima facie* case of obviousness. The '988 patent provides no specific evidence of secondary considerations of non-obviousness. Any evidence of secondary considerations is insufficient to overcome the strong case of *prima facie* obviousness of the claimed subject matter.[38]

3. Obviousness in Light of the Briefing Booklet (Claim 1)

Claim 1 of the '988 patent is obvious over the Briefing Booklet.

Claim 1 of the '988 Patent	Briefing Booklet
A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising:	The Briefing Booklet generally teaches the therapeutic benefits of Xyrem® in treating narcolepsy. (*See* generally Briefing Booklet (e.g., "upon learning about narcolepsy and the clinical results of Xyrem, these parties agreed that the therapeutic need for Xyrem was

[38] Secondary considerations of non-obviousness do not control the analysis where there is an otherwise strong case of obviousness, such as one based upon art not considered during prosecution. *Tokai Corp. v. Easton Enterprises, Inc.*, 632 F.3d 1358 (Fed. Cir. 2011) ("A strong case of prima facie obviousness, such as that presented here, cannot be overcome by a far weaker showing of objective indicia of nonobviousness."); *Sandt Tech. v. Resco Metal & Plastics*, 264 F.3d 1344, 1355 (Fed. Cir. 2001) ("We see no error in the district court's conclusion . . . that the secondary considerations cannot overcome the strong prima facie evidence of obviousness presented.").

Claim 1 of the '988 Patent	Briefing Booklet
	compelling.")). Further, the Briefing Booklet teaches the potential for abuse, misuse, or diversion of Xyrem (e.g., "They [law enforcement] 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...." (Briefing Booklet, at 7.)
receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic patients, the prescription drug, and various credentials of the any and all medical doctors;	"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." (Briefing Booklet at 306). "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." (Briefing Booklet at 311.) The Briefing Booklet teaches that the bulk drug is manufactured at a single site and is formulated into a finished product at a separate site, and each of these sites must be approved by meeting "FDA and DEA requirements for controlled substances." Briefing Booklet at 18.
requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;	The Briefing Booklet teaches data collection into the central database. The reference to "data collection" necessary includes entering the information into the central database. "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

Claim 1 of the '988 Patent	Briefing Booklet
	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." (Briefing Booklet at 19)
checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the company's prescription drug;	The Briefing Booklet discloses that "[t]he 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." The reference to real-time data implies a computer processor managing the data. (Briefing Booklet at 20.) The Briefing Booklet discloses that upon receipt of a prescription from the physician, the central pharmacy will "verify physician's eligibility by checking the AMA, DEA, or State Medical Board on-line databases" to ensure that "the prescription was written by a "real" physician with current privileges to prescribe controlled medications." (Briefing Booklet at 19.) The Briefing Booklet discloses that the collection of 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." (Briefing Booklet at 15).
confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;	The Briefing Booklet teaches that "[o]nce 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." (Briefing Booklet at 20.) While the Briefing Booklet does not explicitly require confirming that the patient has received and/or read the educational material "prior" to shipping the prescription drug, the FDA Safety Review (*See* obviousness analysis infra) and Califano cure this deficiency: Califano requires "confirming with the patient that educational material has been read prior to providing the

Claim 1 of the '988 Patent	Briefing Booklet
	drug to the patient." (*See* Califano ¶ 84; Examiner's Answer OA, dated 10/18/06.)
checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug;	The Briefing Booklet discloses that "[t]he 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." (Briefing Booklet at 20.)
providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;	The Briefing Booklet discloses a distribution system that requires physician verification process "to catch any prescriptions written on stolen or counterfeit prescription pads" and entering patient information in a "patient registry which also aids in diversion prevention" before the Xyrem shipping process begins, where Xyrem is mailed via Federal Express. (Briefing Booklet at 19-20.)
confirming receipt by the narcoleptic patient of the company's prescription drug; and	The Briefing Booklet discloses a distribution system that requires the exclusive central pharmacy pharmacist to contact the patient to confirm receipt of the Xyrem prescription. (Briefing Booklet at 20.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	The Briefing Booklet teaches that "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." (Briefing Booklet at 16.) The Briefing Booklet further teaches that "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." (Briefing Booklet at 15.)

4. Obviousness in Light of the FDA Safety Review (Claim 1)

Claim 1 of the '988 patent is obvious over the FDA Safety Review.

Claim 1 of the '988 Patent	FDA Safety Review
A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising:	The FDA Safety Review teaches a method of distributing a prescription drug (Xyrem®) under exclusive control of an exclusive central pharmacy (or distributor). (FDA Safety Review

Claim 1 of the '538 Patent	FDA Safety Review
	at 108). The FDA Safety review discloses that Xyrem is effective for treating narcolepsy, but also that "medically prescribed Xyrem may be diverted for illegal use." (FDA Safety Review at 7; 108)
receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic patients, the prescription drug, and various credentials of the any and all medical doctors;	The FDA Safety Review teaches a method of distributing a prescription drug (Xyrem®) under exclusive control of an exclusive central pharmacy (or distributor). (FDA Safety Review at 108). Apparently, Orphan Medical proposed Nova Factor to be the central pharmacy. It describes a "closed-loop distribution system," wherein "Xyrem® will NOT be placed in retail pharmacy outlets," and instead, the document describes a "primary and exclusive distributor of Xyrem®." *Id.* at 108. The FDA Safety Review teaches that the prescription drug will be manufactured by two different companies that will be approved for distribution, as these companies would have to be "FDA and DEA-compliant, 'fill-finish' facilities." FDA Safety Review at 108. In addition, the FDA Safety Review teaches that the "drug product will be stored at a facility compliant with Schedule III regulations, where a consignment inventory will be maintained." *Id.*
requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;	The FDA Safety Review teaches that a single, sole, and secure database will store the relevant information. "Every patient and prescribing physician will be registered with [the exclusive distributor] in 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." (FDA Safety Review at 110.)
checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the company's prescription drug;	The FDA Safety review teaches that the exclusive central pharmacy will verify that the physician is eligible to prescribe Xyrem®, including checking whether the physician has an active DEA number and whether any actions are pending against the physician.

Claim 1 of the '988 Patent	FDA Safety Review
	(FDA Safety Review at 109.)
confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;	The FDA Safety Review discloses that the Office of Post-Marketing Drug Risk assessment recommended that confirmation of whether the patient has read and fully understands the education material should be received by Nova Factor "prior to the initial dispensing of the drug." (FDA Safety Review at 114-115.)
checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug;	The FDA Safety Review notes in several in several places checking for potential for abuse, misuse, or diversion: prescriptions refills before anticipation date will be questioned (FDA Safety Review at 110); lost, stolen, destroyed, or spilled prescription/supply will be documented, flagged, and monitored (*Id.*); noting prescribing frequency (*Id.*); among others.
providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;	The FDA Safety Review discloses that "once approval has been established, (b)(4) [exclusive specialty pharmacy] will … arrange shipment though (b)(4) or a similar carrier." (FDA Safety Review at 109.) The approval process requires verification of eligibility to prevent potential abuse. *Id.*
confirming receipt by the narcoleptic patient of the company's prescription drug; and	The FDA Safety Review discloses that "[r]eceipt of the drug by the patient will be ensured through … a phone call by the pharmacy to the patient." (FDA Safety Review at 109.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	The FDA Safety Review notes in several places potential for abuse, misuse, or diversion: prescriptions refills before anticipation date will be questioned (FDA Safety Review at 110); lost, stolen, destroyed, or spilled prescription/supply will be documented, flagged, and monitored (*Id.*); noting prescribing frequency (*Id.*); among others. While the FDA Safety Review does not explicitly disclose generating periodic reports, the Video, Borsand, Briefing Booklet, and Lilly, among others, disclose generating periodic reports to evaluate potential diversion patterns. (*See* obviousness analysis of the Video, Briefing Booklet, and the FDA Safety Review; Lilly ¶¶ 11, 33, 54, 57, 58, 61, 69; Examiner's Answer, OA dated 06/19/06.)

5. Obviousness in Light of the Video (Claim 1)

Claim 1 of the '988 patent is obvious over the Video.

Claim 1 of the '988 Patent	Video
A method of treatment of a narcoleptic patient	The Video teaches using a method that includes

Claim 1 of the '988 Patent	Video
with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising:	a single, centrally-located specialty pharmacy that controls distribution, documentation, and security of prescription drugs, such as Xyrem® to treat narcolepsy, through a closed-loop distribution system in order to minimize abuse, misuse, diversion. (Video, ¶¶ 2-5; 13.)
receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic patients, the prescription drug, and various credentials of the any and all medical doctors;	The Video shows a "shot of pharmacy employee picking up prescription fax and sitting down at a computer to verify physician's eligibility." (Video ¶ 21). The illustration of a computer in the Video teaches using a computer to control distribution. The Video teaches using a computer to process prescription requests. A computer inherently includes a computer processor. The Video discloses a single, centrally-located specialty pharmacy that controls distribution, documentation, and security through a closed-loop distribution system. The prescriptions are sent to the central pharmacy, which verifies that the "physician is an Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data ... to check if there are any pending or previous actions against the physician." (Video ¶¶ 14; 21.) The single, specialty pharmacy stores data about prescriptions by patients; thus, it follows that the prescription sent by the physician includes patient identifying information. (*See, e.g.*, Video ¶ 24.) To the extent the video does not explicitly teach distribution by an approved company, the Briefing Booklet and FDA Safety Review cure this deficiency.
requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;	The Video teaches that all "data about inventory, physicians, reimbursements, patients, and delivery" is stored in one efficient and quickly-accessible location [single, specialty pharmacy]." (Video ¶ 24.) Further, the Video teaches that the "closed-loop distribution system … will 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." (Video ¶ 14.)
checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to	The Video teaches using a computer to process the specialty pharmacy prescription requests. A computer inherently includes a

Claim 1 of the '988 Patent	Video
prescribe the company's prescription drug;	computer processor. The Video discloses that the prescriptions are sent to the central pharmacy, which verifies that the "physician is an Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data ... to check if there are any pending or previous actions against the physician." (Video ¶ 24.)
confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;	The Video teaches sending a patient educational material, "Patient Success Program." (Video ¶ 31.) While the Video does not explicitly require confirming that the patient has received and/or read the educational material "prior" to shipping the prescription drug, the FDA Safety Review (*See* obviousness analysis supra) and Califano cure this deficiency: Califano requires "confirming with the patient that educational material has been read prior to providing the drug to the patient." (*See* Califano ¶ 84; Examiner's Answer OA, dated 10/18/06.)
checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug;	The Video discloses that the central pharmacy staff 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." (Video ¶ 14). The Video also discloses that the specialty pharmacy will keep track of anomalous patient requests to fill their prescriptions. (*Id.* at 38.)
providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;	The Video discloses that Xyrem® will be "shipped overnight by Federal express utilizing a tracking system designed specifically for the specialty pharmacy." (Video ¶ 30.) The Video teaches that during "the process of verification and documentation, if any data or behavior suggest the possibility that Xyrem® may be used inappropriately, the specialty pharmacy is empowered to contact the appropriate authorities." (Video ¶ 29.)
confirming receipt by the narcoleptic patient of the company's prescription drug; and	The Video teaches that receipt of Xyrem® and educational materials is verified by a telephone call placed to the patient where "the specialty pharmacy will confirm receipt of the Xyrem prescription and the Patient Success program." (Video ¶ 35.)
generating with the computer processor periodic reports via the exclusive computer database to	The Video discloses that the closed-loop distribution system "will be able to **generate**

Claim 1 of the '988 Patent	Video
evaluate potential diversion patterns.	**data**, recording prescribers, patients and dosing that could provide information for any possible investigations and prosecutions for state and federal authorities." (Video ¶ 14).

6. Application of the Prior Art (Claims 2-15)

Claim 2 of the '988 patent is directed to the method of claim 1 "wherein one or more of the exclusive central pharmacy and the exclusive central database are distributed over multiple computers, and wherein a query operates over all data in all the databases relating to the prescriptions, the doctors, and the narcoleptic patients." Borsand teaches that "[i]n alternative embodiments of the invention, multiple databases are used to store pharmaceutical information. PBMs 50, payors 60, patients 22, providers 30, and prescriptions can each have their own databases 62, which can in [*sic*] interconnected or kept separate, but each are accessible from the [main] computer 26 housing the computer programs used by the system 20." (Borsand ¶ 43). Accordingly, Borsand teaches using multiple databases, which naturally would be housed in multiple computers, in relation to the prescriptions, the doctors, and the patients. Further, as noted above, while Borsand does not explicitly teach that the patients are narcoleptic patients, the Video, Briefing Booklet, and the FDA Safety Review disclose that the prescription drugs are for narcoleptic patients.

Claim 3 is directed to the method of claim 1, "wherein the providing company's prescription drug to the narcoleptic patient comprises the exclusive central pharmacy authorizing the company's prescription drug to be dispensed to the narcoleptic patient by another pharmacy." The FDA Safety Review teaches that the specialty pharmacy may ship the prescription to another pharmacy for patient pick-up. (FDA Safety Review at 110). The FDA Safety Review also discloses that, where the prescription will be picked up by another pharmacy, the specialty pharmacy must verify that there is a mechanism for the second pharmacy to protect against diversion of the prescription drug. (FDA Safety Review at 110).

Claim 4 is directed to the method of claim 1, "comprising delivering the company's prescription to the narcoleptic patient in order to treat the narcoleptic patient with the company's prescription drug." The FDA Safety Review discloses that Xyrem will be delivered to the narcoleptic patient by the central pharmacy [(b)(4)]using a courier service. (FDA Safety Review at 109). Similarly, the Briefing Booklet discloses that the "specialty pharmacy will contact the patient … and arrange a time for a next-day delivery…." (Briefing Booklet at 19.)

Claim 5 is directed to the method of claim 1, "wherein the exclusive central pharmacy enters data into the exclusive computer database." The prior art references teach that the central pharmacy enters data into an exclusive central database. For example, the Video teaches that all "data about inventory, physicians, reimbursements, patients, and delivery" is stored in one efficient and quickly-accessible location [single, specialty pharmacy]." (Video ¶ 24). Similarly, the Briefing Booklet teaches data collection into the central database. The reference to "data collection" necessary includes entering the information into the central database. "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." (Briefing Booklet at 19.)

Claim 6 is directed to the method of claim 1, "comprising selectively blocking shipment of the company's prescription drug to the narcoleptic patient." The prior art references disclose that shipments of the prescription drug may be selectively blocked. For Example, the FDA Safety Review discloses that if a patient is unavailable to accept a shipment of Xyrem® and execute the required receipt, the package will be returned to the pharmacy. (FDA Safety Review at 109). Similarly, The Briefing Booklet discloses that "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." (Briefing Booklet at 20.)

Claim 7 is directed the method of claim 1, "wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the company's prescription drug is blocked based upon such association." The prior art references disclose that prior to shipment of the prescription drug, the verification process will prevent shipment to patients associated with an abuse pattern. For example, the Video teaches that prior to shipping the patient's medication overnight by Federal Express, a process of verification and documentation will allow the specialty pharmacy to determine "if any of the data or behavior suggests the possibility that Xyrem may be used inappropriately." (Video ¶¶ 29-30). Similarly, the FDA Safety Review teaches that Xyrem® will only be shipped once approval has been established, where approval requires verifying eligibility of the physician to prescribe the prescription drug and obtaining a certificate of medical necessity. (FDA Safety Review at 109.)

Claim 8 is directed to the "computerized" method of claim 1, "wherein the company's prescription drug comprises a gamma hydroxyl butyrate (GHB) drug product." As an initial matter, the method of claim 1 is not a "computerized" method, and appears to be an error that the Examiner failed to observe or require correction. Nonetheless, substantively, at least the Briefing Booklet and the FDA Safety Review explicitly disclose that the prescription drug is GHB.

Claim 9 is an independent claim, but is similar to claim 1. The difference between claim 9 and claim 1 is that claim 9 recites "the prescription drug inventory is owned by a company," whereas, claim 1 recites "the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug." This difference does not overcome the prior art references. For example, the FDA Safety Review discloses that the distributing company will own the inventory (e.g., "The inventory will be owned by Orphan Medical, Inc., and the facility will be managed by (b)(4).") (FDA Safety Review at 108.)

Claim 10 is directed to the method of claim 9 and includes the same limitation as claim 2. Thus, for the same reasons claim 2 is rendered obvious, claim 10 is also rendered obvious by the same references.

Claim 11 is directed to the method of claim 9 and includes the same limitation as claim 3. Thus, for the same reasons claim 3 is rendered obvious, claim 11 is also rendered obvious by the same references.

Claim 12 is directed to the method of claim 9 and includes the same limitation as claim 4. Thus, for the same reasons claim 4 is rendered obvious, claim 12 is also rendered obvious by the same references.

Claim 13 is directed to the method of claim 9 and includes the same limitation as claim 5. Thus, for the same reasons claim 5 is rendered obvious, claim 13 is also rendered obvious by the same references.

Claim 14 is directed to the method of claim 9 and includes the same limitation as claim 7. Thus, for the same reasons claim 7 is rendered obvious, claim 14 is also rendered obvious by the same references.

Claim 15 is directed to the method of claim 9 and includes the same limitation as claim 8. Thus, for the same reasons claim 8 is rendered obvious, claim 15 is also rendered obvious by the same references.

F. INELIGIBLE SUBJECT MATTER UNDER 35 U.S.C. § 101

The claims of the '988 patent are invalid under 35 U.S.C. § 101 because the claimed subject matter is not patentable. The claims of the '988 patent do not satisfy the machine-or-transformation test, and are directed to algorithms and abstract ideas *Bilski v. Kappos*, 130 S.Ct. 3218, 3229-30 (2010); *In re Bilski*, 545 F.3d 943, 962-63 (Fed. Cir. 2008).

In the '988 patent, the process is not tied to a particular machine or apparatus. Although the claims include terms like "computerized method" and "computer processor," there is nothing in the specification indicating that a computer is integral to implementing the process. Further, while some of the steps require use of a "computer processor," 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.*, '988 patent, col. 3, lines 10-14.)[39]

The '988 patent claims do not transform an article into a different state or thing: They merely claim a method of distributing sensitive drugs that does not transform or make the drugs

[39] 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).

any less sensitive. Although some claims require 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. Although 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." *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.*, '988 patent, col. 1, lines 6- 7.)

The Federal Circuit has determined that patent claims are abstract when the "steps can be performed in the human mind, or by a human using a pen and paper." *CyberSource*, 654 F.3d at 1372. In the '988 patent, the process is similar to a clearing house in that the method merely requires collecting and organizing data of doctors who are able to prescribe, and the patients who are able to receive, the medication, and organizing the data describing shipments of the medication, and associated marketing material. This process could equally be performed by pencil, paper, and a traditional filing cabinet system.

The steps of the claims in the '988 patent represent common ways that people have used to restrict allocation of materials, where a central controlling entity confirms with a validated third-party authority whether a substance should be delivered to an individual. Without meaningful limits, the claims effectively preempt the fundamental concept itself and foreclose a wide range of inventions that the patentee never conceived. For example, in *Dealertrack*, the Federal Circuit determined that the patentee's claimed process in its simplest form includes three steps: receiving data from one source (step A), selectively forwarding the data (step B, performed according to step D), and forwarding reply data to the first source (step C). *Dealertrack*, 674 F.3d at 1333. Because this claim "explain[s] the basic concept of processing information through a clearing-house . . . [t]he steps that constitute the method here do not impose meaningful limits on the claim's scope." *Id.* (citing *Bilski*, 130 S. Ct. at 3231; *Bilski*, 545 F.3d at 961-62) (quotations omitted). The Federal Circuit was "compelled to conclude that the claims are invalid as being directed to an abstract idea ***preemptive of a fundamental concept or idea*** that would foreclose innovation in this area." *Id.* at 1333 (emphasis added); *see also Mayo*, 132 S. Ct. at 1294 (the patent should not "risk disproportionately tying up the use of" the abstract idea in future discoveries). Similarly, here, the steps of the claims in the '988 patent are directed to a fundamental concept itself, thus are directed to an abstract idea.

In sum, the claims of the patent-in-suit fail to meet the requirements of § 101 because they: (1) fail the machine-or-transformation test and (2) are directed to the abstract idea of a centralized authorization center for prescriptions drugs , which is a fundamental principle that would be improperly preempted by the patent-in-suit. Here, the computer must be integral to the claimed invention, facilitating the process in a way that a person making calculations or computations could not." *Bancorp*, 687 F.3d at 1278. This method could be performed by someone using pencil, paper, and a standard records-keeping system. For these reasons, the claims of the '988 patent are invalid under 35 U.S.C. § 101.

G. CONCLUSION

For the reasons stated above, claims 1-15 of the '988 patent are obvious over the prior art, and claims 1-15 are invalid 35 U.S.C. § 101. Par reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these patents are invalid, unenforceable or not infringed.

Xyrem® (sodium oxybate) oral solution

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

June 6, 2001

Orphan Medical Inc.

Agenda

◆ Introduction	Dayton Reardan, Ph.D., VP of Regulatory Affairs
◆ Medical Need	Emmanuel Mignot, M.D., Stanford University
◆ Efficacy	William Houghton, M.D., COO, Medical Officer
◆ Polysomnographic Effects of Xyrem	Jed Black, M.D., Stanford University
◆ Safety	William Houghton, M.D., COO, Medical Officer
◆ Summary of Risks Versus Benefits	William Houghton, M.D., COO, Medical Officer
11:00 a.m.	
◆ Abuse Liability	Robert Balster, Ph.D., Medical College of Virginia
◆ Risk Management	Patti Engel, R.N., B.S.N., VP Marketing & Sales

Experts Available for the Committee

Helene Emsellem, M.D.
Center for Sleep and Wake Disorders,
Chevy Chase, MD

Martha Hagaman, M.D.
Sleep Medicine Associate
St. Thomas Hospital, Nashville, TN

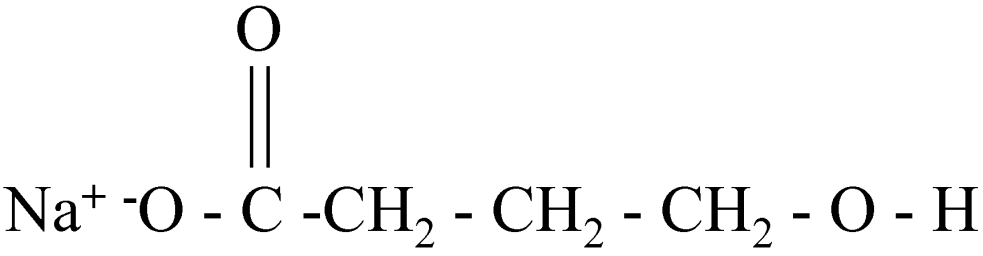
Ruzica Ristanovic, M.D.
Sleep Disorders Center
Evanston Hospital
Evanston, Illinois

Richard Okerholm, Ph.D.
Pharmacokinetic and Drug Metabolism
Consultant

Frederick E. Reno, Ph.D.
Preclinical Toxicology Consultant

Richard Trout, Ph.D.
Statistician
Department of Statistics
Professor (Emeritus)
Rutgers University
New Jersey

Chemical Structure



sodium oxybate

Regulatory Overview

- 1960s discovery of GHB, approval as an anesthetic in France
- 1970s initial clinical narcolepsy evaluation
- 1978 GHB was used as an example for the need of an Orphan Drug Act
- 1980s two independent controlled studies
- 1994 FDA approached Orphan Medical to develop
- 1995 pre-IND meeting with FDA
- 1998 Treatment IND approved
- 2000 Orphan Medical submitted this NDA
  - Priority review

Recognition of Abuse

- Xyrem is not the problem
- Ease of synthesis
- Initial availability of internet GHB kits
- Current availability of precursor GHB substitutes
  - Gammabutyrolactone (GBL)
  - 1,4-butanediol (1,4-BD)
- Federal legislation in 2000 controls only GHB

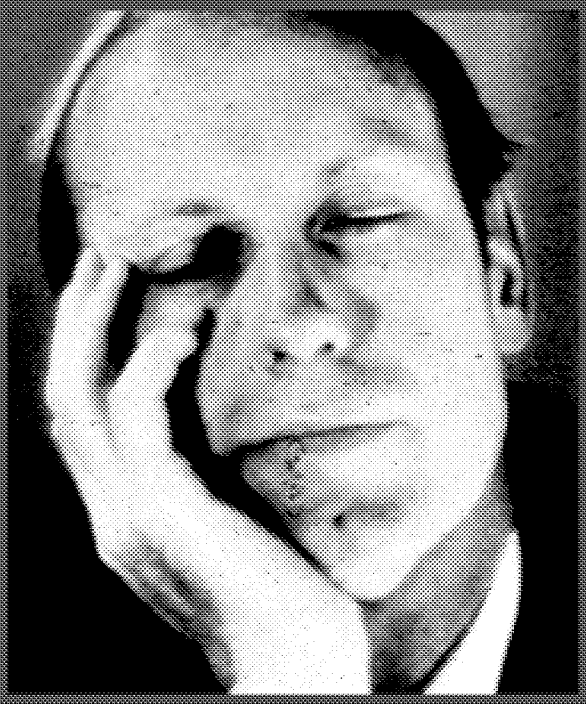
Proposed Indication

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.

Prevalence of Narcolepsy in the U.S.

- Narcolepsy is an orphan disease
- Epidemiology estimates 135,000 patients
- 55% are diagnosed (75,000)
- 32% of those have cataplexy for which they seek treatment (24,000)

Narcolepsy - Medical Need



Emmanuel Mignot
M.D., Ph.D.

Director
Center for Narcolepsy
Stanford University

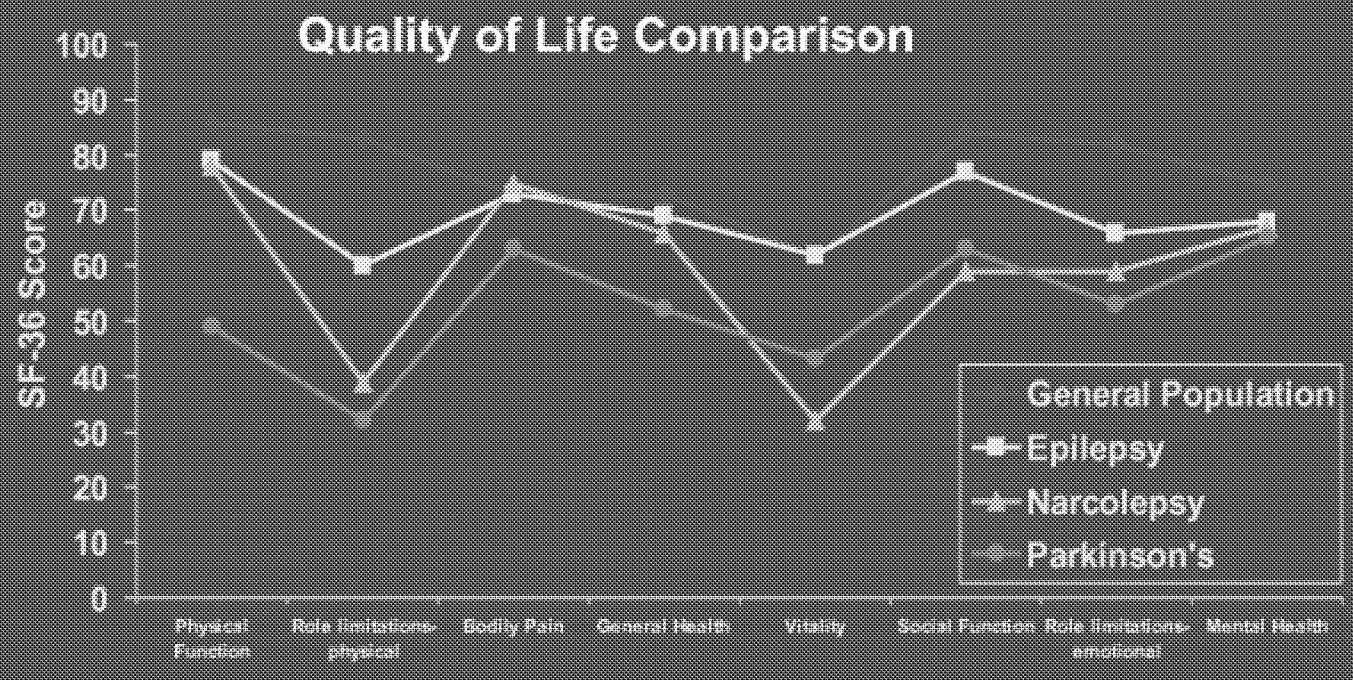
Washington, D.C.
June 6th, 2001

9

Narcolepsy - Cataplexy

- Excessive daytime sleepiness
- Cataplexy
- Hypnagogic hallucinations
- Sleep paralysis
- Disturbed nocturnal sleep

Narcolepsy - A Disabling Disorder

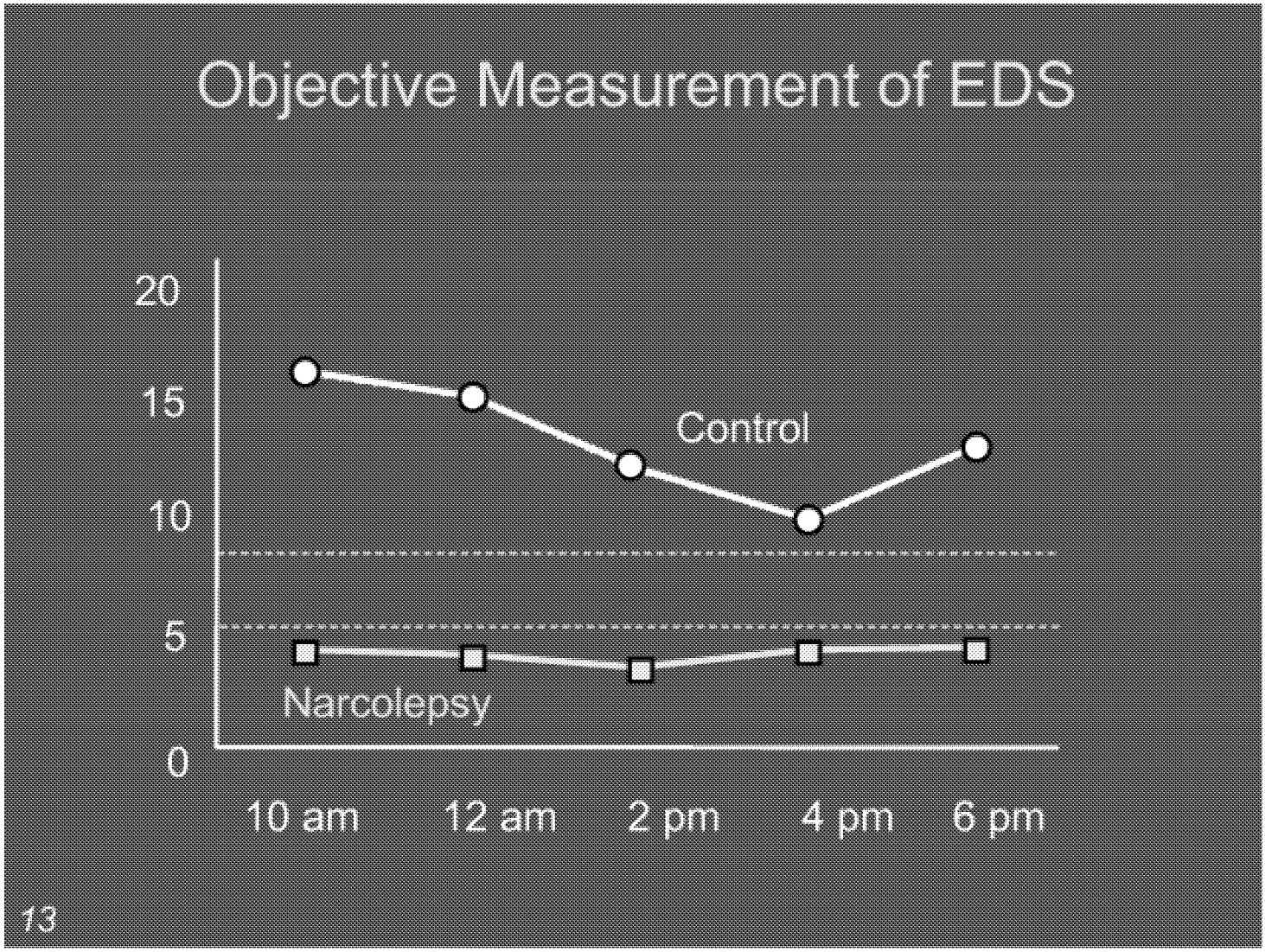


Adapted from Beusterien et al. SLEEP 1999; 22

Driving Effects and Accidents

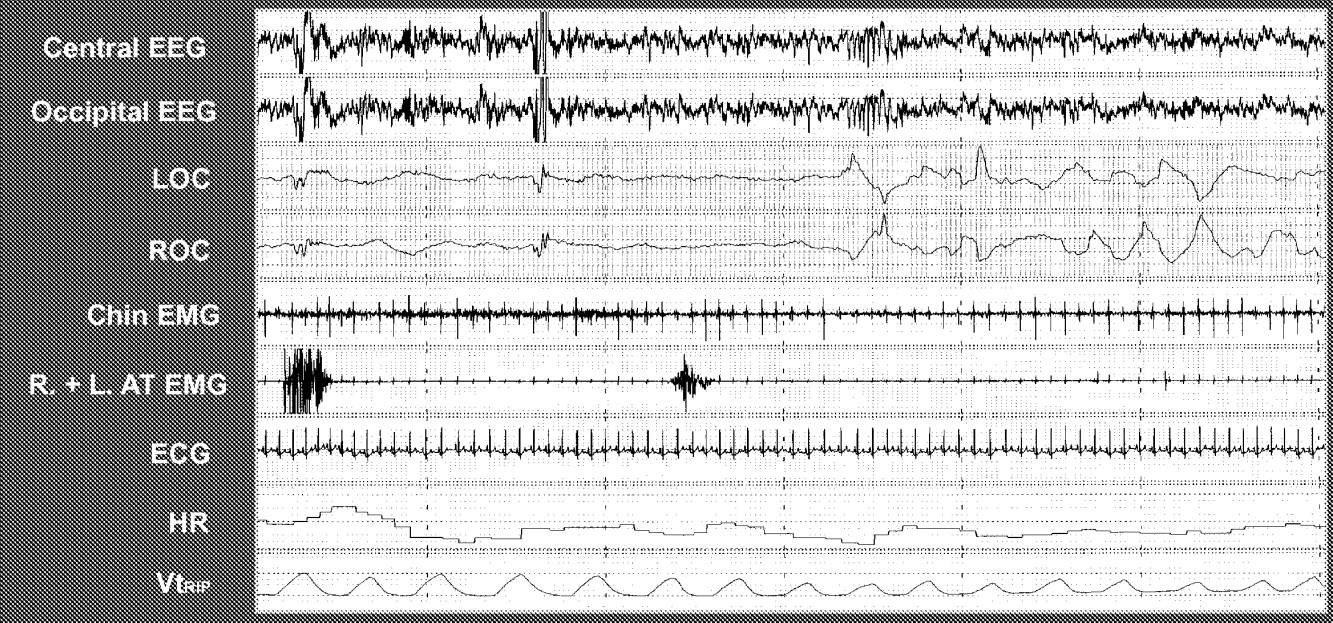
	Narcolepsy	Controls
◆Do you drive?	48%	63%
◆Fall asleep driving	66	6
◆Cataplexy driving	29	0
◆Sleep paralysis driving	12	0
◆Frequent near accidents	67	0
◆Led to accidents	37	5
◆Higher insurance	16	1
◆Suspended license	7	4

From: Broughton et al. Psychophysiological aspects of sleep. Park Ridge, NJ: Noyes Medical Publ, 1981.


Objective Measurement of EDS
20
15
10
5
0
Control
Narcolepsy
10 am
12 am
2 pm
4 pm
6 pm
13

Abnormal Regulation of REM Sleep

Sudden transition from wakefulness to REM sleep



≥ 2 SOREMPs is typical for narcolepsy

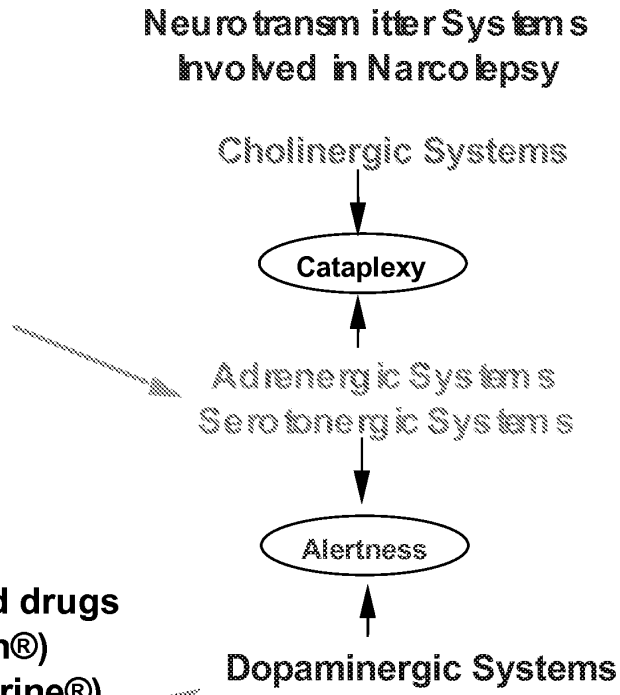
ANTI-NARCOLEPSY-DRUGS

Antidepressants

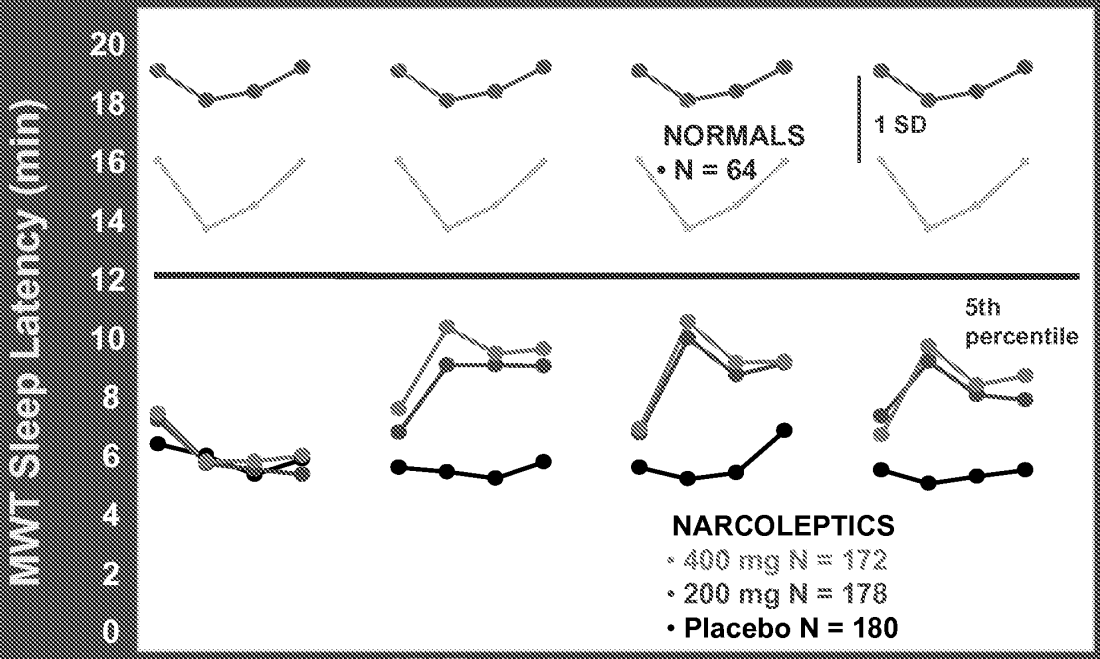
- **Imipramine (Tofranil®)**
- **Clomipramine (Anafranil®)**
- **Protryptiline (Vivactil®)**
- **Fluoxetine (Prozac®)**

Stimulants - All are scheduled drugs

- **Methamphetamine (Desoxyn®)**
- **Dextroamphetamine (Dexedrine®)**
- **Methylphenidate (Ritalin®)**
- **Pemoline (Cylert®)**
- **Modafinil (Provigil®)**



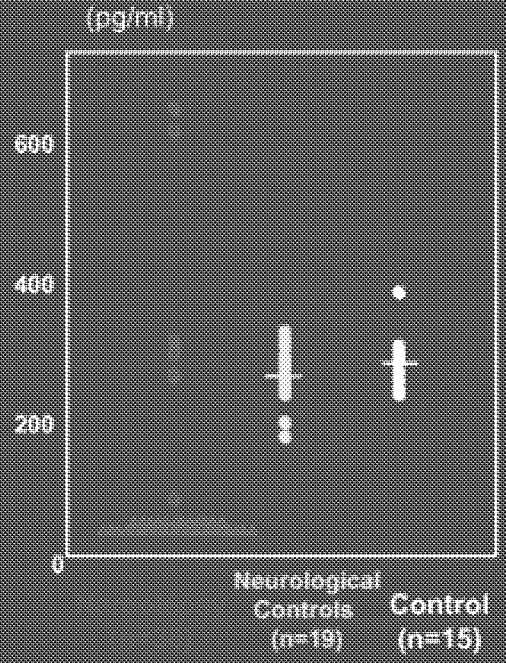
Partial Efficacy of Treatments: MWT



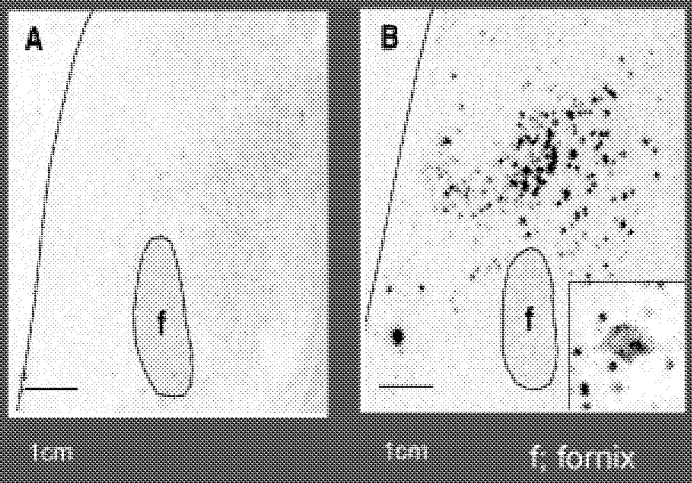
US Modafinil in Narcolepsy Multicenter Study Group. Ann Neurol 1998;43 and Neurology 2000;54.

Hypocretin Deficiency in Narcolepsy

Cerebrospinal Fluid



Lateral Hypothalamic brain tissue



Control

Nishino et al. Lancet, 355:39-40, 2000; Peyron et al., Nature Med, 6: 991-7, 2000

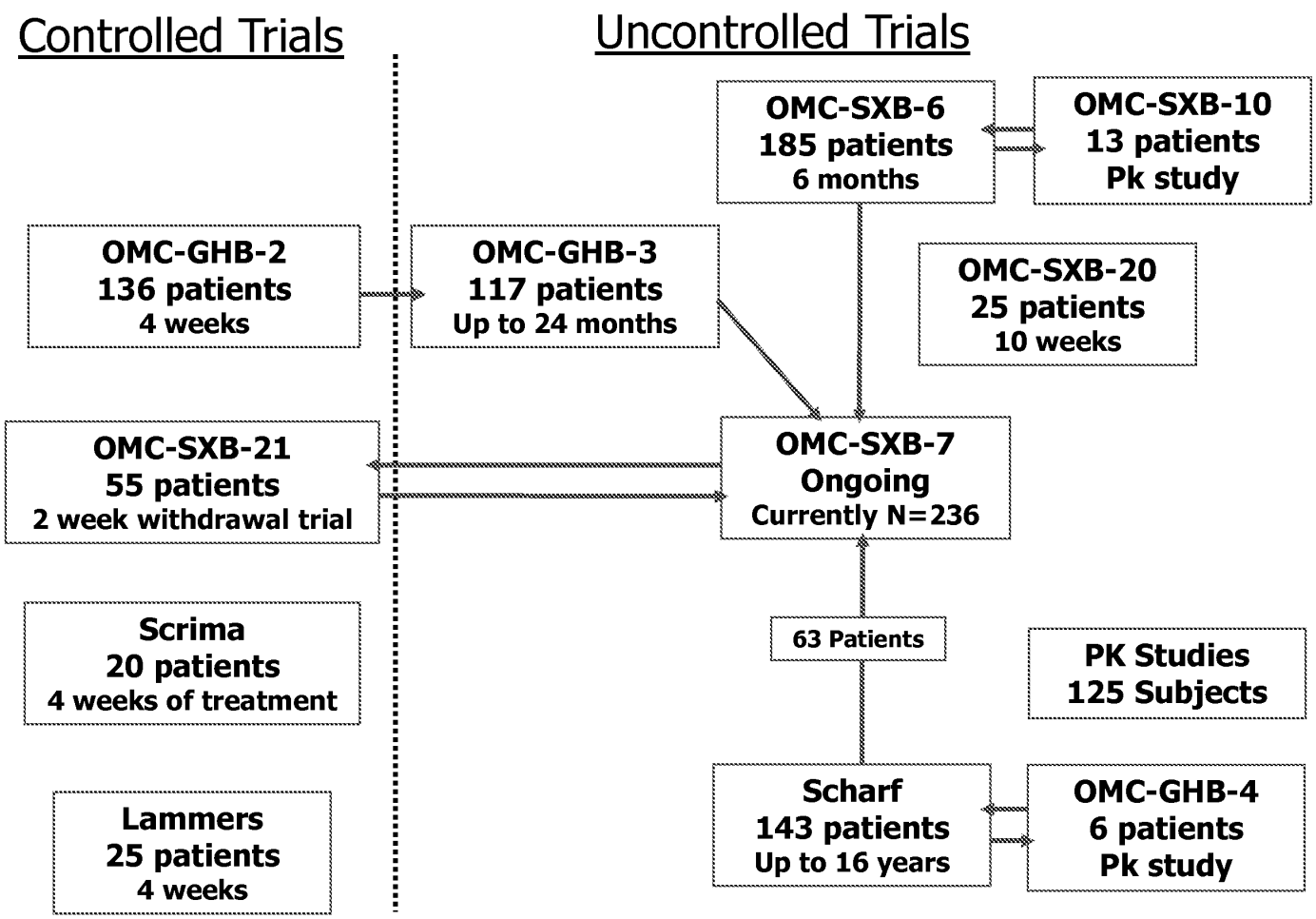
Need for New Treatments

- Narcolepsy is serious and disabling
- Current treatments are unsatisfactory in term of side effects and efficacy
- Current treatments all have a similar mode of action and act symptomatically
- Future treatments that may involve hypocretin agonists are years away

Xyrem® Clinical Data: Efficacy

William Houghton, M.D.

Chief Operating Officer & Medical Officer,
Orphan Medical, Inc.



OMC-GHB-2 Study

- Randomized, double-blind, placebo-controlled, parallel-group, multi-center trial comparing the effects of three doses (3g, 6g, 9g) of orally administered Xyrem with placebo for the treatment of narcolepsy

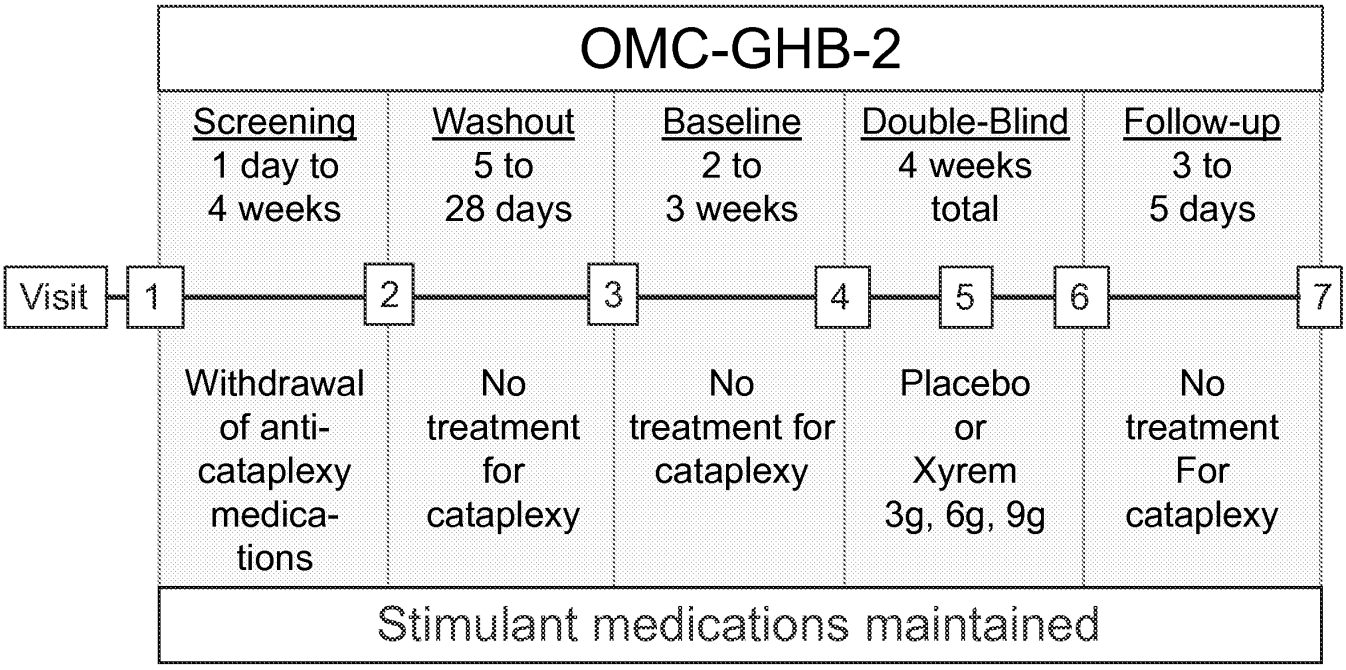
OMC-GHB-2
Efficacy Parameters

- Primary efficacy parameter
  - Total number of cataplexy attacks/week versus baseline
- Secondary efficacy parameters
  - Complete and partial cataplexy attacks
  - Daytime sleepiness / Inadvertent naps
  - Hypnagogic hallucinations
  - Sleep paralysis
  - CGI—Clinical Global Impression

OMC-GHB-2
Inclusion Criteria

- Diagnosis of narcolepsy
  - Polysomnography (PSG) and Multiple Sleep Latency Test (MSLT) within the last 5 years
    - Excluding sleep apnea or other causes of daytime sleepiness
  - History of Excessive Daytime Sleepiness (EDS) and cataplexy for at least 6 months
    - Recurrent daytime naps that occur almost daily for at least 3 months

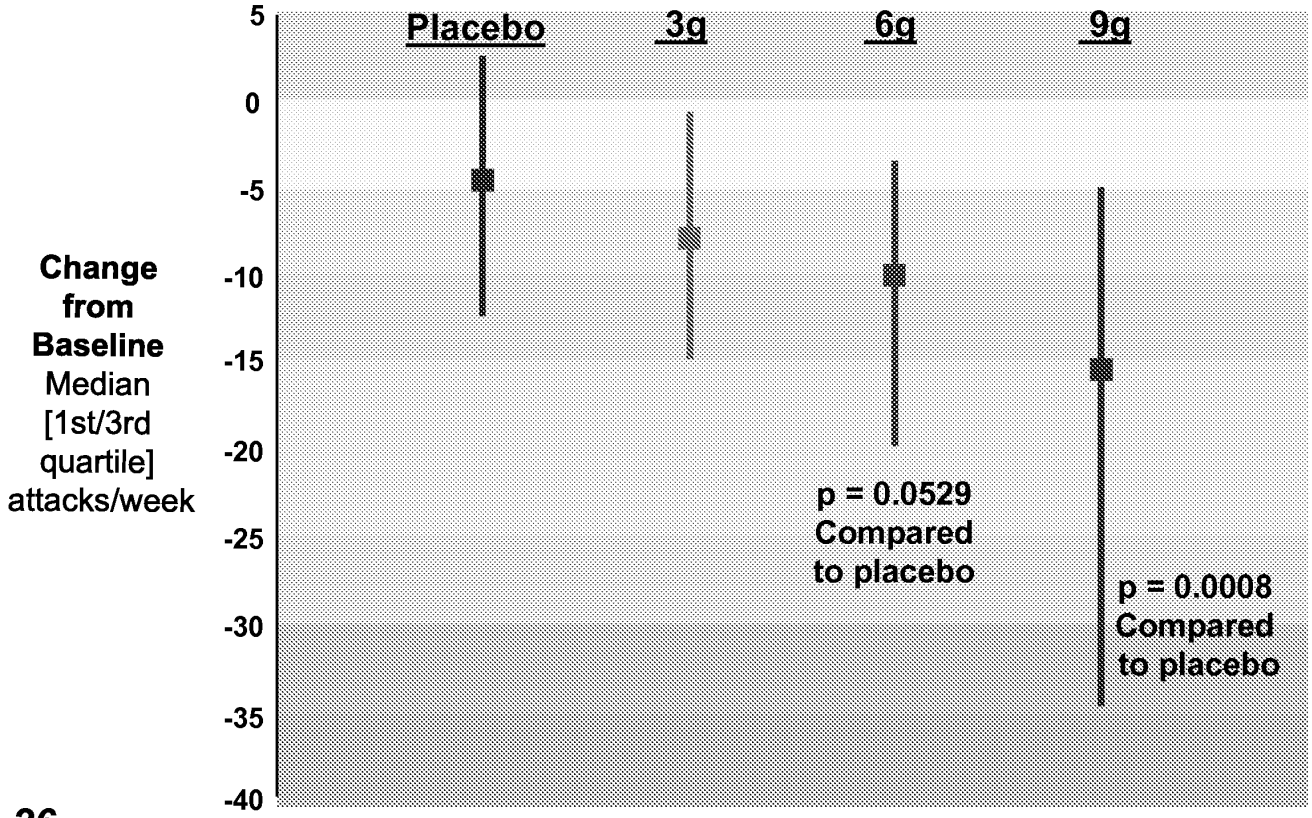
OMC-GHB-2
Overall Study Design



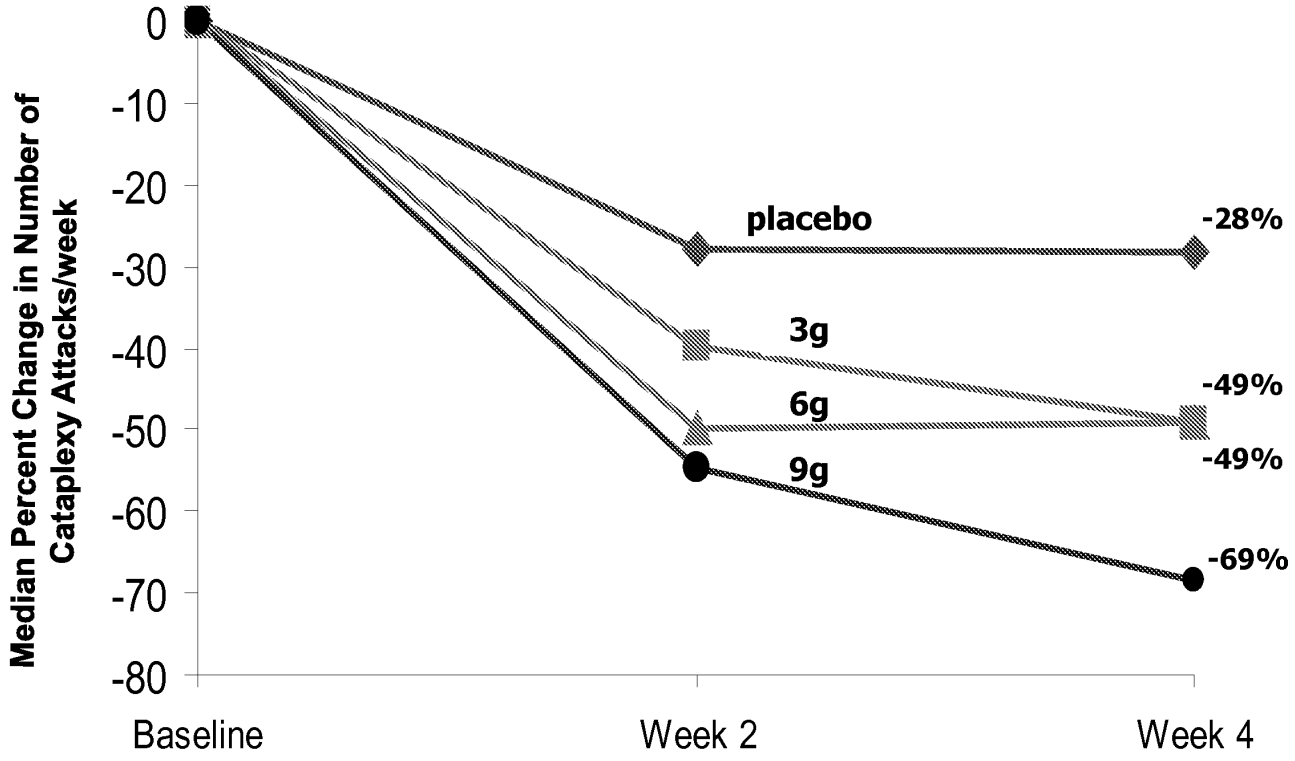
Cataplexy Attacks per Week

Dose Group	Statistic	Observed		Change from BL to EP	Comparison with placebo (p-value)
		Baseline(BL)	Endpoint(EP)		
Placebo	N=33 Mean(SD) Median P-value	35.1 (47.1) 20.5 --	24.0 (28.4) 16.3 --	-11.1 (27.7) -4.3 **0.028**	---
3g	N=33 Mean(SD) Median P-value	28.6 (30.5) 20.0 --	19.5 (27.5) 9.5 --	-9.1 (22.4) -7.0 **0.026**	0.5235
6g	N=31 Mean(SD) Median P-value	33.8 (45.6) 23.0 --	24.6 (62.9) 8.0 --	-9.2 (27.3) -9.9 **0.070**	0.0529
9g	N=33 Mean(SD) Median P-value	35.7 (34.5) 23.5 --	14.4 (19.3) 8.7 --	-21.3 (29.8) -16.1 **<0.001**	**0.0008**

OMC-GHB-2 Primary Efficacy
Total Cataplexy



OMC-GHB-2 Primary Efficacy
Cataplexy (Median Percent Change)

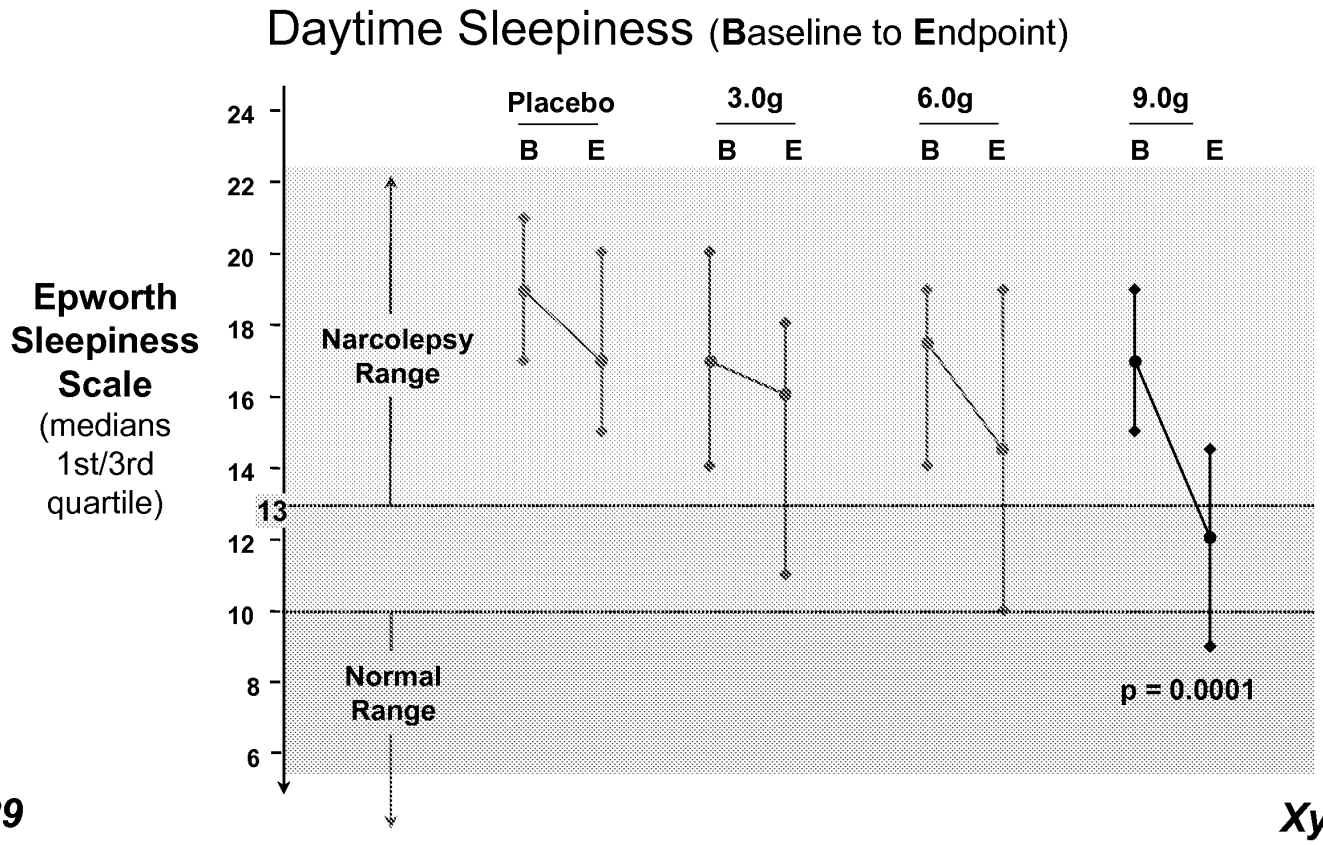


Secondary Efficacy
Epworth Sleepiness Scale

	Situation
1.	Sitting and reading
2.	Watching TV
3.	Sitting, inactive in a public place (e.g. a theater or a meeting)
4.	As a passenger in a car for an hour without a break
5.	Lying down to rest in the afternoon when circumstances permit
6.	Sitting and talking to someone
7.	Sitting quietly after lunch without alcohol
8.	In a car, while stopped for a few minutes in the traffic

Response: Range: 0-24
0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

OMC-GHB-2 Secondary Efficacy Daytime Sleepiness (medians)



OMC-GHB-2 Other Daytime Sleepiness Parameters

Parameters	Treatment	p-value (vs. placebo)
Inadvertent Naps/Sleep Attacks/ Daytime Sleep Attacks	Placebo	--
	3g	n.s.
	6g	**0.0497**
(baseline median = 1.50)	9g	**0.0122**

Clinical Global Impression (CGI)

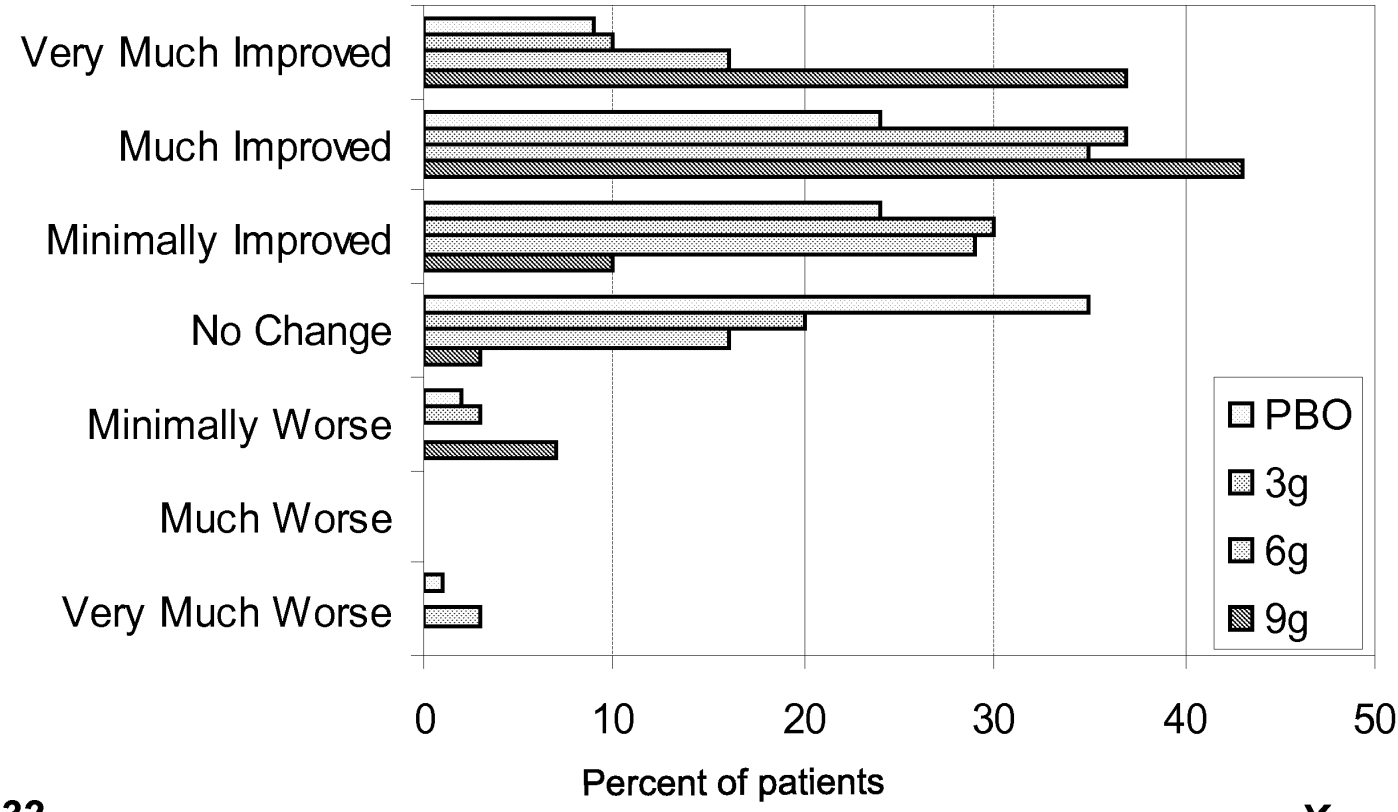
CGI-Severity (Baseline)

1. Normal – shows no signs of illness
2. Borderline ill
3. Slightly ill
4. Moderately ill
5. Markedly ill
6. Among the most extremely ill of patients

CGI-Change (Endpoint)

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

Clinical Global Impression of Change at Endpoint OMC-GHB-2 – By Dose Group



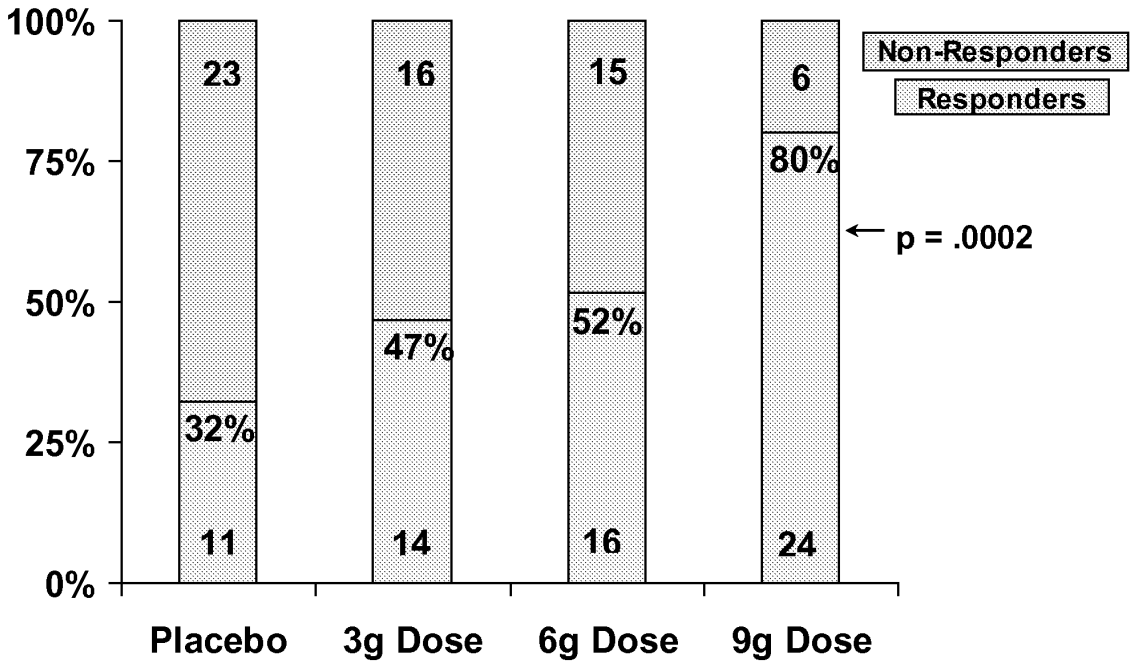
Post-Hoc
Responder/Non-Responder Analysis

- Responder
  - Very much improved
  - Much improved

- Non-Responder
  - Minimally improved
  - No-change
  - Minimally worse
  - Much worse
  - Very much worse

OMC-GHB-2 Secondary Efficacy
CGIc

Investigator's Clinical Global Impressions of Change



OMC-GHB-2
Other Variables

Parameters	Treatment	P-value (vs. placebo)
Awakenings at Night	Placebo	--
	3g	n.s.
	6g	n.s.
Baseline median = 2.27/day	9g	**0.0035**
Sleep Paralysis Episodes		
Baseline median = 0.14/day		n.s.
Hypnagogic Hallucinations		
Baseline median = 0.30/day		n.s.

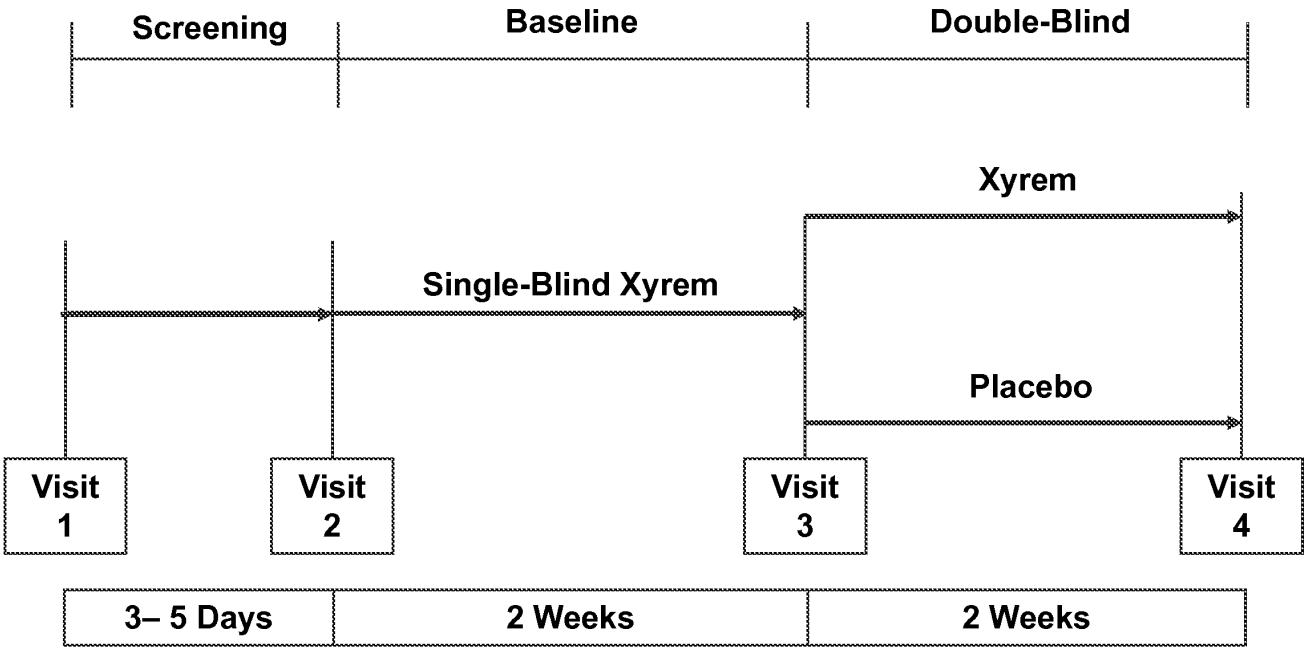
Xyrem® Clinical Data: Efficacy

OMC-SXB-21

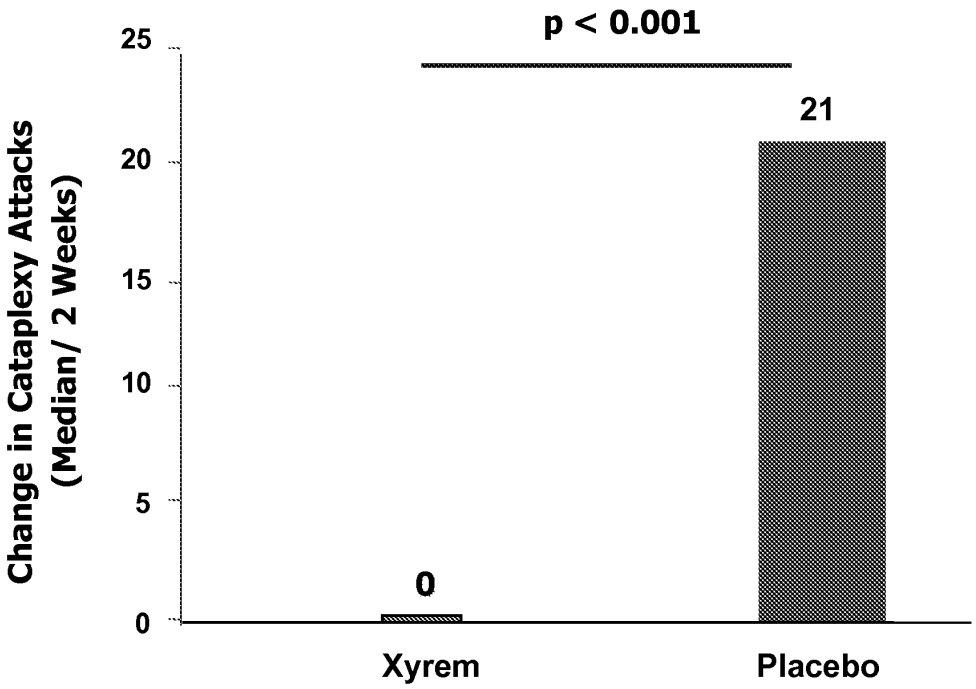
OMC-SXB-21
Objective

- Provide evidence for the long-term efficacy of Xyrem based on the return of cataplexy symptoms upon cessation of a minimum of 6 months of open-label treatment with active drug.

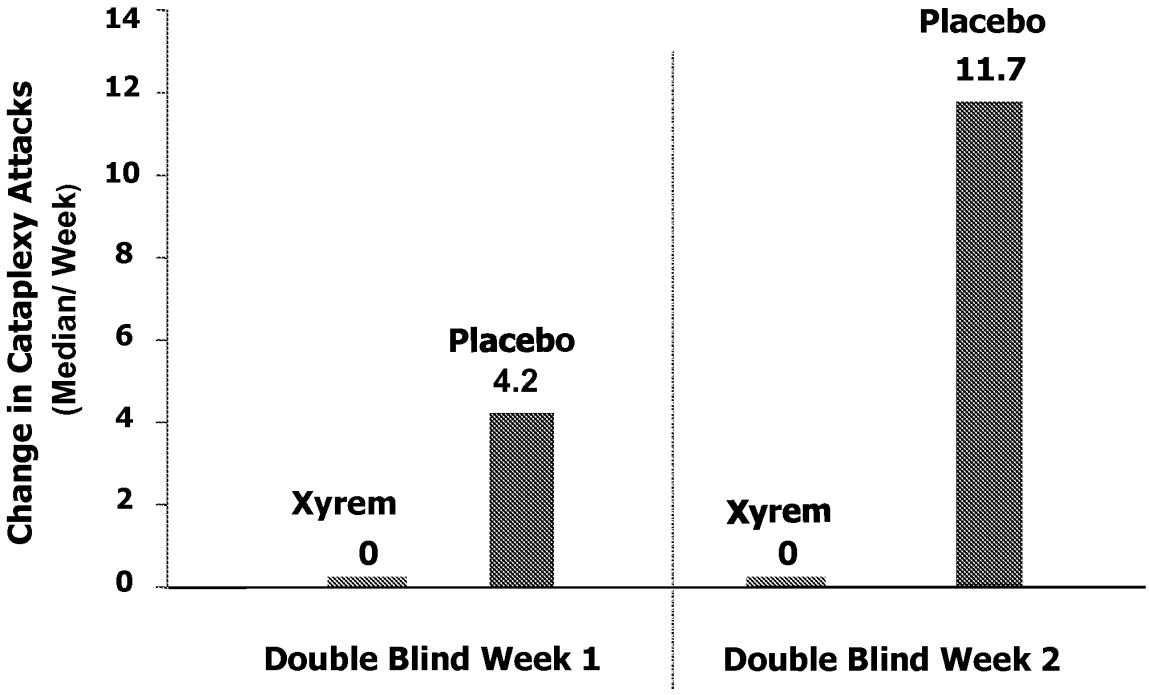
OMC-SXB-21
Study Design



OMC-SXB-21 Cataplexy
Median Change from Baseline



OMC-SXB-21 Cataplexy
Median Change from Baseline



Xyrem® Clinical Data: Efficacy

Other Double-Blind Placebo-Controlled Clinical Trials

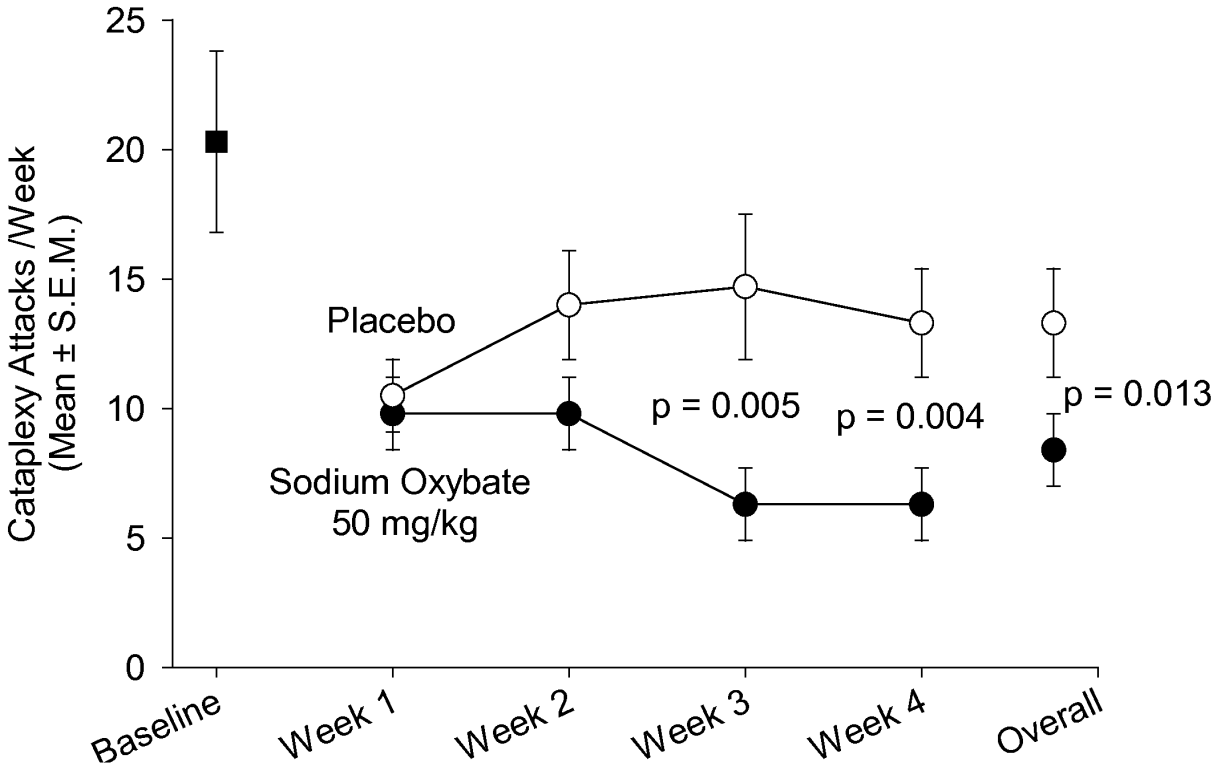
Scrima Trial
Lammers Trial

Scrima Cross-over Trial Study Design

N=20

	Baseline 14 Days	Treatment 1 29 Days	Washout 6 Days	Treatment 2 29 Days	Washout 6 Days
Withdrawal of Cataplexy Meds	X	Sodium oxybate	X	Placebo	X
	X	Placebo	X	Sodium oxybate	X
	Stimulants continued throughout study				

Scrima Trial
Number of Cataplexy Attacks / Week

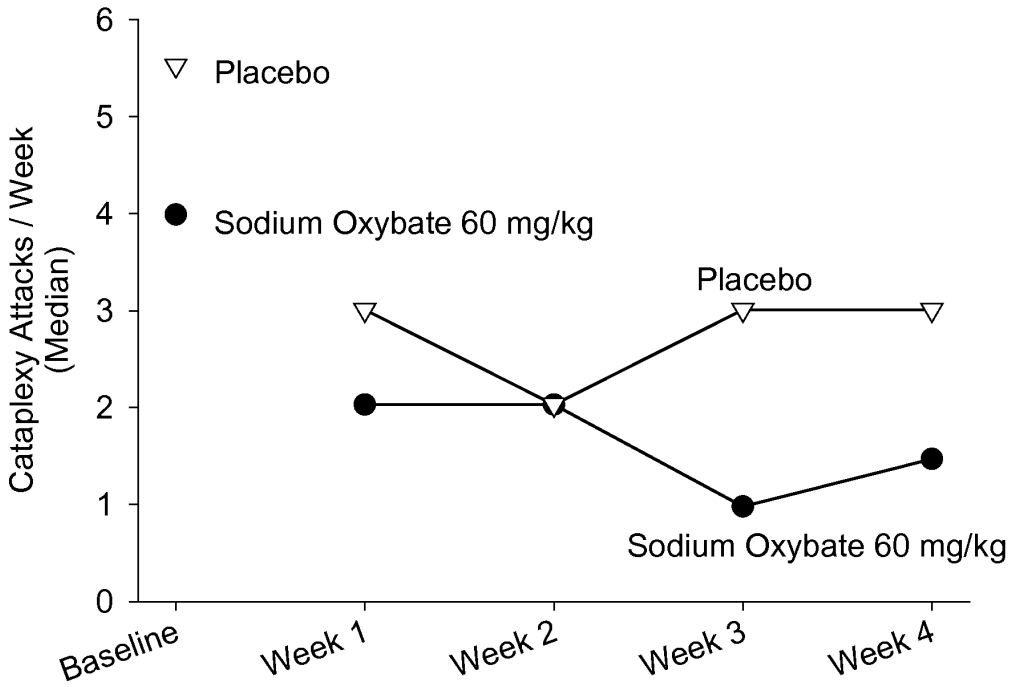


Lammers Trial
Study Design

N=24

Baseline 1 1 Week	Treatment 1 4 Weeks	Washout 3 Weeks	Baseline 2 1 Week	Treatment 2 4 Weeks
X	Sodium Oxybate (60mg/kg)	X	X	Placebo
X	Placebo	X	X	Sodium Oxybate (60 mg/kg)
Concomitant treatment for cataplexy and EDS continued throughout				

Lammers Trial
Cataplexy



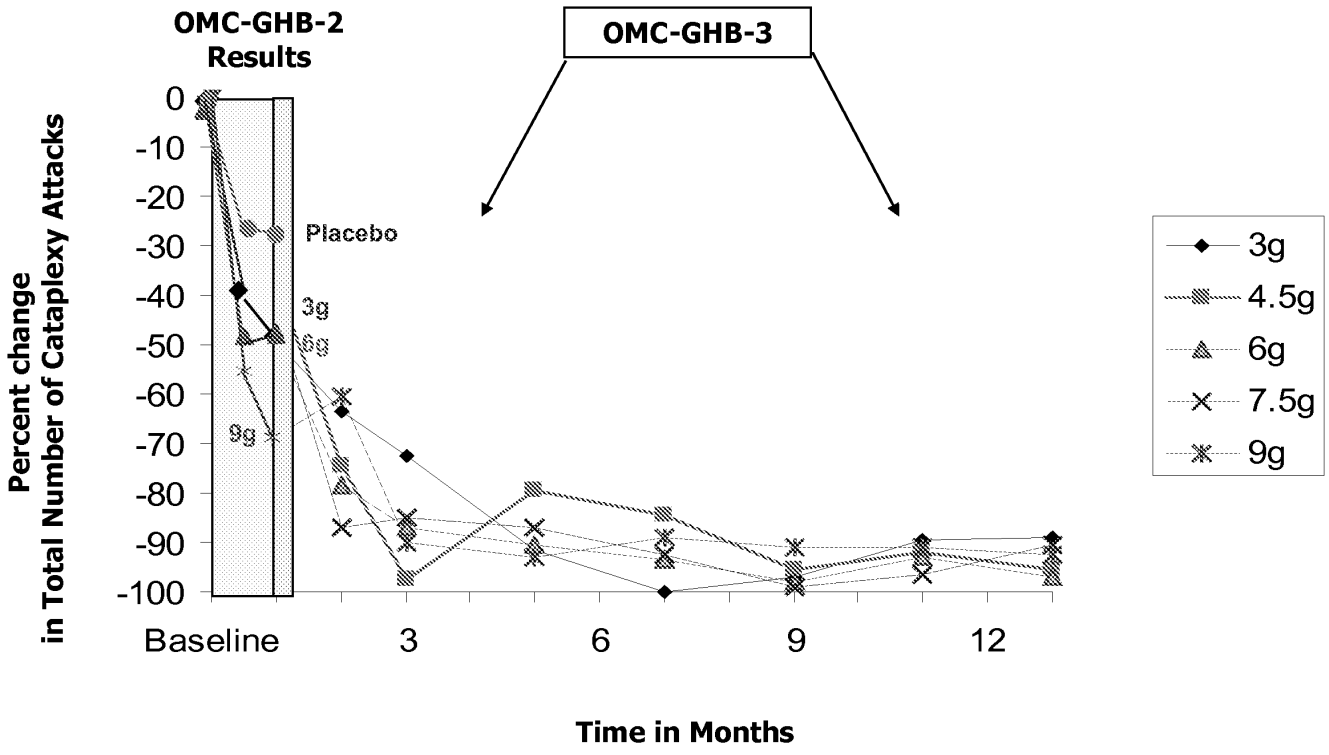
Lammers Trial
Other Measures

Efficacy Parameter	Change	Significance p-value
Hypnagogic Hallucinations	Reduction from 0.87 to 0.28	**0.008**
Daytime Sleep Attacks	Reduction from 2.27 to 1.40	**0.001**

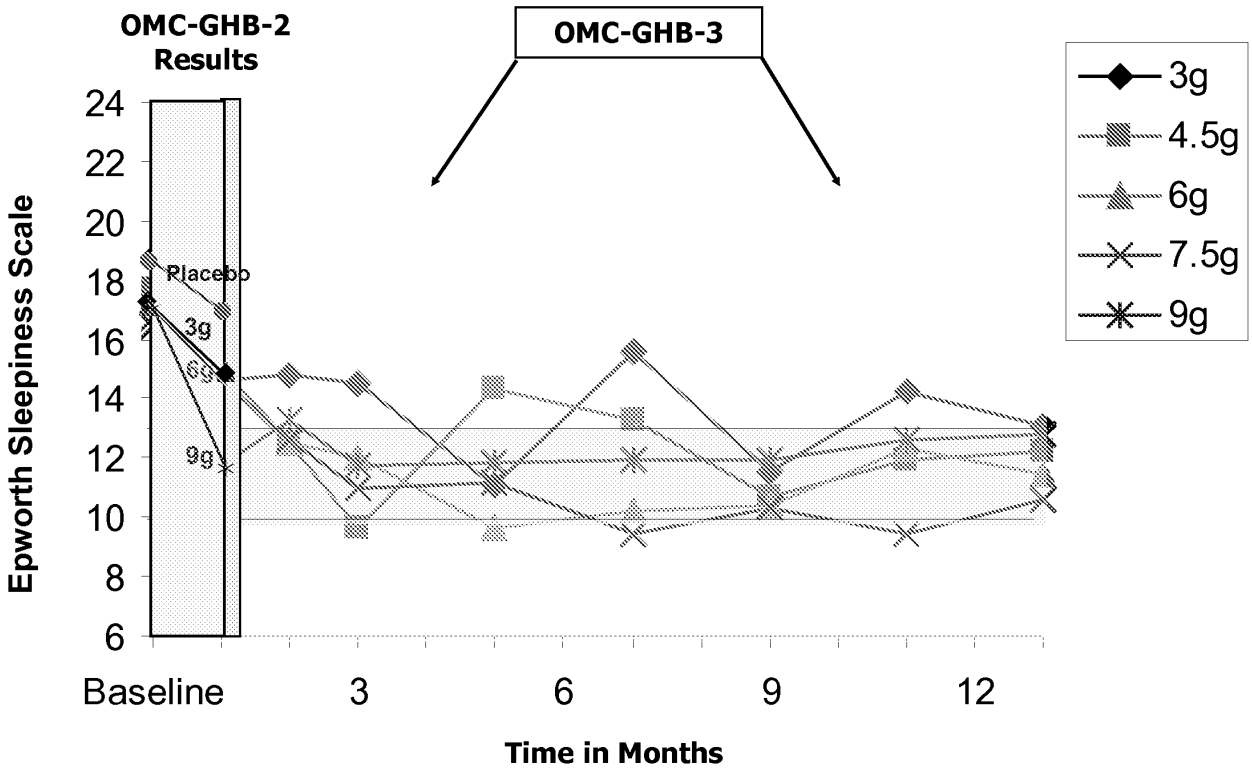
Xyrem® Clinical Data: Efficacy

OMC-GHB-3

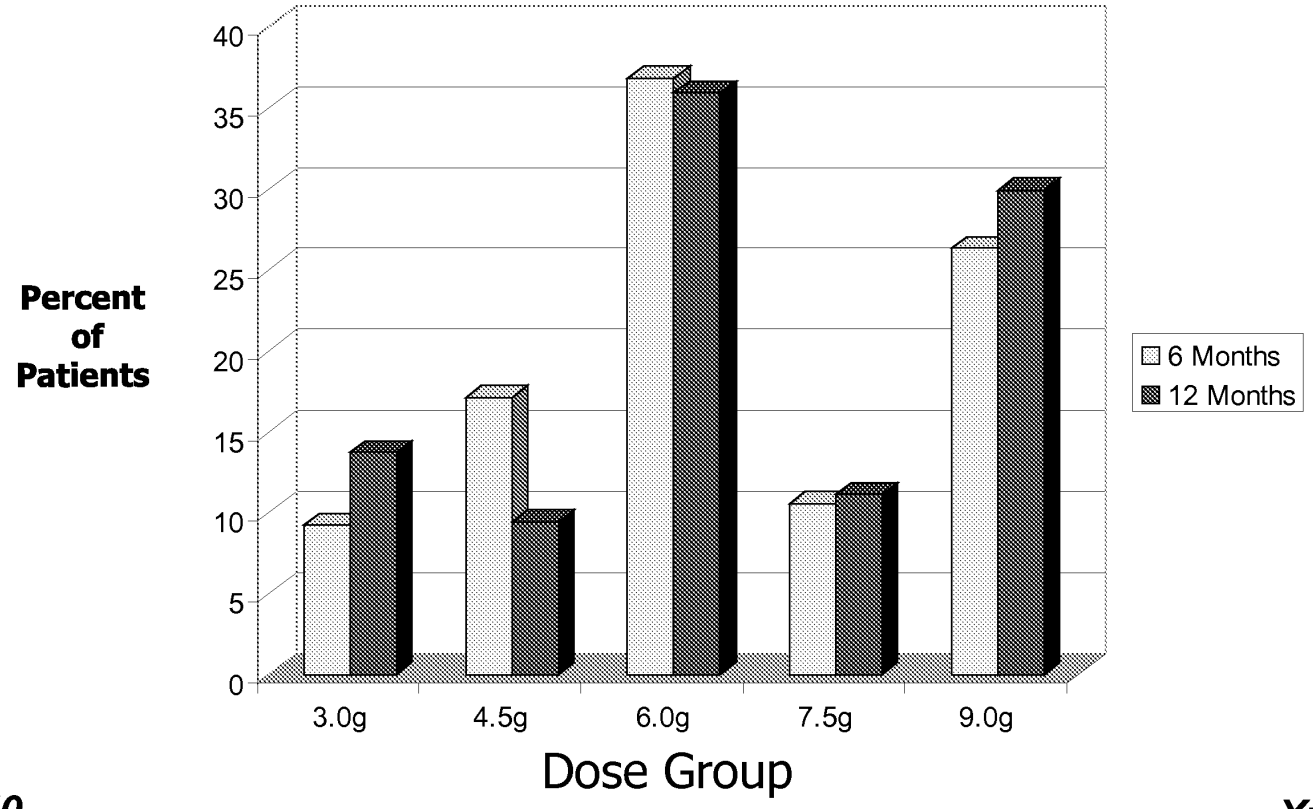
OMC-GHB-3
Cataplexy – Median Percent Change



OMC-GHB-3
Mean ESS for All Dose Groups

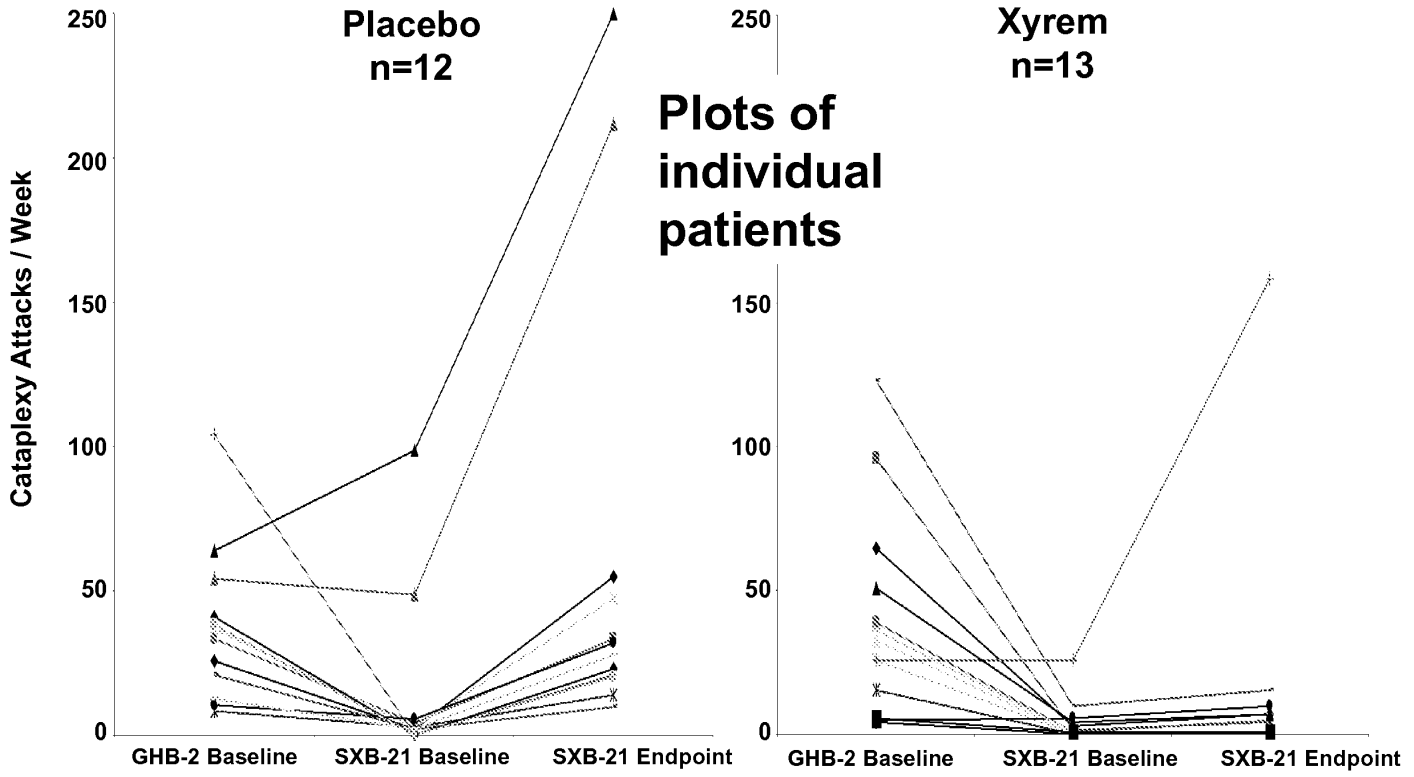


OMC-GHB-3
Dose Distribution – 6 & 12 Months



OMC-SXB-21 Supports Efficacy in OMC-GHB-3

Cataplexy Attacks / Week: OMC-GHB-2/3 Patients in OMC-SXB-21



Summary of Efficacy

Trial/Dose	Change in Cataplexy	Daytime Sleepiness
OMC-GHB-2		
3g	0.5235	0.1137
6g	0.0529	0.1860
9g	**0.0008**	**0.0001**
OMC-SXB-21	**0.001**	--
SUPPORTIVE STUDIES		
LAMMERS--60 mg/kg (4.75g)	**0.002**	**0.028**
SCRIMA--50 mg/kg (3.5g)	**0.022**	n.s.

Clinical Pharmacokinetics, Drug Interactions, and Pharmacodynamics

William Houghton, M.D.

Chief Operating Officer & Medical Officer,
Orphan Medical, Inc.

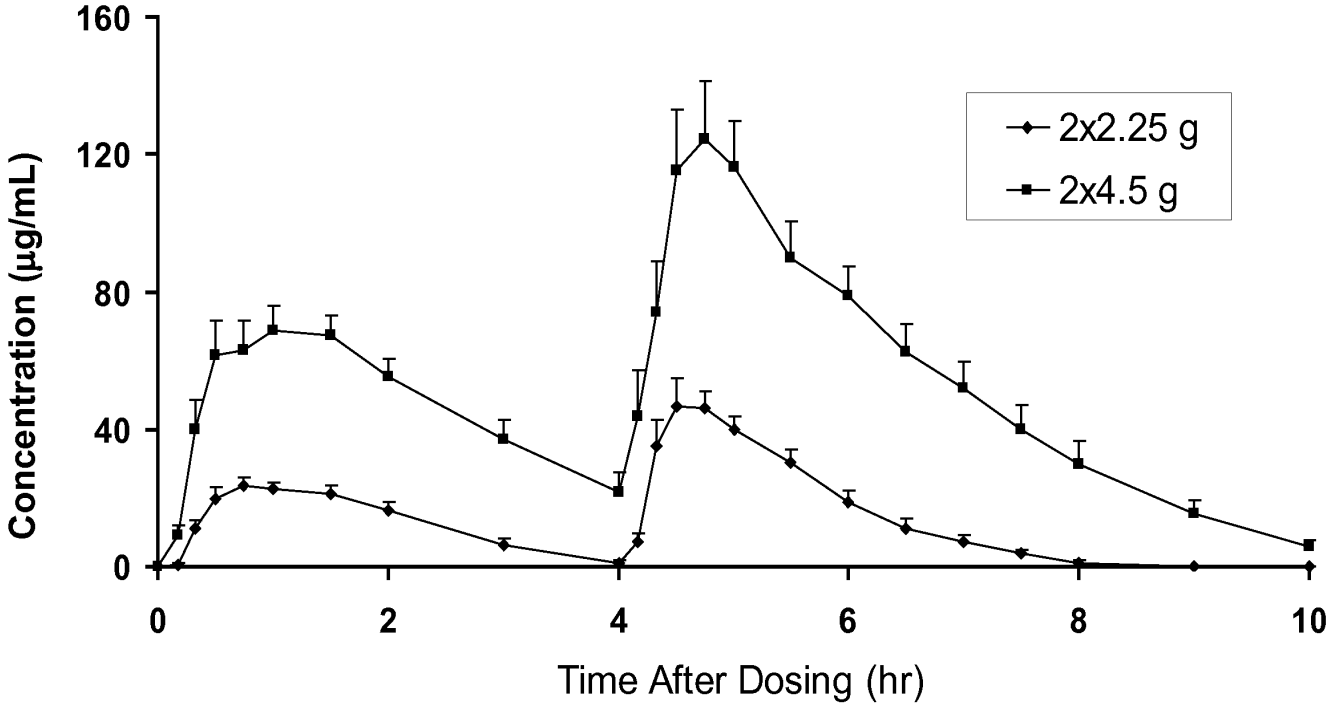
Xyrem Pharmacokinetic Studies

1. Pilot PK study in narcoleptic patients
2. Acute versus chronic dosing in patients
3. Study of gender differences
4. Dose proportionality study
5. Food effect study

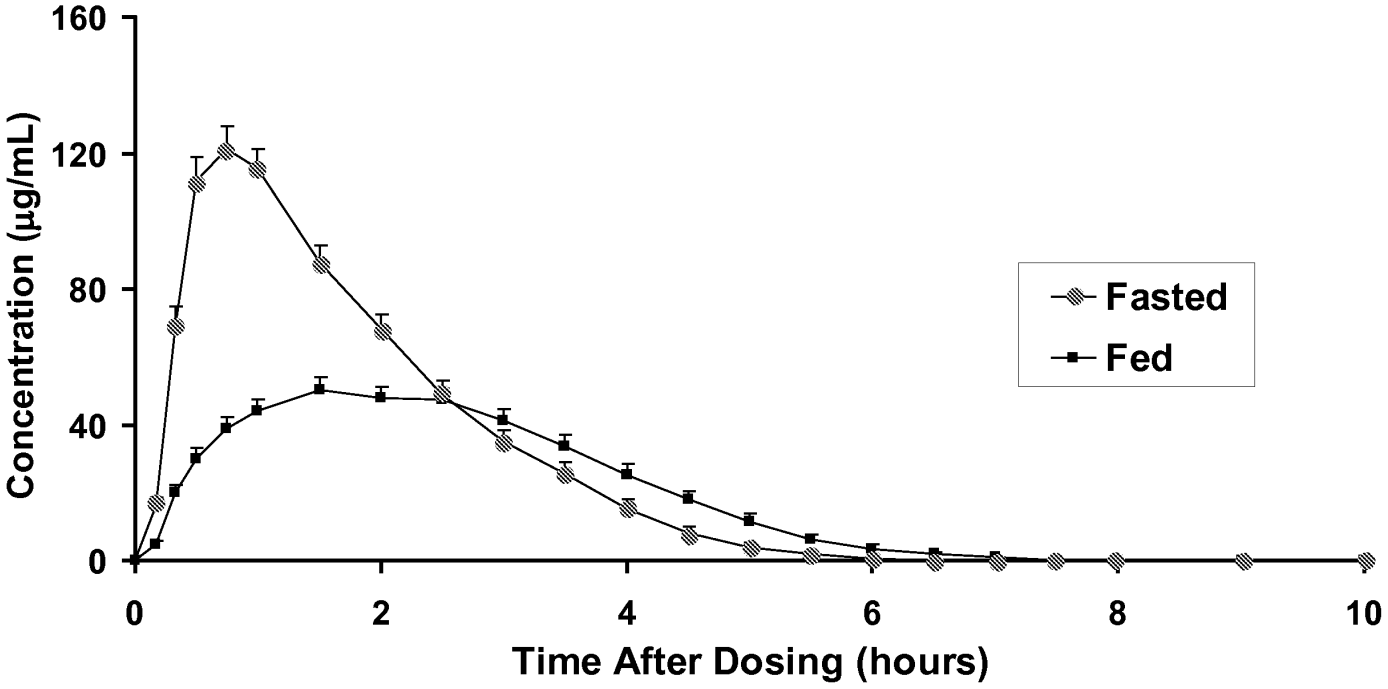
6-8. Three drug interaction studies
(zolpidem, protriptyline, modafinil)

In vitro cytochrome p450 study: negative

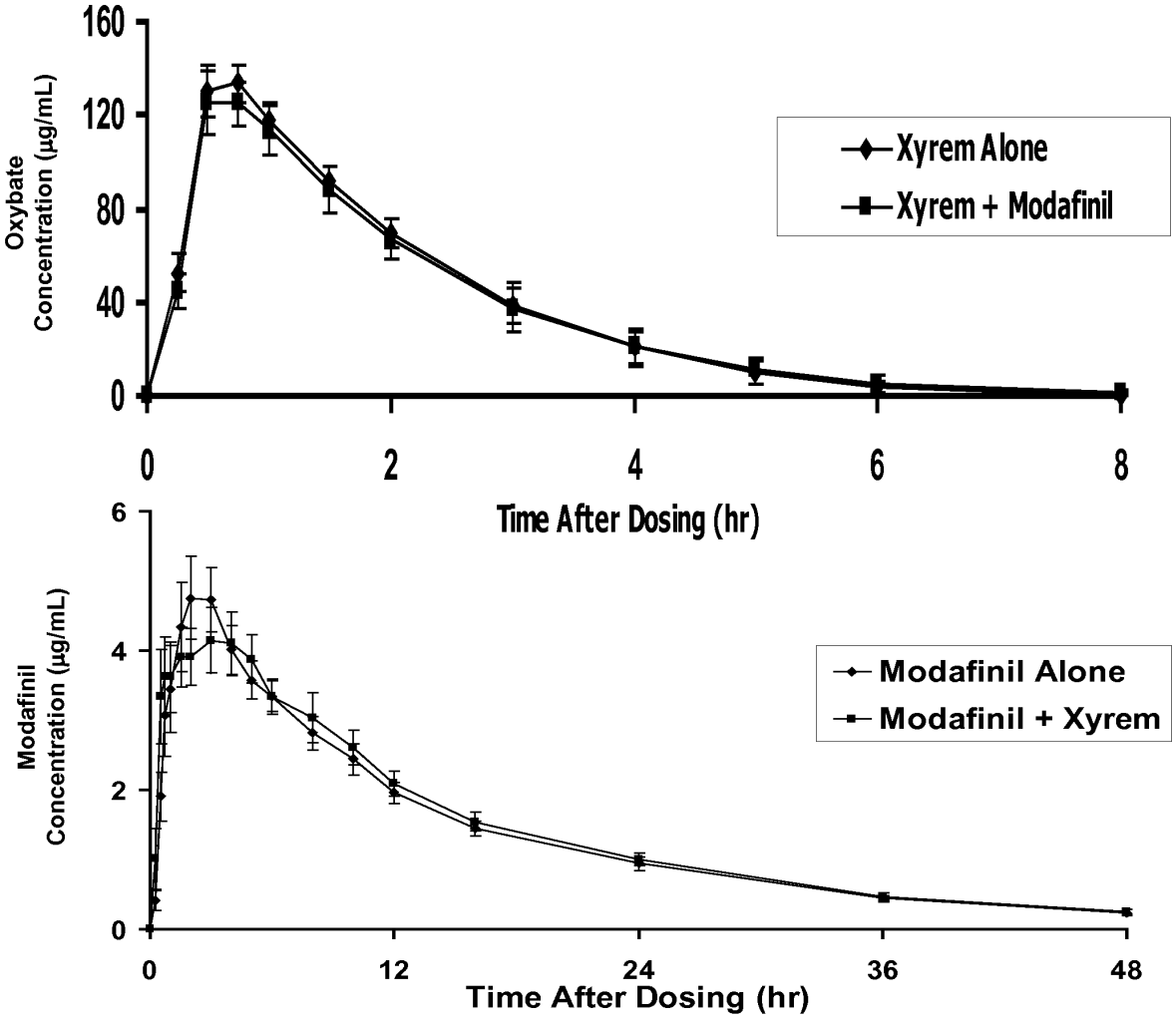
Plasma Concentrations of Oxybate (GHB) After 4.5 Grams (2x2.25) or 9.0 Grams (2x4.5) of Xyrem to Normal Volunteers (Mean, Standard Error)



Plasma Oxybate (GHB) Concentration After an Oral Dose of 4.5 Grams of Xyrem to Normal Volunteers Following a High Fat Meal or after an Overnight Fast



Xyrem – Modafinil Interaction Study



Xyrem Pharmacokinetics: Summary

- Rapid absorption (T_{max} = 30-75 min) and elimination ($T_{1/2}$ = 40-60 min) from plasma
- Non-linear, dose-dependent kinetics
- Capacity limited absorption & elimination
- No gender differences
- No difference between acute and chronic dosing

Xyrem Pharmacokinetics: Summary

- Chronic dosing does not change kinetics
- Food delays absorption and reduces systemic exposure
- No kinetic interactions with 3 other classes of drugs
- No cytochrome p450 effects found

Polysomnographic Effects of Xyrem

Jed Black, M.D.

Director of the Stanford Sleep Clinic
Stanford University

Effects of Sodium Oxybate on Quantitative EEG Parameters in Narcoleptics

- Initial research in narcolepsy (1977+)
  - Broughton and Mamelak (1979)
  - Mamelak (1981, 1977)
  - Modified sleep patterns
    - increase in slow-wave sleep
    - reduced awakenings
- Scrima (1989, PSG and MSLT)
- Lammers (1993, PSG and MSLT)
- OMC-SXB-20 (PSG and MWT)

Scrima and LammersTrials
Nocturnal PSG Data

		Scrima Trial	Lammers Trial
Variable	Result	p-value	p-value
Stage 1 Sleep	Decreased	0.026	n.s.
Stages 3 & 4	Increased	0.001	0.053
Awakenings	Decreased	0.042	0.016
% wake time	Decreased	n.s.	0.007

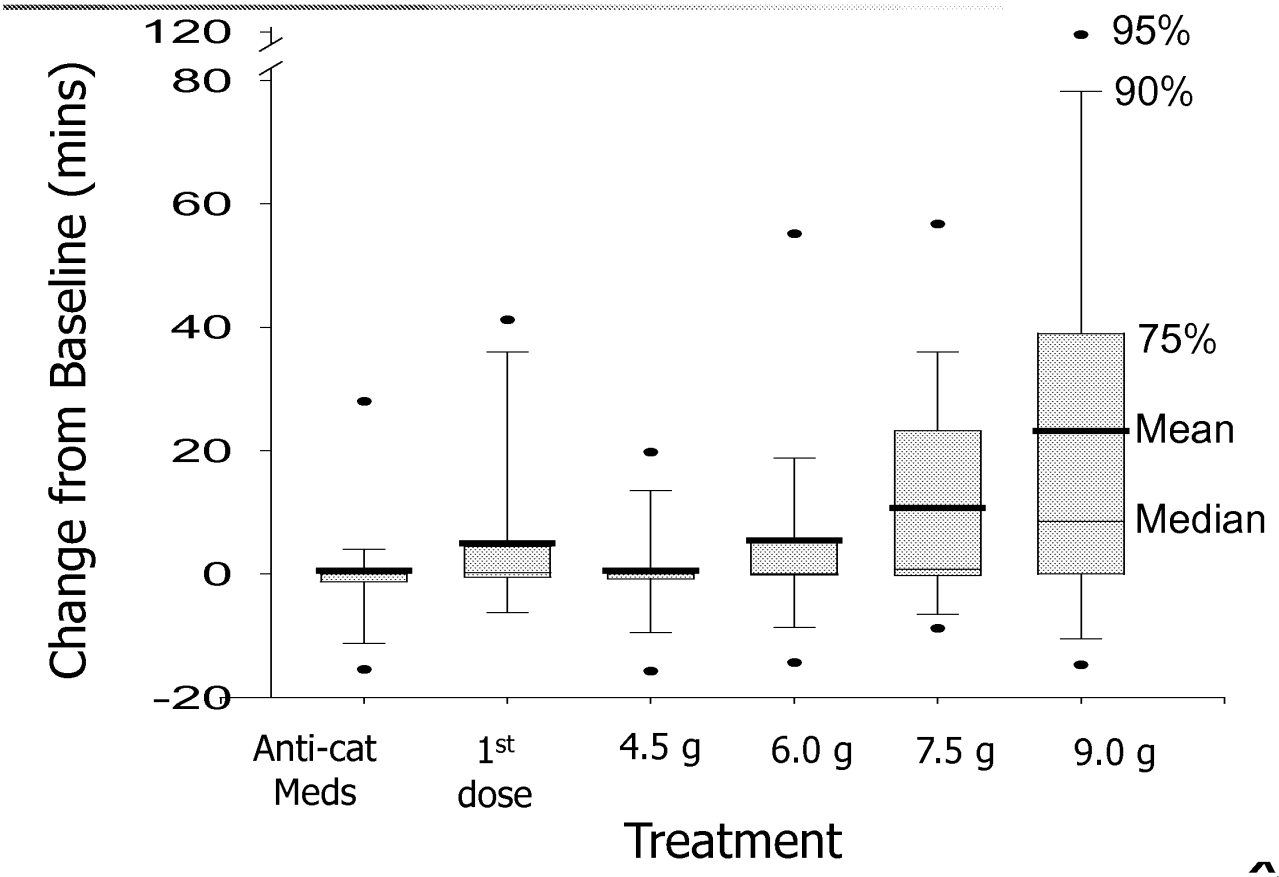
OMC-SXB-20
Study Design

- Open-label, dose-escalation (4.5 g – 9 g)
  - Stimulants continued at stable dose
  - 2 week anti-cataplectic taper
  - 2 week washout
  - 4 weeks 4.5 g Xyrem
  - 2 weeks 6 g, 7.5 g, and 9 g each
- PSG obtained:
  - Prior meds
  - Baseline
  - 4.5 g (1st night)
  - 4.5 g, 6 g, 7.5 g, 9 g (last night)
- MWT obtained: prior meds, baseline, 4.5 g (after 4 weeks),and 9 g

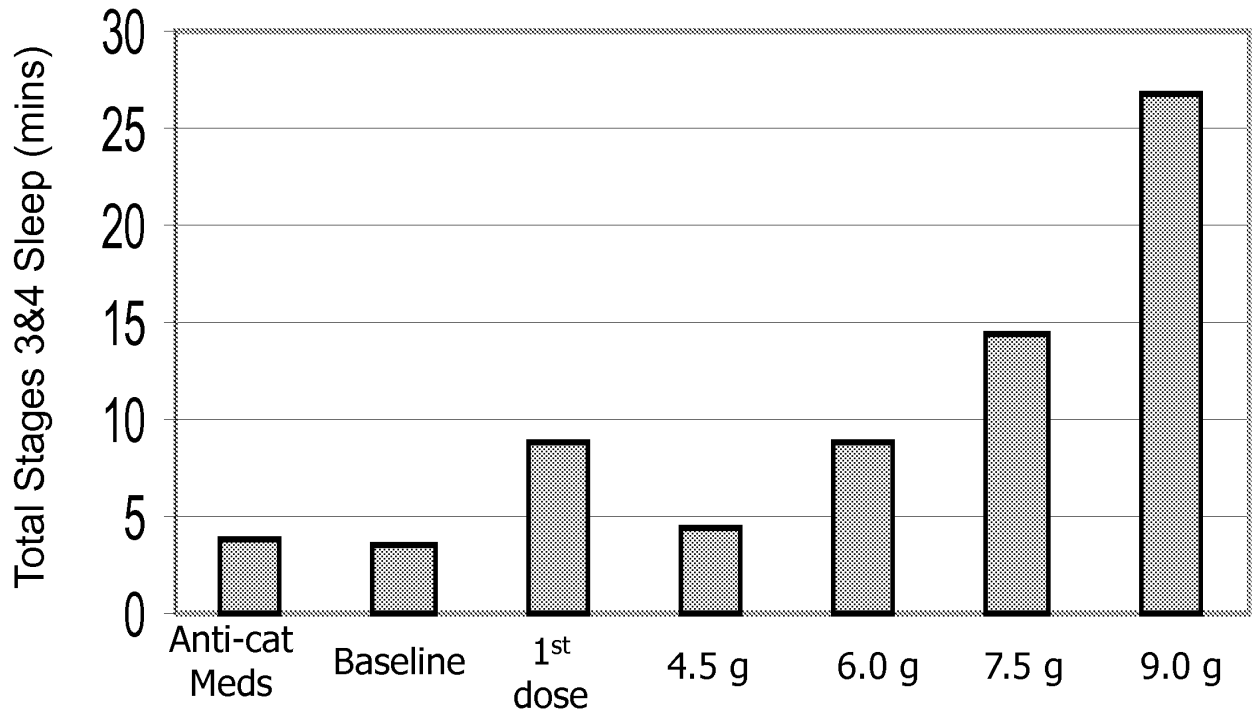
OMC-SXB-20
Study Results

- PSG
  - Dose-related increase in Stage 3 & 4 sleep
  - Dose-related increase in Delta Power
- Daytime measures
  - Dose-related increase in daytime alertness
  - Dose-related reduction in subjective sleepiness

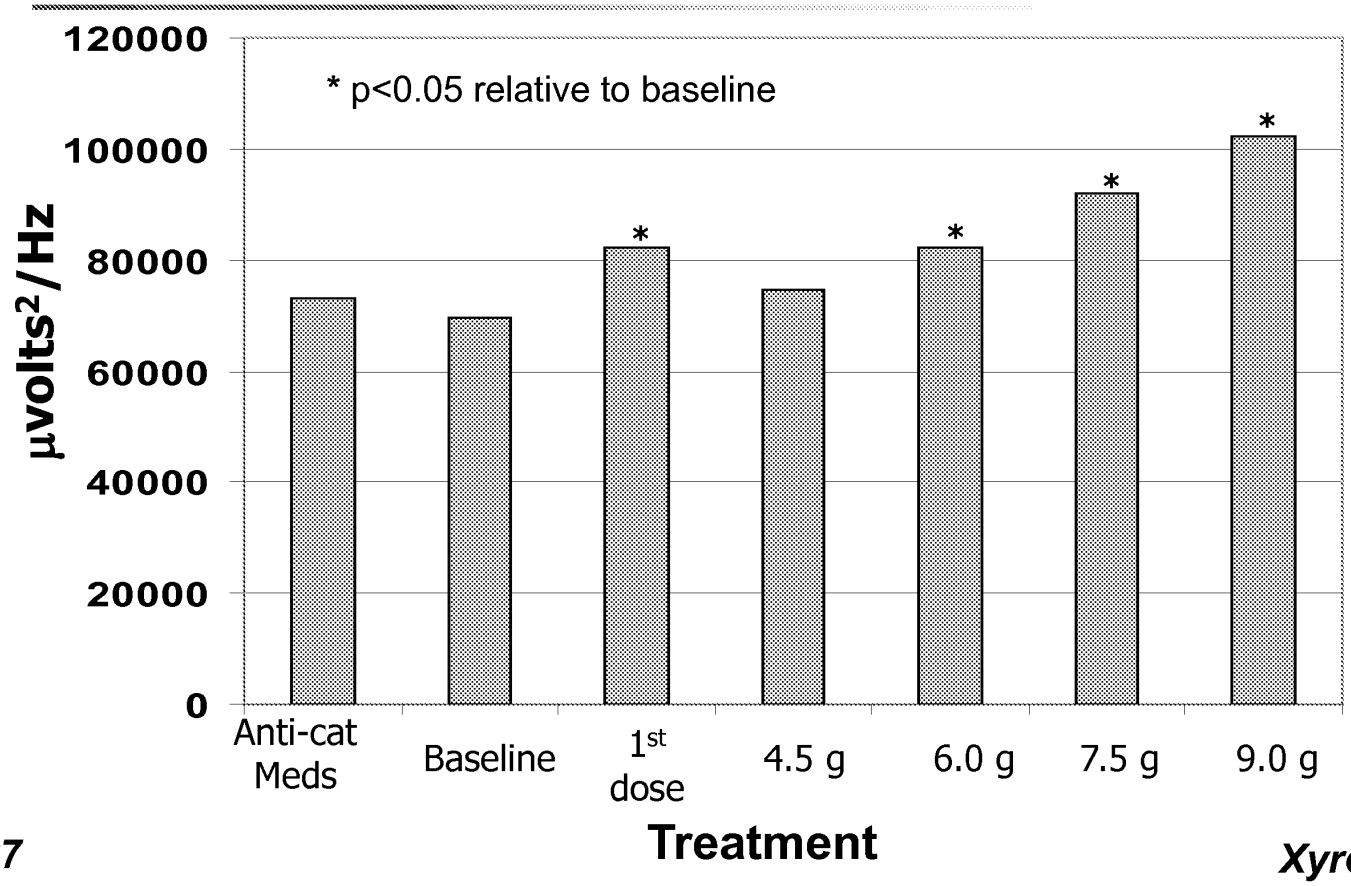
Change in Slow Wave (Stages 3&4) Sleep Duration



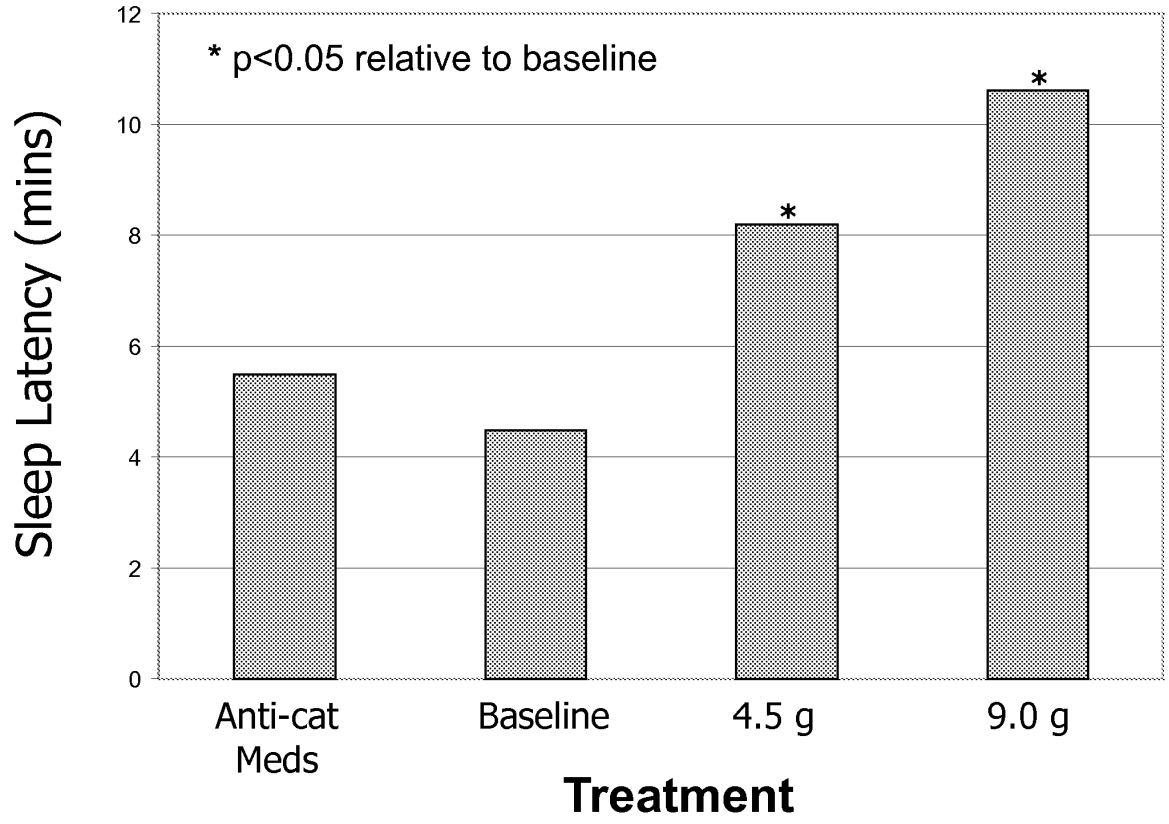
Total Slow Wave (Stages 3&4) Sleep Duration



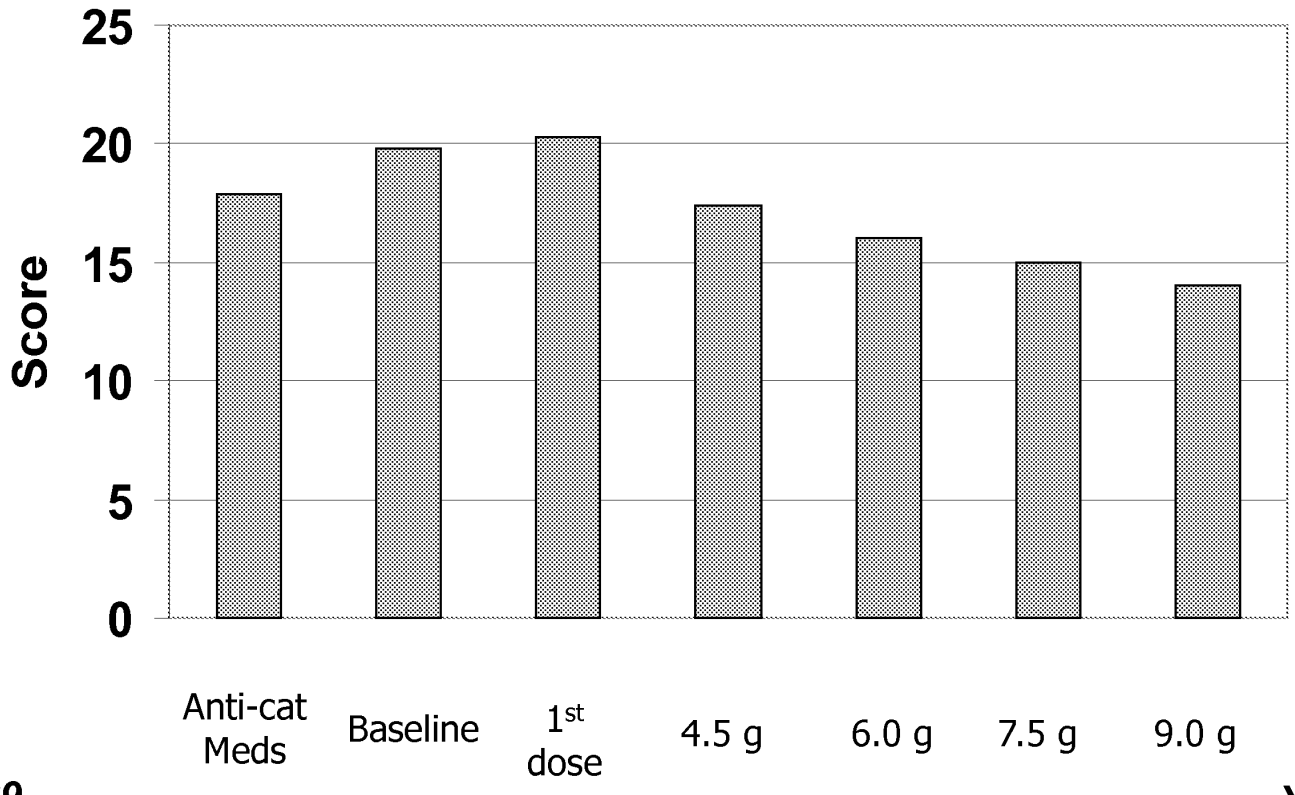
Delta Power



MWT Sleep Latency (Daytime)



Epworth Sleepiness Score (Daytime)



Xyrem

Correlation Between Daytime and Nocturnal Effects

Variable	Variable	Coefficient	P-Value
Delta Power	**Epworth**	**-0.23**	**0.0086**
Delta Power	MWT	0.18	0.0914
Stage 3&4 Sleep	Epworth	-0.17	0.0599
Stage 3&4 Sleep	MWT	0.21	0.0550

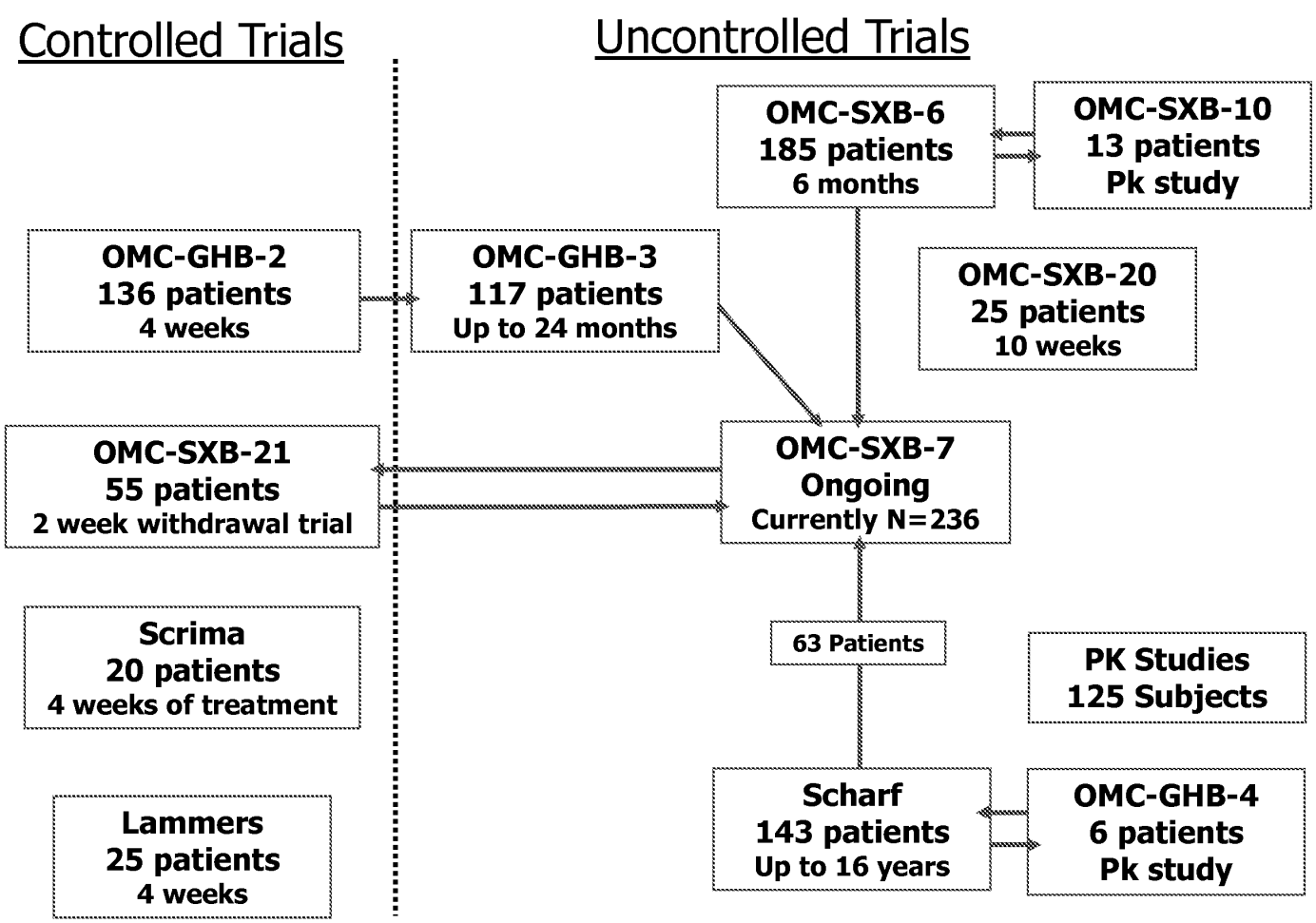
OMC-SXB-20
Overall Conclusions

- PSG parameters modulated as a function of Xyrem treatment
  - Xyrem increases measures of restorative sleep
    - Stages 3 & 4
    - Delta Power
- Daytime sleepiness decreased
  - MWT and Epworth
- Correlation between daytime and nocturnal effects
  - Possible novel neurological mechanism

Safety Summary Overview

William Houghton, M.D.

Chief Operating Officer & Medical Officer,
Orphan Medical, Inc.



Sodium Oxybate Exposure
All Trials Including Scharf

Any Exposure	479 patients
PK	125 subjects
Total	604
≥6 months	360 patients
≥12 months	286 patients
Patient-years	1328

Sodium Oxybate Exposure
Updated ISS Excluding Scharf

Any Exposure	399 patients
PK	125 subjects
Total	524
≥6 months	296 patients
≥12 months	223 patients
Patient-years	330

Updated ISS Database
Summary of Patient Exposure by Dose

	Sodium Oxybate Dosage (g/d)					
	Total	**3.0**	**4.5**	**6.0**	**7.5**	**9.0**
≥ 6 months	296	9	50	115	59	62
≥ 12 months	223	5	27	60	26	34
≥ 24 months	48	2	4	13	9	13

Updated ISS Database
Treated Patient Disposition

Patient Disposition	Sodium oxybate
Patients Treated	399
Completed Treatment	46 (12%)
Ongoing Treatment	210 (52%)
Discontinued Treatment	143 (36%)
Adverse event	52 (13%)
Patient request	34 (9%)
Patient non-compliance	19 (5%)
Other	18 (5%)
Lost to follow-up	11 (3%)
Lack of efficacy	5 (2%)
Protocol deviation/violation	4 (<1%)
Death	2 (<1%)

NOTE: 3 placebo patients did not proceed to active treatment trials

Updated ISS Database
Summary of Adverse Events

	Total	Placebo	Sodium Oxybate
Total Patients	n=402	n=54	n=399
At least 1 AE	82%	70%	82%
Severe AE	20%	6%	20%
D/C due to AE	13%	2%	13%
Serious AE	7%	0%	7%
Deaths	<1% (2)	0%	<1% (2)

Updated ISS Database
Dose Distribution of Adverse Events

Xyrem Dose (g/d)	**3**	**4.5**	**6**	**7.5**	**9**
Total Patients:	97	269	290	133	129
At least 1 AE	60%	51%	62%	54%	78%
Severe AE	3%	9%	12%	5%	16%
D/C due to AE	5%	6%	5%	3%	14%
Serious AE	0%	2%	4%	2%	8%
Deaths	0%	0%	1%	0%	0%

Updated ISS Database
Most Frequent Adverse Events (n=399)

COSTART Preferred Term	All Adverse Events
Headache	28%
Nausea	23%
Dizziness	19%
Pain	18%
Somnolence	14%
Pharyngitis	12%
Sleep disorder	11%
Accidental injury	10%
Flu syndrome	10%
Infection	10%
Viral infection	10%
Asthenia	9%
Vomiting	8%
Nervousness	8%
Confusion	7%
Urinary Incontinence	7%

Placebo-Controlled Clinical Trials Most Frequent Adverse Events

Adverse Event COSTART Term	Placebo (n=79)	Sodium Oxybate (n=147)
Dizziness	3%	23%
Headache	15%	20%
Nausea	5%	16%
Somnolence	9%	12%
Pain (unspecified)	4%	12%
Sleep disorder	3%	9%
Confusion	1%	7%
Infection	1%	7%
Dyspepsia	6%	6%
Vomiting	1%	6%
Urinary incontinence	0%	5%
Nervousness	8%	5%

OMC-SXB-21
Safety Summary

Most Common* Adverse Events
Double-Blind Treatment Period

COSTART Term	Placebo (n=29)	Xyrem (n=26)
Anxiety	2 (7%)	0
Headache	2 (7%)	0
Rash	1 (3%)	1 (3%)

*AEs with ≥ 2 occurrences

OMC-SXB-21
Possible Withdrawal Associated AEs

COSTART Term	Placebo (n=29)	Xyrem (n=26)
Anxiety	2 (7%)	0
Dizziness	1 (3%)	0
Insomnia	1 (3%)	0
Sleep Disorder*	1 (3%)	0
Somnolence	1 (3%)	0

* Verbatim Term: Increased awakenings

Scharf Trial

- Conducted under an Investigator IND without external monitoring prior to Orphan Medical IND
- Represents 16 years of clinical experience (rather than drug development research) without regulatory disciplines
- Patients were located all over the country
- Data source primarily from diary recordings without medical review and interpretation
- Lack of patient compliance contributed to significant discontinuation
- Dosing accountability and dose titration is less clearly defined
- Less defined entry criteria

Adverse Events

- Scharf open-label clinical study
  - Dosing exposure
  - Patient disposition
  - AE incidence (16 years)
  - AE incidence (1st 6 months)

Scharf Trial (16 years)
Patient Disposition

Total Patients	143 (100%)
Ongoing	71 (50%)
Transferred to OMC-SXB-7	63 (44%)
Continued in Scharf Trial	8 (6%)
Early Withdrawal	71 (50%)
Patient Non-Compliance	24 (17%)
Adverse Event	23 (16%)
Cost	13 (9%)
Patient Request	5 (4%)
Lack of Efficacy	4 (3%)
Protocol Deviation	1 (<1%)
Other	1 (<1%)
Screen Failure	1 (<1%)

Scharf Trial (16 years)
AE Incidence

Adverse Event	Incidence (%)
Viral infection	57%
Headache	52%
Pain	48%
Accidental Injury	42%
Nausea	41%
Flu syndrome	39%
Pharyngitis	38%
Rhinitis	36%
Increased cough	34%
Sleep disorder (sleepwalking)	32%
Urinary incontinence	23%

Comparison of Updated ISS Database to Scharf Trial (First 6 months) Most Frequent Adverse Event Incidence

COSTART Preferred Term	Updated ISS (n=399)	Scharf Trial (n=143)
Headache	28%	33%
Nausea	23%	23%
Dizziness	19%	18%
Pain (unspecified)	18%	26%
Somnolence	14%	0%
Pharyngitis	12%	14%
Sleep disorder	11%	9%
Accidental injury	10%	10%
Flu syndrome	10%	11%
Infection	10%	1%
Viral infection	10%	29%
Rhinitis	9%	14%
Sinusitis	8%	11%
Malaise	2%	10%

Adverse Events of Special Interest

- Incontinence / convulsions
- Confusion
- Neuropsychiatric events
- Sleepwalking

Incontinence

Incontinence

- FDA Issue:
  - Are the adverse events of incontinence in clinical trials with sodium oxybate associated with seizures?

Incontinence
Method

- Analysis included:
  - Questionnaire to all affected investigators
  - Examination of safety databases for temporal association with CNS symptoms
  - Prospective overnight EEG in 6 patients with prior history of incontinence
  - Literature review
  - Review by independent experts

Urinary Incontinence

Incontinence Events			Temporal Association With CNS Symptoms	
Clinical Trial	**Number of Patients**	**Number of Events**	**Number of Patients**	**Number of Events**
OMC-GHB-2 N=136	8 (6%)	15	2 (1.5%)	2
OMC-GHB-3 N=118	13 (11%)	51	2 (1.7%)	2
Scharf N=143	33 (23%)	140	7 (5%)	12

Fecal Incontinence

Fecal Incontinence Events			Temporal association with CNS symptoms	
Clinical Trial	**Number of Patients**	**Number of Events**	**Number of Patients**	**Number of Events**
OMC-GHB-2 N=136	1 (<1 %)	1	0	0
OMC-GHB-3 N=118	1 (<1%)	Intermittent	0	0
Scharf N=143	1 (<1 %)	1	1 (<1%)	1
OMC-SXB-11 N=34	1 (3%)	1	1 (3 %)	1

Incontinence Conclusion

- There is limited support for a relationship between incontinence and seizures from clinical trials, prospective EEG studies, or the literature

Convulsions

- Updated Integrated Clinical Trials
  - 14 patients with events coded to “convulsion”
    - 13 of 14 patient events recorded as “cataplexy”
    - 1 complex case (“fugue state”)
- Scharf Trial
  - 9 patients with events coded to “convulsion”
    - 5 of 9 patient events recorded as “cataplexy”
    - 2 patient events attributable to pre-existing history
    - 2 other patients with seizure events associated with polypharmacy

“Confusion”

Summary of Adverse Events COSTART Coded as "Confusion"

- Updated ISS
- 402 patients
  - 30 (7%) patients
  - 48 adverse events
  - 3 (<1%) patients discontinued
  - Possible dose relationship
- Scharf Open-Label
- 143 patients
  - 10 (7%) patients
  - 15 adverse events
  - No discontinuations
  - No dose relationship

Updated ISS
Verbatim Terms for "Confusion"

Verbatim	Number of Patients	Number of Events
Confusion, acute confusion, Confusion on awakening	15	25
Disoriented, disoriented upon awakening, disorientation	14	16
Confusion, disorientation	1	1
Feeling 'drunk' after taking drug	3	3
Dazed feeling	1	1
Couldn't comprehend	1	1
Woozy feeling	1	1

- --2 AEs of "confusion" prior to treatment
- --48 events in total

Updated ISS
Action Taken for AE of Confusion

- No change in dosage in 37 events
- Adjustment in dosage in 4 events
- Temporary discontinuation in 4 events
- Permanent discontinuation of 3 patients

Controlled Trial: OMC-GHB-2
Confusion as AE

Preferred Term	Placebo (N=34)	3g (N=34)	6g (N=33)	9g (N=35)	p-value
Any adverse event	24 (70.6%)	25 (73.5%)	25 (75.8%)	26 (74.3%)	0.986
Confusion	1 (2.9%)	3 (8.8%)	1 (3.0%)	5 (14.3%)	0.2779

- Highest incidence at 9g
- 6/10 developed during 1st week (4 at 9g)
- 7/10 were age >50
- High incidence may reflect fixed dosage without titration

Confusion -- Conclusions

- Information recorded was symptoms only
- Lack of contemporaneous, formal mental status examinations for patients with “confusion”
- This reported “confusion” and other associated symptoms (e.g. unsteadiness) are not unexpected with sedating medications
- Higher incidence may result without dose titration

Neuropsychiatric Events

Summary of Neuropsychiatric Adverse Events

- Updated ISS
- 402 patients
  - 52 (13%) patients
  - 57 adverse events
  - 12 (3%) patients discontinued
- Scharf Open-Label
- 143 patients
  - 41 (29%) patients
  - 84 adverse events
  - 2 (1%) patients discontinued

Updated ISS
Summary of Neuropsychiatric Events

COSTART Term	Number of Patients
Total	**(57 Events in 52 Patients)**
Depression	27
Hallucinations	9
Stupor	6
Suicide Attempt	4
Paranoid Reaction	4
Coma	2
Psychosis	2
Manic Depressive Reaction	1
Personality Disorder	1

Scharf Open-Label Trial
Summary of Neuropsychiatric Events

COSTART Term	Number of Patients	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

Conclusions
Neuropsychiatry and Confusion

- Most patients with major events had a pre-existing psychiatric disorder
- Many events do not qualify as neuropsychiatric symptoms
- Assignment of causality is difficult
  - Narcolepsy – depression, psychosis
  - Stimulant medications
  - Pre-study screening deficiencies

Sleep Disorders

Sleepwalking (Somnambulism)

Sleepwalking
Summary of Events

- Integrated Trials
  - 28/402 (7%) patients reported events
- Scharf Trial
  - 45/143 (31.5%) patients reported events
  - Reported primarily in diaries

Sleepwalking Differential Diagnoses

- Arousal disorders
  - NREM parasomnias
  - REM parasomnias
- Partial complex seizures
- Prolonged absence seizures
- Others
  - Oxybate-induced confusional state
  - Automatic behavior in narcoleptics

Sleepwalking in Controlled Trials

	Number of Patients			
	Placebo		Sodium Oxybate	
Trial	Total	Sleepwalking	Total	Sleepwalking
OMC-GHB-2	34	0	102	2
OMC-SXB-21	29	0	26	0
Scrima	20	1	20	0
Lammers	25	0	25	0
Total	108	1 (0.9%)	173	2 (1.2%)

Sleepwalking -- Conclusions

- Incidence in integrated safety database trials (7%) is similar to the range reported in the literature (4-10%) [Mahowald 1998]
- Diary recording without medical classification possibly represents an increased reporting as sleepwalking events in the Scharf trial
- Slight increase in incidence over the general population may be representative of:
  - Xyrem effects – increase in slow wave sleep
  - REM behavior disorder, common in narcoleptics

Summary of Safety

- Exposure to date: 604
  (524 excluding Scharf)
- Dose: 3-9 g/day
- Common adverse events
  - Headache, unspecified pain, nausea, dizziness
- Less common adverse events
  - Vomiting, confusion, restlessness, agitation, sleepwalking, and enuresis

Summary of Safety

- All events have been reversible
- No significant changes in lab values or vital signs identified
- No evidence of organ toxicity
- No consumption by other family members
- No Xyrem diversion

Safety Conclusion

Xyrem is generally well-tolerated

Integrated Summary of Benefits and Risks

William Houghton, M.D.

Chief Operating Officer & Medical Officer,
Orphan Medical, Inc.

Benefit-Risk Assessment
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.

Narcolepsy - Overview

- Rare disease with an incidence of approximately 0.05%
- No currently approved treatment for cataplexy
- FDA priority review
- Off-label use of TCAs, SSRIs inadequate
- Stimulants used to treat daytime sleepiness
  - Do not treat cataplexy

Benefits of Xyrem

- Established by:
  - Patient diary recordings
  - Investigator rating of overall clinical improvement
  - Objective measures of change in sleep architecture and daytime response

Clinical Benefits of Xyrem

- Short and long-term control of cataplexy
- Subjective and objective improvements in daytime sleepiness
- Beneficial changes in sleep architecture
- Overall benefit of therapy indicated by investigator and patient evaluations

Safety of Xyrem

- Generally well tolerated
- Most common symptoms include:
  - Nausea, dizziness, headaches, pain and confusion
- Less common, but important are enuresis and sleepwalking
- Some dose relationship is suggested for nausea, confusion, enuresis
- No deaths associated with the drug in clinical trials

Somnambulism

- Possible association

Confusion

- May be associated with therapeutic doses

Enuresis

- There is a definite association with the drug that may have a dose-relationship
  - No reliable association with seizure

Convulsions

- There is no reliable link in seizure causality with Xyrem
  - 2 patients with known history
  - 2 patients with confounding factors (concomitant alcohol, benzodiazepine withdrawal)

Laboratory Measures

- Changes seen were small, not clinically significant and comparable across treatment groups
- No evidence of organ toxicity at therapeutic doses

Tolerance

- No evidence of kinetic or dynamic tolerance
- No drug-drug interactions observed

Withdrawal Phenomenon

- Serious syndrome in abuse population, relating to escalated dose and frequency
- No evidence in patients in clinical trials

Abuse Issues

- Well-recognized public health issue
- No evidence in patients with narcolepsy, treated with Xyrem
- Company commitment
  - Support of federal and state controls
  - Restricted distribution system
  - Patient and physician education

Conclusions

- We have established statistically and clinically significant evidence for the reduction in cataplexy, and 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 with long-term exposure
- The medical benefits clearly outweigh the risks

Abuse Liability and Overdosage

Robert Balster, Ph.D.

Medical College of Virginia

Abuse Liability of Xyrem

- The current abuse of GHB-like substances probably reflects their ready availability more than their pharmacology.
- If approved, Xyrem will not contribute to the public health problem of abuse of GHB-like substances.

GHB and GHB-like Substances

- Gamma hydroxybutyrate (GHB)(SCH III)
- Precursors
  - Gamma butyrolactone (GBL)
  - 1,4-butanediol (1,4-BD)
- Others
  - Tetrahydrofuran (THF)
  - Gamma hydroxyvalerate (GHV)

Abuse of GHB-like Substances Results Primarily From Availability

- Retail sales
- GHB and precursors were readily available through internet sources
- Precursors have wide commercial use
- Any of these precursors can easily be converted to GHB by anyone
- These precursors themselves are now widely abused

Scientific laboratory studies of GHB suggest low inherent abuse potential.

Scientific Data on the Abuse Potential of GHB

- *Unique Pharmacology*
- *Drug Discrimination* - lack of equivalence to abused depressants
- *Self-Administration* - weak reinforcing effects
- *Physical Dependence* - more difficult to produce than with abused depressants

Conclusions From Abuse Potential Studies

- GHB has abuse potential generally consistent with Schedule IV drugs
- Similar conclusion reached by others
  - WHO recommended Schedule IV
  - UN Commission places GHB in Schedule IV under the Psychotropic Convention

Potential Sources of Abuse of Xyrem

- Abuse or misuse among patients
- Diversion for illicit use

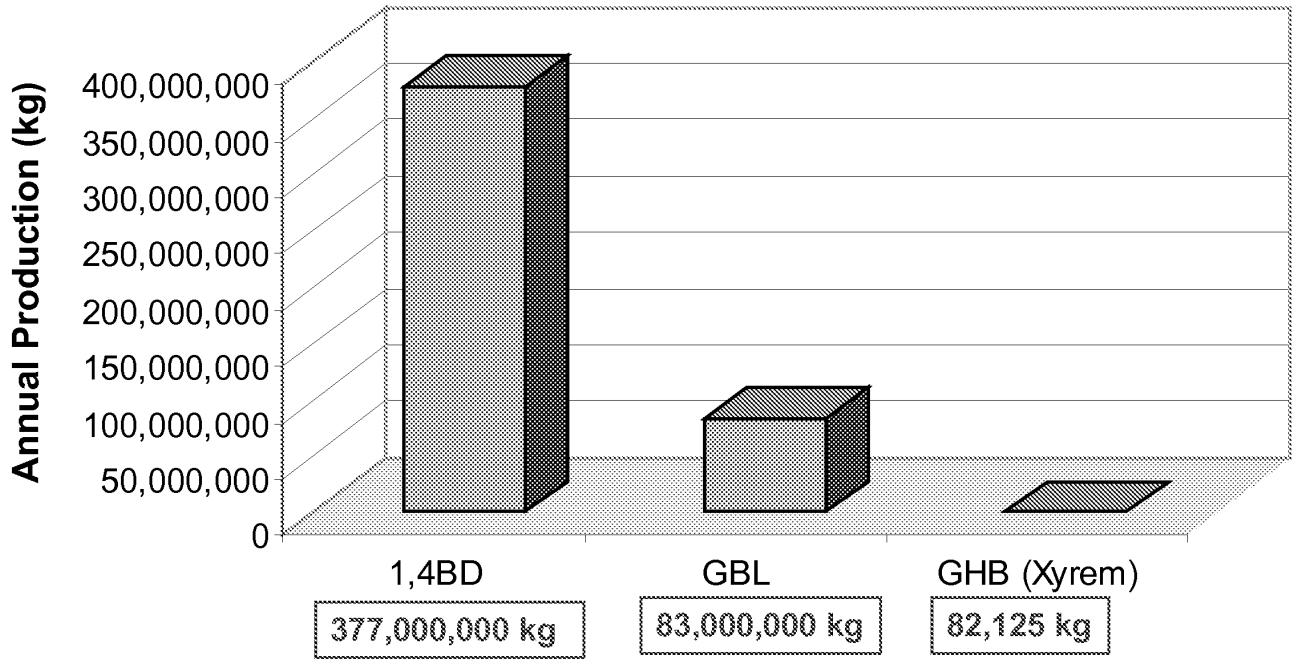
Abuse Among Patients is Unlikely

- In general, substances given as therapeutic treatment rarely are abused by patients
- No reports of abuse in Xyrem trials
- Narcolepsy patients already being treated with medications with abuse potential
- Short duration of action requires multiple daily administrations to maintain elevated levels in the body necessary for physical dependence

Illicit Diversion of Xyrem Unlikely

- No evidence of diversion of Xyrem
- Patient Success Program for distribution should prevent diversion
- Xyrem would be an insignificant source of GHB-like substances to the general public

GHB, GBL and 1,4- Butanediol Comparison of Production Quantities



Abuse Liability Summary

- Epidemic of abuse of GHB-like substances has resulted primarily from ready availability
- Scientific studies of GHB show modest abuse potential
- Xyrem abuse unlikely in patients
- Contribution of Xyrem to public health problem of GHB-like substance abuse will be insignificant.

Risk Management Through Responsible Distribution and Appropriate Education

Xyrem Success Program

Patti Engel, R.N., BSN

Vice President of Marketing & Sales,
Orphan Medical, Inc.

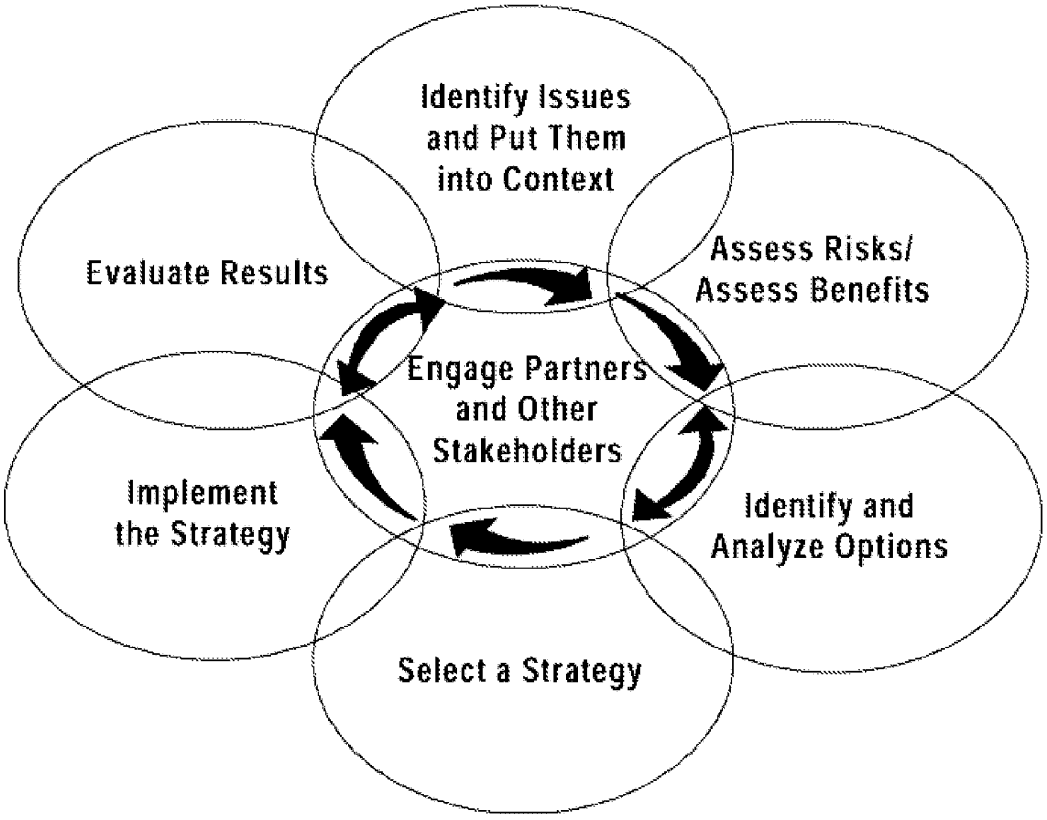
Xyrem Success Program

- A comprehensive system designed to ensure responsible distribution and use of Xyrem
- Goals:
  - Allow access to Xyrem for patients who need it
  - Make Xyrem inaccessible to those who would use it inappropriately

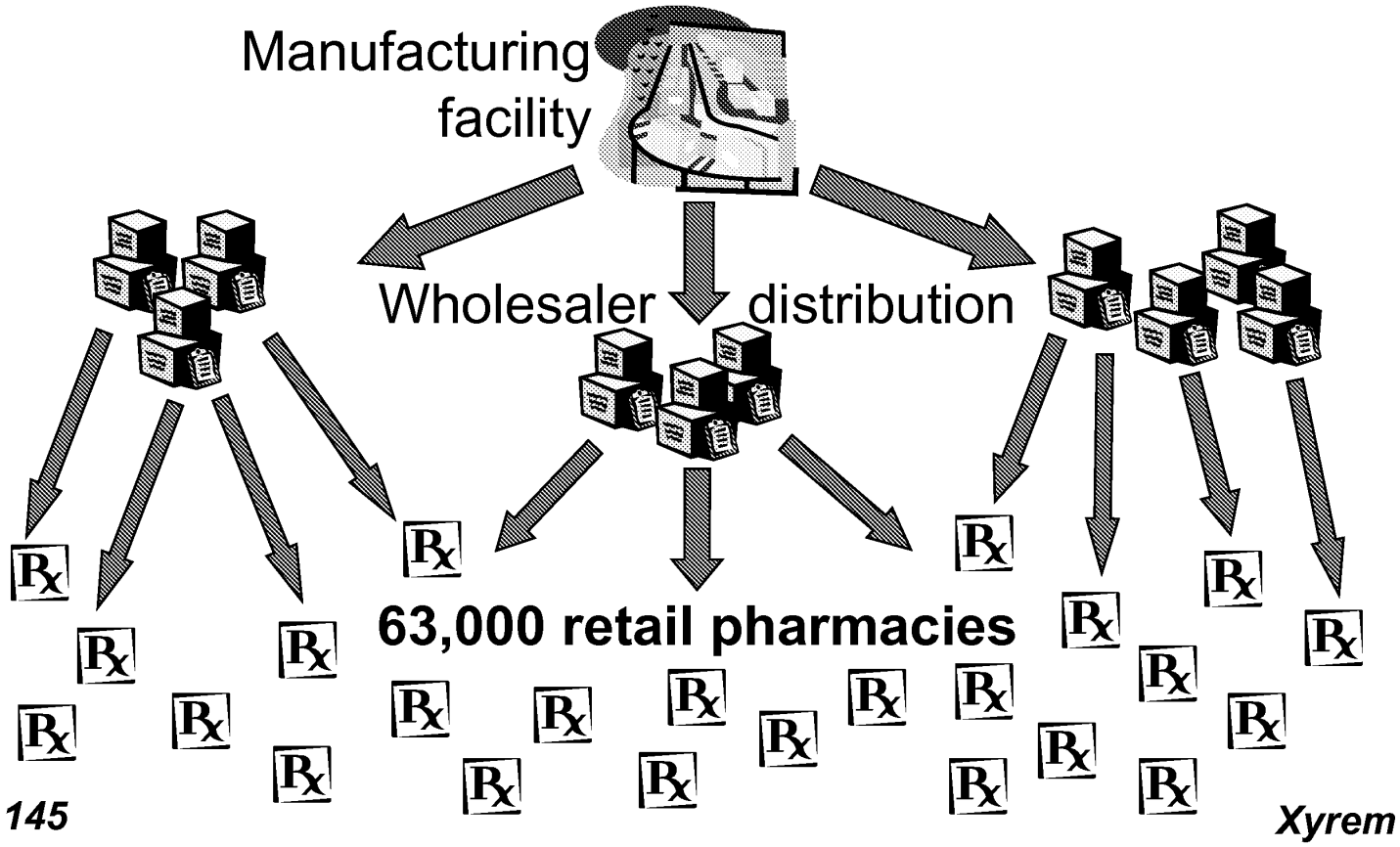
Xyrem Success Program

- Initiated by Orphan Medical and developed after extensive consultation with:
  - Narcolepsy patients
  - Patient/Family support groups
  - Physicians who treat narcolepsy
  - Emergency medicine physicians
  - Poison control center directors
  - Pharmaceutical distribution experts
  - Toxicologists
  - Forensics experts
  - Drug diversion investigators
  - Field law enforcement
  - State controlled substance authorities
  - Drug abuse trend experts

Risk Management Through Risk Confrontation



Standard Pharmaceutical Distribution



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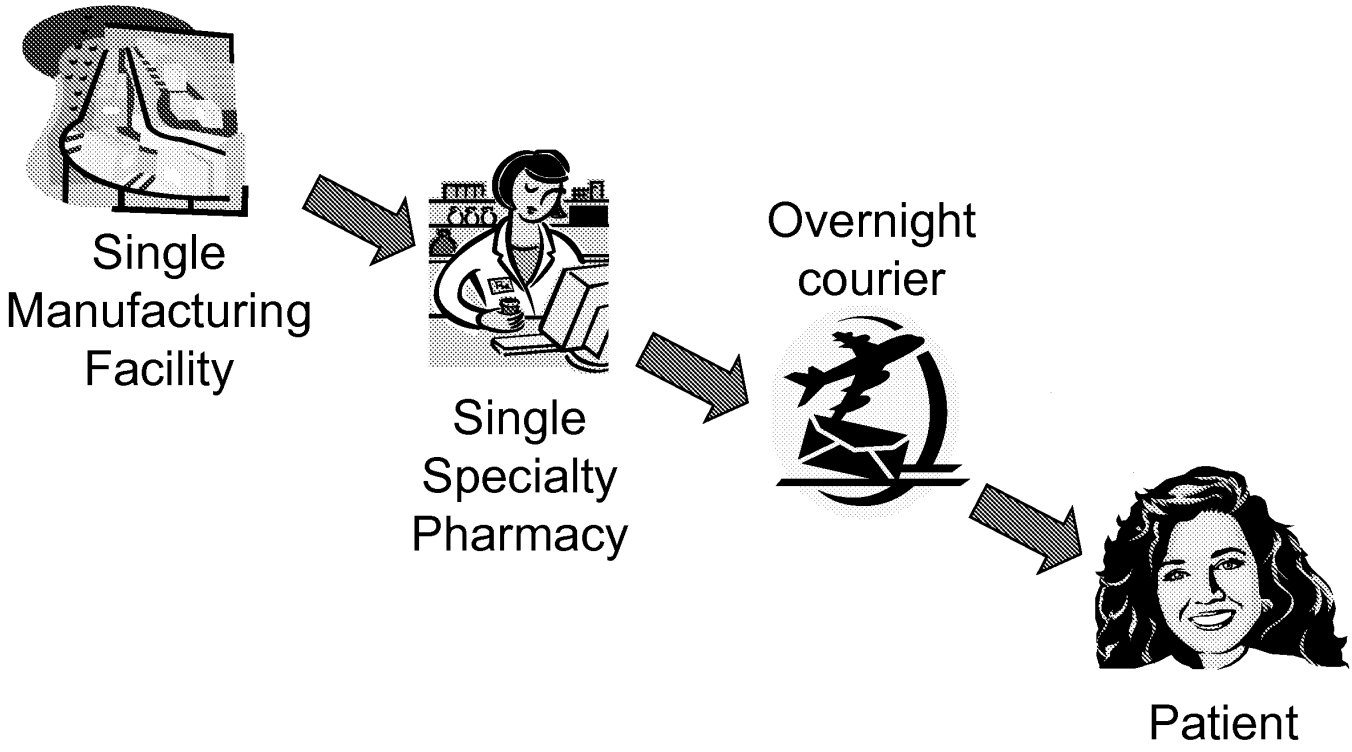
Xyrem

Xyrem Closed Distribution System



Xyrem's Distribution

- One Specialty Pharmacy
  - Xyrem distributed from a single location
    - Controls
    - Records

Physician Promotion and Education

- Xyrem promotional and educational efforts will focus on potential physician prescribers
- Key specialties include:
  - Neurology
  - Pulmonary diseases
  - Psychiatry
  - Internal medicine
  - Sleep medicine (includes several primary specialties)

Physician Promotion and Education

- Approximately 35 sales representatives will call on physicians and their clinical staffs
  - Communicate clinical benefits of Xyrem
  - Present Xyrem Physician Success Program℠
    - Physician signature required
- No physician sampling

Physician Success Program Materials

- Multi-faceted education program
  - Distribution process
  - Xyrem dosing and administration
  - Home storage and secure handling
  - “Doctor be wary”
- Unique prescription form
- Contact information at Specialty Pharmacy

Prescription Process

- Physician decides to prescribe Xyrem
- Physician faxes a special Rx to Specialty Pharmacy
- Specialty Pharmacy assigns patient to dedicated pharmacy team

Physician Verification

- Specialty Pharmacy verifies physician is “eligible” to prescribe Xyrem:
  - DEA’s NTIS database
    - MD licensure
    - Current CIII prescribing privileges
  - State medical board

Patient Verification

- Specialty Pharmacy calls prescribing physician's office
  - Verify the Rx

Pre-Shipment Patient Counseling

- Specialty Pharmacy contacts patient:
  - Determine patient/designee location and availability for receipt of Rx shipment
  - Explain contents of shipment

Rapid Trac® System

- Detailed, real-time tracking
- Delivered ONLY by authorized signature
- If patient/designee unavailable, package returned to Specialty Pharmacy after one re-delivery attempt
- If lost, investigation begins regarding shipment's whereabouts

Patient Success Program Materials

- Multi-faceted education program
  - Distribution process
  - Xyrem dosing and administration
  - Home storage and secure handling
  - Criminal and civil penalties for illicit use
- Contact information at Specialty Pharmacy
- Reimbursement information

Post-receipt Contact

- Once received, Specialty Pharmacist contacts patient within 24 hours to:
  - Confirm receipt of package
  - Discuss with patient:
    - Penalties for illicit use
    - Xyrem dosing and administration
    - Home storage and secure handling
  - Discuss child resistant packaging

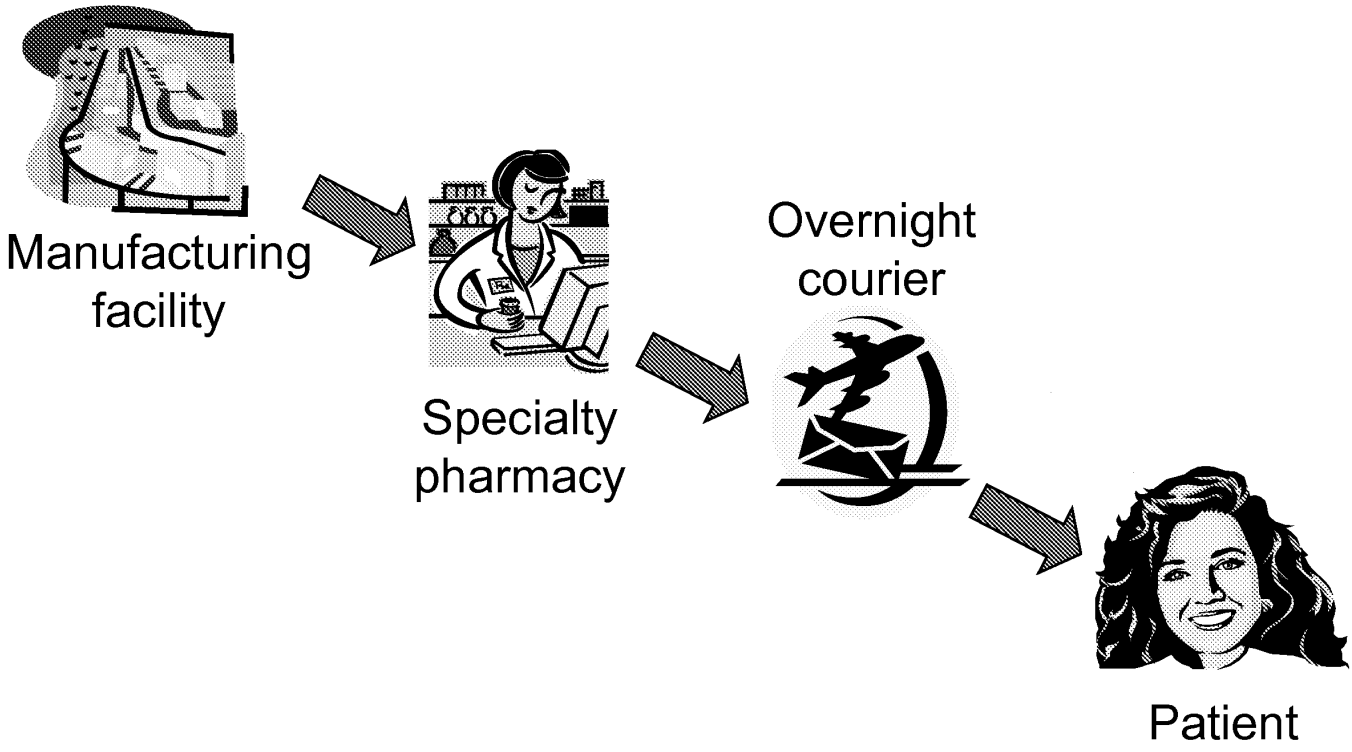
Benefits of Central Data Repository

- Identification of:
  - Duplicate prescriptions
  - Over-prescribing
  - Over-use by patients
- Information *prior* to filling Rx
- Appropriate pharmacist intervention

Xyrem Success Program

- A comprehensive program that ensures the responsible distribution of Xyrem, resulting in:
  - Availability of Xyrem to patients who need it
  - Inaccessibility to those who would use it illicitly

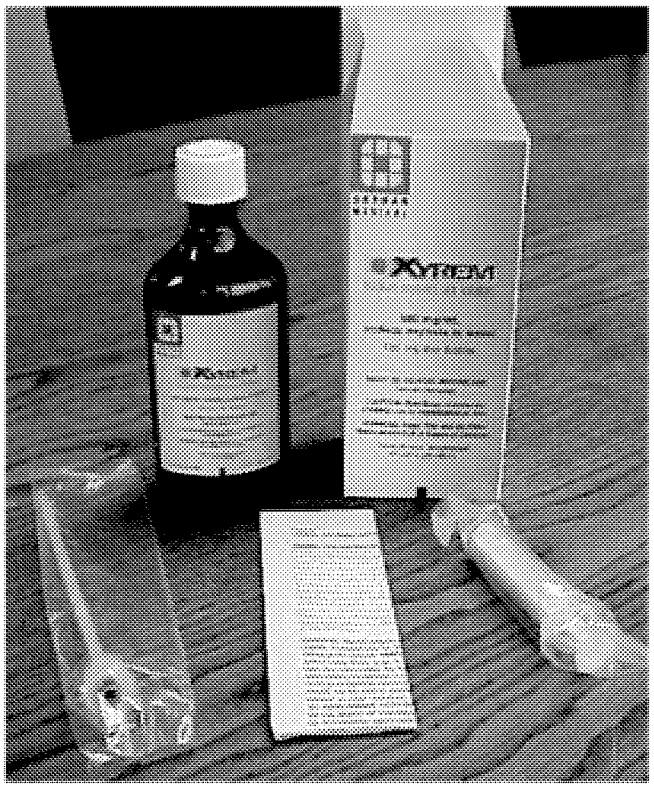
Xyrem Closed Distribution System



Back-up Slides Displayed at Peripheral and Central Nervous System Drugs Advisory Committee Meeting

June 6, 2001

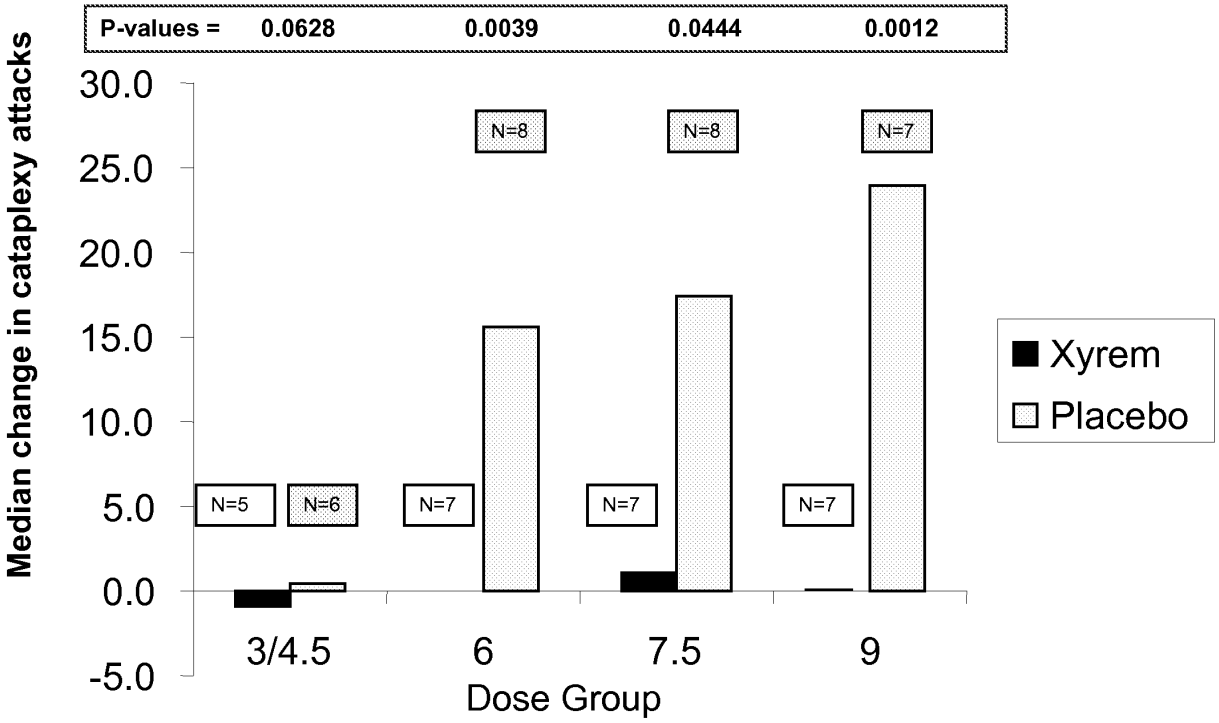
Xyrem®
(Sodium Oxybate) oral solution



- Formulation
  - Sodium oxybate 500 mg/mL
  - Malic acid 1.3 mg/mL
  - pH 7.5 in purified water USP
- Package Components
  - Child resistant cap
  - Press In Bottle Adapter (PIBA)
  - Syringe for measuring each dose
  - Child resistant dosing cups (2)

OMC-SXB-21

Median Change In Cataplexy Attacks by Dose



Updated ISS Database
Summary of Patient Exposure by Dose

	Sodium Oxybate Dosage (g/d)					
	Total	**3.0**	**4.5**	**6.0**	**7.5**	**9.0**
≥ 6 months	296	9	50	115	59	62
≥ 12 months	223	5	27	60	26	34
≥ 24 months	48	2	4	13	9	13

Updated ISS Database with Scharf
Summary of Patient Exposure by Dose

	Sodium Oxybate Dosage (g/d)					
	Total	**3.0**	**4.5**	**6.0**	**7.5**	**9.0**
≥ 6 months	360	25	87	171	83	70
≥ 12 months	286	12	55	114	50	42
≥ 24 months	150	6	26	66	34	23

Updated Integrated Summary of Safety Summary of "Confusion" Events

- Demographics:
  - Gender: 9 males; 21 females
  - Age: 25.7 – 73.8 years (67% ≥ 50 years)
  - Dose at Onset:
    - 3.0g – 4 events
    - 4.5g – 10 events
    - 6.0g – 12 events
    - 7.5g – 8 events
    - 9.0g – 13 events
    - Placebo – 1 event

Xyrem® (sodium oxybate) oral solution

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

June 6, 2001

Orphan Medical Inc.

PEDIATRIC SUBCOMMITTEE OF THE

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

June 6, 2001

Slides

Consideration of (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.

Orphan Medical Presentations ppt html

Disclaimer

The statements contained in this document are those of the product's sponsor, not FDA, and FDA does not necessarily agree with the sponsor's statements. FDA has not made a final determination about the safety or effectiveness of the product described in this document.

NDA 21196 Xyrem for Narcolepsy, Orphan Medica, Inc., Comments About Sleepwalking, Ranjit Mani, MD pdf htm

Effect of GHB on Measures of Daytime Sleepiness in Narcolepsy, Ranjit Mani, MD pdf htm

GHB the CEWG Perspective, Carol Falkowski pdf

GHB Abuse in the United States, Carol Falkowski ppt htm

Gamma Hydroxybutyrate, Jo Ellen Dyer, PharmD ppt htm

Public Hearing

Written Testimony of Sharon A. Fitzgerald pdf

Testimony by Abbey S. Meyers, National Organization for Rare Disorders, Inc. pdf

Statement of Robert L Cloud, Narcolepsy Network pdf

Statement of Cindy Pekarick pdf

Statement of Eric C. Strain, MD, College on Problems of Drug Dependence pdf

Public Statement of Deborah Zvosec, PhD, Hennepin County Medical Center pdf

Zvosec, Deborah L. PhD, Stephen W. Smith, MD. et al, "Adverse Evens, Including Death, Associate with the Use of 1,4-butanediol," *N Engl J Med,* Vol. 344, No. 2, January 11, 2001, pp 87-94.*

Statement of Trinka Porrata pdf

Testimony of Richard L Gelula, MSA, National Sleep Foundation pdf htm

"Living with Narcolepsy," National Sleep Foundation*

Statement of Matt Speakman pdf

Statement of Charles F Cichon, National Association of Drug Diversion Investigators Inc pdf

Michael's Message Foundation Inc., Debbie Alumbaugh pdf

Statement of Brian A Hunter, Young Adults with Narcolepsy - YAWN pdf

Statement Regarding GHB (Xyrem) Approval, Joe Spillane, PharmD, ABAT pdf htm

Agenda

6/20/01

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PPT Slide

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Need for New Treatments

William Houghton, M.D.Chief Operating Officer &
Medical Officer, Orphan Medical, Inc.

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William Houghton, M.D.Chief Operating Officer & Medical Officer, Orphan Medical, Inc.

Xyrem Pharmacokinetic Studies

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Plasma Oxybate (GHB) Concentration After an Oral Dose of 4.5 Grams of Xyrem to Normal Volunteers Following a High Fat Meal or after an Overnight Fast

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Xyrem Pharmacokinetics: Summary

Xyrem Pharmacokinetics: Summary

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OMC-SXB-20 Overall Conclusions

William Houghton, M.D Chief Operating Officer & Medical Officer, Orphan Medical, Inc.

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Summary of Safety

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William Houghton, M.D.Chief Operating Officer & Medical Officer, Orphan Medical, Inc.

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Narcolepsy - Overview

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Clinical Benefits of Xyrem

Safety of Xyrem

Somnambulism

Enuresis

Laboratory Measures

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Abuse Issues

Conclusions

Robert Balster, Ph.D.Medical College of Virginia

Abuse Liability of Xyrem

GHB and GHB-like Substances

Abuse of GHB-like Substances ResultsPrimarily From Availability

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Potential Sources of Abuse of Xyrem

Abuse Among Patients is Unlikely

Illicit Diversion of Xyrem Unlikely

GHB, GBL and 1,4- ButanediolComparison of Production Quantities

Abuse Liability Summary

Patti Engel, R.N., BSNVice President of Marketing & Sales,Orphan Medical, Inc.

Xyrem Success Program

Xyrem Success Program

Risk Management Through Risk Confrontation

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Physician Promotion and Education

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Xyrem®(Sodium Oxybate) oral solution

OMC-SXB-21 Median Change In Cataplexy Attacks by Dose

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Updated ISS Database with SchartSummary of Patient Exposure by Dose

Updated Integrated Summary of Safety Summary of "Confusion" Events

PPT Slide

NDA 21196
Xyrem® for Narcolepsy
Orphan Medical, Inc.

Comments About Sleepwalking

Background

In this NDA and especially in the Scharf Study, the term "sleepwalking" has been used as a verbatim (investigator) term for a common adverse event. The COSTART preferred term under which this entity has been coded is "sleep disorder."

The sponsor has not discussed this adverse event, either in the original NDA submission or in this Amendment. Given the frequency and potential/actual consequences of this adverse event (see below) I have chosen to discuss it further briefly

In most instances of "sleepwalking" in this NDA, a detailed description of patient behavior during that adverse event is not available.

The medical term "sleepwalking" refers to a non-REM parasomnia classified as an arousal disorder. During episodes patients exhibit complex behaviors including automatic and semi-purposeful motor activities: sitting up in bed, walking, climbing stairs, opening and closing windows and even more complex tasks, such as preparing food, may be features. Acts that are destructive or harmful may be seen, such as throwing objects, and climbing out through a window. During and immediately following episodes patients are confused; they have amnesia for the episodes. It is not at all clear that the term "sleepwalking" has a similar connotation when used in this NDA, or that it refers to a single clinical entity. In the majority of instances of sleepwalking in the Scharf study, this term appears to be derived from daily logs maintained by patients

There does not appear to be an association between narcolepsy and typical sleepwalking as defined in the paragraph above. However about 50% of narcoleptic patients have periods of automatic behavior that are described as memory lapses or blackouts; patients have amnesia for their activities during these episodes. Semi-purposeful activity is possible during such episodes which may manifest with phenomena such as walking into objects, getting lost while driving, and writing unintelligibly. Such episodes are believed to be due to micro-sleeps that intrude into wakefulness, and are most frequent in the mornings. Again there is no information supplied with the NDA that would strongly suggest

that any of the “sleepwalking” episodes correspond to automatic behavior occurring as part of narcolepsy.

Incidence Of “Sleepwalking” In Xyrem® NDA

Controlled Clinical Trial OMC-GHB-2

The incidence of adverse events coded under the COSTART preferred term “sleep disorder” is as follows among the 4 treatment groups

Dose Group	Total Number Randomized	Number of Patients with “Sleep Disorder” (COSTART)	% of Patients with “Sleep Disorder” (COSTART)
Placebo	34	1	2.9
3 g/day	34	2	5.9
6 g/day	33	4	12.1
9 g/day	35	5	14.3

The sponsor has attempted to characterize the term “sleep disorder” further in the following table which I have copied from the OMC-GHB-2 clinical trial report

		GHB		
Description	**Placebo**	**3g**	**6g**	**9g**
Prolonged sleep paralysis	1	1	2	5
Sleep walking	0	0	0	2
Poor sleep maintenance/ frequent arousal	0	1	2	1
Microsleep	0	0	1	0

Integrated Clinical Trials (of which OMC-GHB-2 is a component)

“Sleep disorder” (COSTART) occurred in 46/402 (11.4%) of patients participating in these trials. There was no dose-response seen and the sponsor has not characterized this adverse event further except in the case of those participating in OMC-GHB-2. Thus it is unclear how many patients recorded as having a “sleep disorder” (COSTART) might have been considered to have “sleepwalking”

Scharf Trial

Based on my review of all the Case Report Forms for this study, 45/143 (31.5%) of patients were listed as having one or more episodes of “sleepwalking.” A single patient (# 01-042, initials MJM) is described as having 346 episodes, and many patients had multiple episodes.

The patients listed as having “sleepwalking” constitute the entire cohort of those coded under the COSTART preferred term “sleep disorder” in this study

Characterization Of "Sleepwalking" Episodes

As already indicated the sponsor has not provided more detailed descriptions of patient behavior during these episodes except in a very small number of instances.

I have not attempted to characterize the "sleepwalking" episodes in regard to patient demographics, duration, severity and seriousness of episodes, GHB dose at onset, concomitant medications and illnesses, outcome and other parameters. I currently lack both the time and resources to perform such an analysis. The sponsor should, however, be required to perform such an analysis prior to approval. Such episodes, regardless of their etiology, have had serious consequences as outlined below.

Consequences Of "Sleepwalking" In Xyrem® NDA

Narratives are provided below for patients who were reported to have events of serious or potentially serious consequence during episodes of "sleepwalking." These consequences include taking an overdose of GHB as well as other actions. Several of these narratives are elsewhere in this review but are reproduced here for convenience. All instances occurred in the Scharf study.

Patient 01-215 (Initials AEB)

This 46 year old woman with narcolepsy, who sustained a skull fracture 5 years prior to study entry, took GHB in a variable dose of 4.5 to 10.5 g/day in 2 or 3 divided doses despite being prescribed 7.5 g/day (this is not consistent with what has been entered in the medication logs in the Case Report Form. About 4 months after entering the study she reported symptoms of nausea, a tipsy feeling, blurred vision, and a swollen face and hands. These symptoms persisted for 14 days, no action was taken, and her doses subsequently were variable and as high as 10.5 g/day. She continued in the study for a further 4 years when she was discontinued on account of non-compliance which involved not submitting daily sleep log diaries and modifying dosing schedules without prior consultation with Dr Scharf.

A number of unexplained fits of laughter (termed "hysterical" in one instance, and "uncontrollable" at other times), and **episodes of "sleepwalking" (during one of which she tried to drink nail polish remover)**. Episodes of headache, nausea, dizziness, blurred vision, enuresis, "fogginess", "stumbling around-unsure of self on feet after gamma", "drugged effect, vision blurred, unsteady on feet", "drunken stupor; rage", other similar events, and sleeplessness, were also noted during the study.

A telephone contact with the patient 12 ½ years after she discontinued from the study indicated that her neurological adverse events, with the exception of blurred vision, had resolved once GHB was discontinued.

Patient 01-017 (Initials WF)

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.

Patient 01-267 (Initials RMM)

This 65 year old woman had a history of obesity, sleep apnea on treatment, and narcolepsy. She began taking GHB in a dose of 4.5 g daily.

About 4 ½ years after study entry she was reported to have taken an overdose of GHB, consuming a third nightly dose instead of merely two doses. The patient's daughter reported that the patient was shortly afterward incontinent of urine, awoke and (for unclear reasons) was covered with spaghetti sauce. She also appeared dazed and confused. Her diaries are unavailable for that period and it is therefore unclear what her regular dose of GHB was at the time. She was taken to an emergency room but had recovered by that time. She was reported to have continued GHB after that episode but ceased returning any daily diaries at all beginning about 5 ¼ years after study entry and was therefore recorded as having left the study on account of non-compliance. Repeated letters to the patient from the study center were reportedly unanswered. Further information about this patient is unavailable.

During her participation in the study she was also recorded to have multiple episodes of sleepwalking and multiple additional episodes of urinary incontinence, not apparently occurring contemporaneously. She was also seen at an emergency room for an episode of somnolence which was felt to be related to her sleep apnea. She reported swollen ankles and wrists, and pain, numbness and tingling in her feet.

(It is not clear from the above or from the Case Report Form whether the overdose occurred during an episode that would have been considered to represent "sleepwalking")

Patient 01-206 (Initials DRS)

This 62 year old woman had a history of narcolepsy, hypertension and heavy smoking. She began taking GHB in a dose of 3 g/day.

While participating in the trial she had 7 episodes of sleep walking. 2 episodes which occurred, separated by a 2-day interval, 7 ½ months after she entered the study, led to her discontinuing GHB. During each of these episodes she was found by her husband with a burning cigar or cigarette in her hand, apparently not aware of having been smoking. On one of these occasions she was found

in a room other than their bedroom asleep with a cigar in her hand. On the second occasion the cigarette was found to be burning her nightgown; her husband threatened at that point to leave her unless she stopped taking GHB. The patient's entries in her daily sleep log indicate that she was unaware of her actions during these episodes and had no personal recollection of them subsequently .

Reviewer's Comments

- In the absence of adequate clinical descriptions in most instances it is unclear what the adverse event investigator term "sleepwalking" represents, or whether it refers to single or multiple entities.
- Regardless of what the term "sleepwalking" means in the context of this NDA, it is clear that such episodes are common; almost one-third of patients participating in the long-term Scharf safety study did have one or more such occurrences, and a single patient is recorded as having as many as 346 episodes. The incidence of this adverse event in the entire Integrated Clinical Trials grouping is unknown (except for a single study, OMC-GHB-2)
- The few clinical descriptions of this adverse event that are available in this NDA suggest that during "sleepwalking" episodes patients may be confused and may act in a manner that could be prejudicial to their own safety and that of others.
- The sponsor has not, so far, attempted to analyze this adverse event as an entity
- The fairly high incidence and potential consequences of such episodes make it essential that the sponsor should be asked to better characterize the instances of sleepwalking in this NDA prior to the drug being approved for marketing.
- In this reviewer's opinion (and on a largely speculative basis) it is possible that the term "sleepwalking" as used in this entity could be describing one or more of the following entities
    - An acute confusional state induced by GHB
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NDA 21196
Xyrem® for Narcolepsy
Orphan Medical, Inc.

Comments About Sleepwalking

Background

In this NDA and especially in the Scharf Study, the term "sleepwalking" has been used as a verbatim (investigator) term for a common adverse event. The COSTART preferred term under which this entity has been coded is "sleep disorder."

The sponsor has not discussed this adverse event, either in the original NDA submission or in this Amendment. Given the frequency and potential/actual consequences of this adverse event (see below) I have chosen to discuss it further briefly

In most instances of "sleepwalking" in this NDA, a detailed description of patient behavior during that adverse event is not available.

The medical term "sleepwalking" refers to a non-REM parasomnia classified as an arousal disorder. During episodes patients exhibit complex behaviors including automatic and semi-purposeful motor activities: sitting up in bed, walking, climbing stairs, opening and closing windows and even more complex tasks, such as preparing food, may be features. Acts that are destructive or harmful may be seen, such as throwing objects, and climbing out through a window. During and immediately following episodes patients are confused; they have amnesia for the episodes. It is not at all clear that the term "sleepwalking" has a similar connotation when used in this NDA, or that it refers to a single clinical entity. In the majority of instances of sleepwalking in the Scharf study, this term appears to be derived from daily logs maintained by patients

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FDA Presentation To PCNS
June 6, 2001
Ranjit Mani, M.D.

EFFECT OF GHB ON MEASURES OF DAYTIME SLEEPINESS IN NARCOLEPSY

MEASURES OF DAYTIME SLEEPINESS IN GHB TRIALS

OMC-GHB-2

- Epworth Sleepiness Scale (Secondary)
- Frequency Of Sleep Attacks (Secondary)
- Duration Of Sleep Attacks (Secondary)

Scrima Study

- Sleepiness Index Of Multiple Sleep Latency Test (Primary)
- Frequency Of Sleep Attacks (Secondary)

Lammers Study

- Frequency Of Sleep Attacks (Secondary)
- Duration Of Sleep Attacks (Secondary)

OMC-SXB-21

None

Total Number Of Secondary Efficacy Measures In GHB Trials

OMC-GHB-2:	10
Scrima:	17
Lammers:	7
OMC-SXB-21:	0

OMC-GHB-2: Analysis Of Measures Of Daytime Sleepiness

Parameters	Treatment	Change in medians from baseline to endpoint	P-value for overall comparison *	P-value GHB group vs placebo
Excessive Daytime Sleepiness (Epworth Scale)	Placebo	-2.0	0.0006	
	3 g	-1.0		0.1137
	6 g	-3.5		0.1860
	9 g	-5.0		0.0001
Frequency of Daytime Sleep Attacks	Placebo	-0.26	0.0101	
	3 g	-0.20		0.1022
	6 g	-0.48		0.0497
	9 g	-0.48		0.0122
Duration of Daytime Sleep Attacks	Placebo	-3.10	0.0282	
	3 g	-5.00		0.9995
	6 g	-9.75		0.4413
	9 g	-7.95		0.0689

* based on ANCOVA

SCRIMA STUDY: ANALYSIS OF MEASURES OF DAYTIME SLEEPINESS

Sleepiness Index Of Multiple Sleep Latency Test

Treatment Group	GHB N = 20	Placebo N = 20
Mean Baseline Sleepiness Index	88.5	
Mean Overall Sleepiness Index During Treatment	87.2	90.3
Mean Overall Change From Baseline During Treatment	-1.3	1.8
GHB-Placebo Difference For Overall Treatment Effect	-3.1	
P-value for overall GHB-placebo difference	0.085	

SCRIMA STUDY: ANALYSIS OF MEASURES OF DAYTIME SLEEPINESS

Frequency Of Daytime Sleep Attacks (Attacks/Day)

Treatment Group	GHB N = 20	Placebo N = 20
Mean Baseline Frequency Of Sleep Attacks	2.8	
Mean Overall Frequency Of Sleep Attacks During Treatment	1.9	2.1
Mean Overall Change From Baseline During Treatment	-0.9	-0.7
GHB-Placebo Difference For Overall Treatment Effect	-0.2	
P-value for overall GHB-placebo difference	0.530	

LAMMERS STUDY: ANALYSIS OF MEASURES OF DAYTIME SLEEPINESS

Measure	**Treatment Group**	**Median/Mean of Daily Score ***			**p-value for Change from Baseline to Endpoint (GHB vs placebo)**
		Baseline	Endpoint	Baseline-Endpoint Change	
Severity of Daytime Sleepiness (n =24)	Placebo	1.60	1.59	-0.01	0.034 (Wilcoxon)
	GHB	1.60	1.28	-0.32	
Frequency Of Daytime Sleep Attacks (n =24)	Placebo	1.83	2.14	0.31	0.0008 (ANCOVA*)
	GHB	2.17	1.36	-0.81	

*Not a protocol-specified analysis

PROBLEMS WITH PROPOSED CLAIM FOR EXCESSIVE DAYTIME SLEEPINESS

- Most measures for excessive daytime sleepiness were secondary
- Only measure that was primary was “negative”
- Majority of measures “negative” (after adjustment of Type I error for multiple comparisons)
- Effects inconsistent across studies
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- **Duration Of Sleep Attacks (Secondary)**

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OMC-SXB-21

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GHB - the CEWG perspective

December 1990

Miami "Florida Poison Information Center reports 7 cases of adverse effects"

June 1991

Miami "at least 7 cases of adverse effects . . ."

June 1993

New York City - "GHB has recently become available in nightclubs"
Mixed with amphetamine; mixture called "Max"

December 1993

Miami – resurfaced as drug of abuse in nightclubs, among body builders

New York City – "still available in nightclubs"

June 1994

Miami - 5 accidental overdoses. The drug has resurfaced since it was banned over 3 years ago. It is marketed in nightclubs and among body builders.

December 1994

Miami - "at least 7 overdoses in 1994"

June 1995

Boston – reports from Rhode Island of a cocktail mixture of GHB and amphetamine

June 1996

Texas "has become a problem in the Dallas/Ft. Worth area"

Miami -increased reports abuse in club settings

New Orleans "GHB becoming widely available and abused"

December 1996

Atlanta- "remains available and has become popular"

Detroit - Used in nightclubs for effects similar to flunitrazepam

Miami- made in homemade labs and associated with sexual assault and robbery

New York City "GHB is more conspicuous" GHB & ketamine & alcohol = "Special K-lude"

Phoenix "increased at raves and nightclubs"

Texas "GHB use is spreading across the state" "scoop" ED mentions

June 1997

Atlanta - GHB used in gyms and fitness centers

Baltimore - raves are a source of GHB

Boston – GHB synthesized by college students, implicated in poisonings with alcohol

Detroit - several seizures of GHB

Honolulu –DEA reports in Honolulu nightlife scene

Miami - GHB emerged as homemade club drug responsible for increasing number of medical emergencies. State law makes GHB Schedule 2.

New York City – GHB used by club patrons

Phoenix - GHB used at raves, nightclubs, gay clubs as a pleasure enhancer

San Francisco – Internet recipe for GHB being used. Marked increase in ED mentions

Texas – GHB becoming more commonly used in Texas

December 1997

Atlanta- used among adolescents and young adults in the urban club scene

Baltimore- GHB available

Boston- availability increased recently in connection with clubs and raves

Honolulu- GHB available in small amounts in Oahu's nightclub scene

Miami – "GHB is the fastest growing new problem in the depressant category, replacing flunitrazepam. GHB clandestine labs in Jacksonville area.

Newark- recipes on Internet and ads for precursors proliferate

New York City – GHB especially visible in nightclubs

San Francisco- "GHB has made a strong debut on the local club and party scene" Used by men and women, gay and straight, as a disinhibiting party drug

Texas -28 overdoses of GHB in 1997

June 1998

Atlanta- GHB at gay circuit parties and at nightclubs

Baltimore- available

Boston- GHB still legal and not controlled in MA, 2 clan labs

Detroit – 3 law enforcement seizures

Miami- "dramatic increase in GHB medical emergencies especially for those under age 20. A GHB analog appears

New Orleans- GHB shipped overnight in to LA and New Orleans from Texas

Phoenix- GHB as date rape drug, cooked on stove top labs

San Diego – GHB in media accounts

San Francisco- Club drugs not seen much except for GHB

Texas- GHB overdoses increasingly reported/110 poison center calls regarding GHB

December 1998

Atlanta – GHB available, popular

Boston- GHB now controlled, implicated in rapes, poisonings, and deaths
"slight overdose can cause drowsiness or unconsciousness"

Denver- daily users tend to be in teens or twenties. During parties GHB is often given away

Detroit – GHB schedule I in Michigan effective July 1998

Miami - "GHB and its analogs are widely abused, increasingly by adolescents"
4 deaths in Broward County, FL (Ft. Lauderdale)

Minneapolis- GHB surfaced as new drug of abuse among adolescents and
appeared in city crime labs

Seattle - several reports of drug rape with GHB and homicide
One ED case every other week "This trend bears watching."

Texas- "GHB overdoses, some with life threatening symptoms continue to be reported. 71 Poison Center calls in first half of 1998.

SPECIAL REPORT: ***GHB Overdoses and Deaths in South Florida***
Joe Spillane, Pharm. D., ABAT and
Madeline Camejo. Pharm.D.

June 1999

CEWG Meeting Summary:

"GHB continues to spread across the country, with recipes proliferating on the Internet. It has been increasingly involved in poisonings, overdoses, date rapes and fatalities in at least 14 CEWG areas, up from 8 last year. GHB is a rave drug used mostly by adolescents and young adults in: Baltimore, Atlanta, Baltimore, Boston, Chicago, Denver, Detroit, Los Angeles, Miami, Minneapolis, Newark, New Orleans, San Diego, San Francisco, Seattle, Arizona, and Texas. GBL and 1,4 BD metabolize in to GHB in the body and produce GHB-like symptoms."

December 1999

- **Atlanta**: "Reports of overdoses from a combination of GHB and alcohol among gay men suggest that the drug continues to be available and popular in certain settings. "

  Baltimore: GHB/GBL was responsible for 10 overdoses in the first 3 months of 1999.

  Boston: "Heavy GHB use has been reported in some Boston clubs, some-times associated with overdoses requiring ED treatment. "

  Newark - a GHB precursor (GBL) was suspected of sending 18 people to hospitals, and 2 GBL-related overdoses were reported among Princeton students.

  Minneapolis - one to five GHB-related overdoses are treated per month. Minnesota legislature designated GHB and its salts, compounds, derivatives or preparations as Schedule III controlled substances, effective August 1, 1999

  San Francisco - "The most often mentioned 'club drug' lately, at least among gay men, has been GHB as well as its precursor, gamma-butyrolactone (GBL) or 'Blue Nitro. '"

  Seattle - ED staff continue to report anecdotal accounts of three to four incidents per month of incapacitation, induced intoxication, rape and other criminal behaviors.

  South Florida: "Eleven of the 26 ED patients with GHB toxicity in the first half of 1999 were completely comatose, 3 experienced respiratory failure requiring endotracheal intubation, and 9 were combative at some point during their visit. "

Meeting Summary/Advance Report:

"On March 13, 2000, gamma hydroxybutyrate (GHB) was placed in Schedule I of the Controlled Substances Act. GHB is easily produced by combining gamma butyrolactone (GBL) with either potassium hydroxide or sodium hydroxide in a container. Kits for making the drug are sold over the Internet. Because the drug is easily synthesized and manufactured, local operators serve as distributors. GHB is usually sold by the capful at a cost of $5 to $10 per cap.

Overdose of GHB can occur rapidly and may produce dizziness, drowsiness, nausea, and visual disturbances. Higher dosages can lead to unconsciousness, seizures, severe respiratory depression, and coma. Overdoses typically require emergency room treatment and, for coma and respiratory depression, intensive care. In 1999, the Food and Drug Administration received 122 reports of GHB abuse from health professionals. The DEA documented 60 GHB-related deaths as of January 2000; almost 60 percent of the deaths occurred among young people age 20 to 29.

GBL, the precursor chemical for the manufacture of GHB, has been marketed as a health supplement and became a List 1 chemical on February 18, 2000. Kits for manufacturing GBL are sold on the Internet. GBL also is synthesized in the body to produce GHB so that some partygoers drink small quantities of GBL "straight." This often causes violent regurgitation of the fluid or other severe reactions.

Atlanta - GHB is increasingly available

Boston The Massachusetts Poison Control Center reported receiving more calls involving GHB and its precursor GBL than was the case for other club drugs. GHB/GBL accounted for 32 percent of illicit drug-related calls.

Chicago GHB is sold as a liquid in amounts ranging from drops from a dropper (at raves or parties) to capfuls.

Detroit The Detroit Poison Control Center reported 100 cases of GHB/ GBL in 1999, with 22 of these being life-threatening. Six cases involved GHB.

Los Angeles GHB use continues to increase in Los Angeles.

Minneapolis - Two GHB toxicity deaths occurred in 1999. A growing but small number of people who sought treatment reported GHB/GBL as the primary substance of abuse, physical dependence, tolerance, and withdrawal

Newark GHB is routinely used at rave parties and around college campuses. GBL was recently linked to 18 hospitalizations.

St. Louis GHB use increased in the St. Louis area. Five GHB-related deaths were reported in Missouri. GHB is sold in clubs for $5 a capful or $40 an ounce.

San Francisco GHB is available but that it is not as commonly used as MDMA.

Texas GHB, GBL, and similar precursor drugs remain a serious problem. Increasing cases were reported by poison control centers in 1999.

23 GHB-related deaths reported in five CEWG areas: 2 in Minneapolis/St. Paul (in 1999); 9 in Broward County (between 1996 and the first half of 2000); 3 in Miami-Dade County (since July 1999); 3 in Texas (in 1999); one in Washington State; and 5 in Missouri.

Atlanta - "GHB is easily accessible at raves and is commonly used by both teenagers and young adults. The DEA continues to report that its use is associated with sexual assault."

Boston - "In press reports, GHB, often called 'liquid ecstasy' or 'liquid X,' is sometimes confused with ecstasy. Although both are so-called club drugs and are often used in the same settings, their effects are quite distinct, with GHB presenting higher risk for both overdose and dependence."

Chicago - "Compared with other club drugs, overdose experiences are more frequent with GHB, especially when used in combination with alcohol. GHB is not tracked in most quantitative indicators, but use is perceived to be low in comparison to that of ecstasy."

Detroit – reports of GHB and GBL abuse have been numerous and continuing in 1999 and 2000.

Los Angeles – GHB continues to be a major club drug

Minneapolis – a St. Paul hospital ED reports treating 5 GHB-related cases per week since September

Missouri- Two near-deaths reported in St. Charles, Missouri, where GHB was used for drug rape.

Newark – It is increasingly reported that GHB and ketamine are used at rave parties around college campuses. "Unfortunately no reporting system tracks the use of such substances in the state."

Phoenix – GHB and GBL are readily available.

South Florida – "when GBL products were banned, new brand names for 1,4 butanediol products appeared almost weekly, and overdose and addiction are reported frequently. In virtually every GHB-related case, the reason for the ED visit was decreased responsiveness/coma usually lasting less than 3 hours."

Texas – "GHB and its precursors remain a dangerous problem, with poison control center cases increasing in 1999.

Washington DC – GHB used by individuals who attend music and dance clubs. "Some club owners do not want to deal with the problems that people suffer from when taking GHB (especially with alcohol) on their premises. They are now removing GHB users and dealers from their clubs.""

compiled by Carol Falkowski, June 2001

GHB Abuse in the United States

6/13/01

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WRITTEN TESTIMONY
OF
SHARON A. FITZGERALD

FOR THE

JUNE 6, 2001 NEUROPHARMACOLOGY ADVISORY COMMITTEE MEETING

Prior to my involvement in the Xyrem study, beginning in late 1995, the quality of my life was being destroyed by narcolepsy.

Almost everyone knows that narcoleptics fall asleep at odd times. Unfortunately, daytime sleepiness is just one of a complex of narcolepsy symptoms, all of which are either eliminated or improved by using Xyrem. Not all narcoleptics have all of the symptoms. I have experienced all of the following.

DAYTIME SLEEPINESS:

Since the age of 25 (1969), falling asleep at unpredictable times has made it difficult for me to work. As an employee, I learned to hide in the restroom to take 10-15 minute naps when the uncontrollable urge to sleep came over me. No matter when I went to bed at night, no matter how many vitamins I took, I could not stay awake all day at work, and I couldn't plan to make the sleep attacks occur at 10:00 o'clock and 2:00 o'clock for scheduled breaks.

This is a symptom narcoleptics attempt to hide from everyone else. It is almost impossible. Narcoleptics fall asleep in meetings. Jobs that allow for escape for a hidden nap at unpredictable times are rare. Not everyone has an office with a door that closes. Employers notice sleeping employees, and, even with today's protective laws, sleepers lose their jobs.

After the death of my husband in 1976, as my narcolepsy was still relatively mild and undiagnosed, I completed my undergraduate degree and then began law school. Increasingly severe symptoms made completing law school slow and difficult. While taking notes during lectures I would begin to dream. Several times I actually wrote a few words about my dreams before dropping my pen. I began to fear for my sanity. Who was writing these things about helicopters and my mother in the middle of my notes on civil procedure? I sought medical help. After four months of testing my doctor inquired, "Do you ever feel muscle weakness when you laugh or get emotional?" I asked, "Doesn't everybody?" and Eureka! I had a diagnosis: Narcolepsy. The good news was, I wasn't crazy. The bad news: At the time, my doctors knew of no treatment.

I am not easily deterred. I graduated. Not with my class. Not among the top 25%, as had been my goal, but I did, finally, graduate. However, I was afraid to take the job offered, clerking for a District Court Judge, because I feared that I would fall asleep in court, sitting up in front for all to see. In Boulder, Colorado, I established a reputation as a compassionate and effective advocate in family and juvenile law. However, I was unable to serve enough clients as a part-time sole practitioner and mediator, during my wakeful hours, to make a sufficient living to support my children and myself. I paid a charitably small rent to live with generous friends. I had to ask that my student loans be deferred.

For a parent, daytime sleepiness is very troublesome, in fact, dangerous. I was a single parent, a circumstance faced by many narcoleptics whose marriages suffer from this condition. I was lucky. My kids survived. I have fallen asleep in a pediatrician's waiting room; at a production of Hansel and Gretel in which my son played Hansel; while reading stories to my kids; at parks while they played on the swings; and while helping with their homework. They got very good at watching for our stop so they could awaken me to get off the bus.

Things got a bit better for me in 1992 when my physician recommended I try Ritalin for daytime wakefulness. However, Ritalin and other wakefulness medications contribute to my high blood pressure, and have other problematic side effects. Xyrem makes it possible to get good, effective nighttime sleep, so I can take significantly less of the wakefulness drugs. I've taken Xyrem for most of the past 6 years, with no side effects.

HYPNOGOGIC HALLUCINATIONS AND NIGHTTIME WAKEFULNESS:

While everyone else is sleeping, an untreated narcoleptic alternates between vivid, often frightening dreams, and hours of worried wakefulness.

Falling asleep at night, and sometimes awakening, can be a horrific experience. You believe you are awake. You know where you are sitting or lying, and your awareness of your surroundings is clear and accurate. But you experience hallucinations. For me, often it was hearing the sounds of an intruder entering my home from behind me. I was paralyzed, and unable to turn around to confront my attacker to defend my children and myself. In a real-life experience, an actual intruder had tried to sexually assault me, so these hallucinations were terrifying.

A 16-year old narcoleptic I met at a sleep clinic told me about his horrifying dreams of space aliens and other monsters. His experiences and mine were parallel, in that sometimes we were so aware that we were dreaming that we would attempt to will ourselves into wakefulness, and actually dream that we were awake, doing ordinary

morning things like going to the bathroom or eating breakfast, only to have our attacker jump out at us from the shower stall or the cereal box. Trust me, it was no compliment if either of us said, "I'll see you in my dreams!"

Before Xyrem, I had hypnogogic experiences virtually every night, on my way to sleep. When I lived alone, I dreaded going to bed, knowing that it would happen, and knowing that no matter how I prepared myself, when I was in that experience, I would believe that it was real. When I remarried, I learned to fear for my husband's safety. He would hear me making fearful noises in my dreams, and would awaken me and try to comfort me into more restful sleep. He stopped trying to help in this way after I attacked him and bit him severely, as I thought he was my attacker.

After finally getting to sleep, for the rest of the night I would alternate between dreams and hours of wakefulness, during which I worried about the inevitably sleepy tomorrow. Before diagnosis, the dreams became very vivid and intricate. They repetitively concerned similar themes, developing into stories over time. It was as if I had one life during the day, and another at night. I began to feel unable to distinguish between dreamed events and realty. This contributed to the fear of insanity that drove me to seek medical help.

Prior to Xyrem, anti-depressants helped with the serial dreams, but did nothing for the hypnogogic hallucinations, and I experienced troublesome side effects. On Xyrem, the nightmares are gone. What dreams I have are normal, and rarely recalled, like a normal person. I get good, restful sleep, and no side effects.

AUTOMATIC BEHAVIOR:

When sleepy during the day, instead of falling asleep, some narcoleptics will continue doing an activity while not fully conscious. Before I was informed of it's clinical name, I named it "going to stupid."

For me, the experience was annoying and embarrassing, but did not cause serious problems. While working on the computer, I have "gone to stupid," finding myself unable to do simple functions, like saving a document, and have had to re-do some work as a result. I learned to recognize the condition and simply stopped and took a nap, losing time instead of ruining or losing a document. I was lucky.

I've heard stories of other, much more dangerous events, such as a woman who brought a pot of oil, rather than water, to a boil, which resulted in severe burns and property damage.

Since I've been on my present medication regimen, including Xyrem, I haven't experienced any events of "going to stupid."

CATAPLEXY:

Early symptoms were just momentary muscle weakness when I laughed. My face felt strange, and my knees felt wobbly. By the time I found Xyrem, my cataplexy was severe. When my granddaughter, Alexis, was a toddler, she kissed my cat while the two of them were sitting in my window seat. I found it so adorable that I collapsed totally to the floor. All muscles go limp. You can't protect yourself from hitting your head on the coffee table on the way down. You just fall.

Walking in the hall at work, then as a mediator for the Colorado Department of Labor and Employment, my supervisor told a joke. Instead of laughing, without warning, I fell to the floor. Employers worry about liability. A couple of cataplexy attacks at work, especially when you work for the Division of Workers' Compensation, are pretty likely to lead to unemployment. I had an unbelievably supportive supervisor, and fortunately, I was only a week away from starting Xyrem when this occurred.

Based on stories my grandmother told, I think my grandfather had undiagnosed narcolepsy and cataplexy. He was not so fortunate as I. He spent a lot of time alone in his room at unpredictable times, demanding silence from his family. When he was about 45, he had become so concerned about the possibility of falling off a roof, in his business as a general contractor, that he tried to change careers. It was shortly after the Great Depression. A potential employer promised to hire him if he purchased a particular kind of truck. He spent all his savings on the truck. When the job fell through, my grandfather decided that his insurance policy would be more helpful to his wife and three daughters than he was, and he ended his life.

I had the good fortune of knowing what cataplexy is before mine became severe. Before I found Xyrem, I did what I could to anticipate problems. As an example, I asked friends to stick close by on Law School Graduation Day, so they could support me if the sheer joy of it put me on the ground. I got pretty wobbly, and my friends kept me upright. I've never been seriously injured by a fall, suffering only some severe bruising. Fortunately, before Xyrem, I never had an emotional experience on the stairs, which at my home present a clear and present danger of a potentially fatal fall.

Many others have not been so fortunate. I've heard stories. The most startling was about a narcoleptic who was not able to escape a house fire because his fear caused cataplectic collapse. When you collapse, the muscles used for speech also fail, so you cannot cry out for help. Cataplexy, at best is hugely embarrassing. At worst, it is extremely dangerous.

Various anti-depressants I've tried had only partial success in controlling my cataplexy, caused distressing side effects, and the pharmacist's warnings threatened worse ones. Going off anti-

depressants resulted in an extreme rebound of cataplexy, far worse than any cataplexy I experienced before trying them.

In contrast, since I began using Xyrem, my cataplexy has been nearly totally eliminated. Only on rare occasions have I had a slight facial relaxation or a tiny knee wobble in response to a very emotional situation. These were so insignificant that no one else noticed them at all. I've experienced no side effects from Xyrem. Additionally, when I had to abruptly stop using Xyrem for a short time, my cataplexy returned slowly, over a three-week period. Other than the return of all the other symptoms of narcolepsy, I had no additional negative symptoms from terminating my Xyrem regimen. Thankfully, the time that Xyrem was unavailable to me was brief.

WHAT A DIFFERENCE XYREM MAKES!

Since going on Xyrem in the fall of 1995, I have been able to function as an essentially normal person in spite of my diagnosis of "Severe Narcolepsy with Cataplexy."

I have had some career success. I am now a full time Administrative Law Judge with the Colorado Department of Labor and Employment. I can work an 8 to 10 hour day, reliably stay awake to hear all my cases, share a funny anecdote with an attorney, and decide emotional issues involving people who are severely disabled by industrial injuries, without collapsing.

Because of my employment, I am presently current on my student loan payments. If I am able to continue to meet the demands of my job, they will be paid off within the next 18 months.

I am a responsible and happy member of a great family that I thoroughly enjoy. I am able to be a full partner to my husband, to whom I've been happily married for precisely seven years as of June 6, 2001, rather than a nighttime endangerment or a financial burden.

I enjoy helping out with my three grandchildren, rather than falling down when they do something cute or have a problem. Three years ago I was able to assist at the birth of Justin, Alexis' little brother, with no cataplexy. I was thrilled to carry him from the delivery room to his first physical examination. Last fall, we traveled to California to get to know my son's firstborn, little Griffin. Later that week, when he became quite ill, I was fully competent to drive him and his frantic parents to the emergency room, and comfort them during his examination and treatment. I was also able to rejoice over his swift and complete recovery. And when I was granted the distinction of being the first to see the empty place after Alexis lost her first tooth, I picked her up, hugged her, and shed a tear of joy, all in an upright position!

I was privileged to be the primary family caregiver for my mother when she suffered a year of dementia. I was with her to provide comfort as she succumbed to pneumonia. I stood up and spoke of the beauty of her life at her funeral.

Without Xyrem, Cataplexy would have robbed me of all of those experiences.

Without Xyrem, I could be unemployable.

Without Xyrem, it would not be safe for me to hold my grandchildren.

Without Xyrem, I would have to try to avoid emotion. Please think about that. Thinking about it makes me very emotional.

The things that make life worthwhile are facing challenges that make us angry, or sad, or frightened, and overcoming them; and celebrating the joy of our successes and our blessings. Xyrem returns the value in life to narcoleptics who have cataplexy. Without Xyrem, my life would be worse than empty.

Please understand. I am a very fortunate narcoleptic. God blessed me with sufficient intelligence to graduate from law school while half asleep, and enough inborn tenacity and stubbornness to never take "You can't!" as the final answer. I live in Denver. My mother's doctor, unlike most physicians in the area even today, heard about the study of the substance we now call "Xyrem," being done in a nearby suburb. That happenstance has allowed me to reclaim a productive life. Thousands of narcoleptics in this country are not nearly so lucky. They desperately need for Xyrem to be available, by prescription, in their towns, in order to complete high school, hold jobs, build successful marriages, and raise children safely.

Xyrem gives back to narcoleptics the bottom-line American Dream, the opportunity to pursue happiness, without falling down when the going gets tough, or when the goal of happiness is attained. As a member of the Narcolepsy Network, and of Orphan Medical's Xyrem Patient Counsel, I am testifying, not only for myself, but also as an ambassador for all those other narcoleptics, and for our children and grandchildren, who may inherit this condition from us. Please find a way to balance the concerns of all persons interested in this drug. Please allow the approval and distribution of Xyrem for treatment of narcolepsy to go forward, now.

Thank you for taking the time to consider our side of this story.

Sharon A. Fitzgerald,
11824 West Belmont Drive
Littleton, CO 80127-6244

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. . . out of the darkness, into the light . . .®

May 16, 2001

Sandra Titus
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-21)
5600 Fishers Lane
Rockville, MD 20857

Dear Ms. Titus:

I will be appearing at the June 6, 2001 FDA Advisory Committee meeting for sodium oxybate, a treatment for narcolepsy and cataplexy. Attached is a written history of the drug for use by committee members. I will confine my oral comments to the lessons we have learned from restricted distribution systems for Clozaril and Thalidomide.

I look forward to seeing you on June 6.

Very truly yours,

Abbey S. Meyers
President

ASM:aa

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Testimony by
Abbey S. Meyers, President
National Organization for Rare Disorders (NORD)

Regarding
Xyrem (sodium oxybate), Orphan Medical Inc.

Before the
FDA Peripheral & Central Nervous System Drugs Advisory Committee

June 6, 2001

A TWENTY YEAR SAGA

Sodium Oxybate was one of the original therapeutic compounds that led to enactment of the *Orphan Drug Act of 1983*. Its value in treating the most devastating symptoms of Narcolepsy, known as Cataplexy, has been known since the late 1970s. Even after the law was enacted, no company was willing to develop the drug for the commercial market because they believed it would not be profitable enough.

During the 1980s, the FDA's Office for Orphan Products Development funded a research grant to an academic scientist for a small clinical trial of sodium oxybate. After several years, he published the study, which raised the expectations of the narcolepsy community. Still no company was interested. We turned to the generic drug industry, and a generic manufacturer agreed to adopt the drug. He spent about five years stabilizing the compound but did not launch a new clinical trial. Finally that company was merged with another, so FDA again sought a new sponsor. Orphan Medical stepped in where no other company was willing to tread.

About that time, the drug began to appear in health food stores with bogus muscle building claims. But the one thing sodium oxybate does very well is put people to sleep. When young people started arriving at emergency rooms, doctors realized they were in a deep sleep, and they started raising warnings. FDA eventually ordered the supplement off the market when it became associated with the "date rape" drugs. DEA wanted to make it illegal for all uses, without regard to it's valid medical use for narcolepsy. We pointed out that none of the illegal use of the drug was associated with the pharmaceutical formulation, and instructions for making sodium oxybate are on the Internet. Therefore, the FDA and DEA cannot stop use of the compound unless they take the instructions off the Internet.

Now after more than 20 years, the studies are done and Orphan Medical has submitted an NDA for approval of sodium oxybate for narcolepsy and cataplexy. People with the most severe form of narcolepsy need this orphan drug desperately. The question is safety of a distribution process that will assure it gets into the hands of patients who need it, and not to the young people who will use it for the wrong purpose.

Keep in mind that people with narcolepsy currently struggle with an inequitable distribution system for amphetamines. If they need Ritalin or Dexedrine, they usually have to tell their pharmacist days in advance because most pharmacies do not want to stock those drugs. They cannot order amphetamines through the mail, and in many states they are forced to see their doctor more than medically necessary in order to get new prescriptions. It is not easy to have a disease that is treated with medicines that have potential for abuse.

I submit that safe distribution systems can be implemented, notwithstanding the Internet. Unless law enforcement and Congress are willing to take the information off the World Wide Web, those who misuse sodium oxybate will be able to continue manufacturing it in their kitchen sink. We already have good models for controlled distribution of prescription drugs, and these are the models that this committee should consider.

The best model is probably thalidomide, a drug that matches no other in the history of medicine in terms of horror, but is nevertheless an approved orphan drug on the American market today. Doctors who prescribe it, and pharmacies that dispense it, register with the manufacturer so that every pill can be monitored and traced in the distribution system. Another important drug is Clozaril for schizophrenia. That drug also is carefully distributed through registered pharmacies, and patients have to prove that they received a satisfactory blood test before their next weekly prescription is dispensed. Our primary concern about these systems is that manufacturers should not be privy to patients' names and addresses. An independent party should guard personally identifiable information.

Both Thalidomide and Clozaril have been approved by the FDA and successfully marketed in the United States even though their distribution is tightly controlled. For serious diseases that do not respond to other therapies, it is incumbent on FDA to find safe ways to get the treatments to the patients who need them. Narcolepsy with cataplexy is a very serious disease, as dangerous as epilepsy because patients lose consciousness suddenly and uncontrollably. We know the most important rule of medicine is, "First, do no harm". To deny this drug to people with cataplexy will do harm to them. We ask you to allow this drug to get to market with a carefully controlled distribution system so we can put this nightmarish saga of sodium oxybate behind us and let these patients get back to living productive lives.

Thank you.

NARCOLEPSY NETWORK
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Cincinnati, Ohio 45242

Tel: (513) 891-3522 **Fax: (513) 891-3836** **E-mail: narnet@aol.com**

February 28, 2001

Peripheral and Central Nervous System Drugs Advisory Committee
c/o Sandra L. Titus
Center for Drug Evaluation and Research (HFD–21)
US Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
e-mail: tituss@cder.fda.gov

Subject: New Drug Application 21-196
Xyrem (Sodium Oxybate)

Dear Committee Members and Ms. Titus:

Thank you for this opportunity to address your study of safety, efficacy, and risk management issues regarding Xyrem (a.k.a. GHB). I will briefly inform you of both my long personal use of GHB, and my very serious concerns as Executive Director of Narcolepsy Network. My hope and purpose are that you will allow the estimated 25,000 Americans who suffer from the disabling cataplexy symptom of narcolepsy the same positive and even life-saving benefits I have received from this product.

First, my personal experience with GHB as a narcolepsy patient. I am 57 years old, married, with two adult children, and am an attorney in private practice (family and criminal law). **I may be the first American to have used GHB for narcolepsy, and the longest continuing user of this drug, now approaching 19 years.** My narcolepsy/cataplexy symptoms first appeared in my mid-30's, and by age 39 included severe and recurring cataplexy, together with excessive daytime sleepiness and sudden recurring sleep attacks. My cataplexy was causing numerous daily episodes of complete body collapse, such that I could no longer even walk from my home or office without serious risk of harm to myself

and others. Feeling any emotion (humor, anger, and even mere surprise or enthusiasm) would cause me to suddenly collapse like a puppet without strings. I would usually fall backwards, with my head whipping down last on concrete, metal, table corners, stairs – whatever was there. I have often been "rescued" by emergency crews, police, lifeguards, strangers and friends. Some falls resulted in hospital visits for injuries, fortunately none permanent. But there are others whose falls have been fatal. Moreover, I would fall suddenly into REM sleep, even in mid-sentence. Disability was staring me in the face.

Then, in August 1982 my treating doctor sent me to Sunnybrook Medical Center in Toronto, Canada to begin prescriptive use of GHB under the research studies being conducted by Dr. Mortimer Mamelak. After three weeks, I returned home and continued using GHB, as monitored by my local physician under an approved FDA individual investigational new drug application. My significant cataplexy and sudden sleep attacks disappeared almost overnight. I was immediately able to return to my full-time law practice. Since then, I have continued using GHB under the FDA clinical investigative procedures conducted first by my local physician, and in recent years by Orphan Medical. **During these 19 years, I have never changed the dose, have never experienced tolerance, and have noted no side effects. Simply stated, the drug is as safe and effective now as it was at the start.** (Frankly, it is difficult to imagine a pharmaceutical product offering such quick, complete, safe and enduring benefits.)

Secondly, my privileged service as Executive Director of Narcolepsy Network in recent years is motivated by the effective medical treatment I received, and a desire that others with narcolepsy might be as fortunate. Narcolepsy Network is a national nonprofit organization whose mission is to educate the public, healthcare professionals, and government representatives regarding this disabling neurological disease, and to facilitate more prompt, informed and effective treatment for persons with narcolepsy. We work closely with the National Center for Sleep Disorder Research at the National Institute of Health,

the American Academy of Sleep Medicine, the National Sleep Foundation, sleep disorder centers as well as Orphan Medical and other pharmaceutical companies developing orphan products for narcolepsy. We have sought to inform federal and state government officials, whenever appropriate, of the dramatic medical benefits provided by GHB to patients participating in the clinical trials. A fortunate result has been the present bifurcated scheduling of GHB on the federal level and in many states. I have often stated to congressional committees and legislative representatives over recent years that the greatest tragedy in the development of treatments for narcolepsy has been the unavailability of GHB, in prescriptive form, to other patients like myself with narcolepsy and cataplexy. Now I respectfully ask this committee to assist in eliminating such an unnecessary situation.

Finally, we are very mindful of and cannot ignore the injuries, deaths, and other "victimizations" which many young Americans have suffered from unlawful and/or uncontrolled consumption of GHB or its related chemical compounds. Narcolepsy Network and myself have cooperated extensively with law enforcement agencies, medical professionals, and community drug agencies. Our continuing purpose is to minimize unlawful use of GHB, and to design safeguards to reduce access and availability. These concerns deserve your and our utmost attention.

However, equally deserving of your highest consideration is the promise and potential of medically controlled GHB to allow persons with narcolepsy with severely disrupted lives and frequent disability to again rejoin their jobs, communities and families.

Thank you for your professional consideration.

Respectfully,

Robert L. Cloud
Executive Director
Narcolepsy Network, Inc.

Titus, Sandra L

From: ciindy [redacted]
Sent: Monday, June 04, 2001 8:12 AM
To: Titus, Sandra L
Subject: fda hearing statement

----- at
My name is Cindy Pekarick, and I would like to describe how ghb analogs killed my daughter.

In ***October of 1998***, my daughter Nicole, a college student, waitiress, and gym enthusiast met a new boyfriend who

introduced her to a product called "Renewtrient. In ***November*** she researched the product via 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 competely recovered and ready for another workout. In ***December*** I found out she was taking this

supplement, didn't believe all 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.

By ***April***, she returned home. She became behind in all her bills. She was bruised on her legs

and arms. She stopped attending classes, and kept losing her keys, wallet, and her pager. In May I discovered she had

essentially "dropped out of school".

By June, I could see mild changes in Nicole's behavior. She began taking "power naps" as she called them. She

would sleep for 3 hours in the middle of the day and get up at 4 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 wierd, then she goes to sleep.

When she wakes up she never remembers anything that she did. She started taking it once in a while so she

could go to sleep right away when she got home from work, 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 analogs all along, since November. I began my

quest for information regarding Renewtrient, Revivarent, and Invigorate, which my younger daughter claimed Nicole took.

In ***August***, Nicole was found having a seizure in a public bathroom. She had urinated and defacated on herself while

pulling at her clothes and flailing her arms. She was rushed to the hospital where we arrived to see her unconscious,

intubated, with her arms, legs, and waist strapped to the bed. They claimed her seizure was violent, and she barely had a

pulse when they found her. It was at this time that 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. We told them

what we thought she had taken, but they didn't have a test for it. I begged the doctors to transfer her to a treatment center

for chemical dependency, but they couldn't do it without the patient's permission. She was clueless as to why she was

hospitalized. She had no recall of anything that happened to her. In fact,she wanted to know where her clothes were. She was

discharged, but began psychological counseling a few days later.

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 this "g" had a hold on her was

a step in healing. I assured her we would find a treatment center as soon as possible and that everything would be ok.

On Monday morning, on our way to the treatment center, Nicole refused to go. She claimed the "g" wasn't addictive,

that she did research and she was just having reactions to it. She said she was now in control of her life and future. She

remained in counseling and by the end of September, Nicole had applied, transferred, and was accepted at the university.

She was so excited, that she stopped at my school on her way home to tell me that she would start classes in

January. Things seemed OK on the surface, but she was hiding tremors, hallucinations, and insomnia. She went days without

sleeping, but never told me.

On October 3, 1999 around 2 PM, 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 PM, but she would never hear it. She was in her final sleep. My firstborn child

was found in bed, blue about 6 PM. We found a bottle of Jolt in the trunk of her car. The autopsy revealed she had gbl and

ghb in her system at the time of death. No other chemicals were found.

Nicole was an honor student while captain of two varsity teams and she belonged to a ballet company.She graduated

3rd in her high school class, and was both a Bloustein and a Garden State Scholar. For her undergraduate studies she

majored in biology, with the plan to major in engineering for her masters degree. Her ultimate goal was to become a bio-

medical 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, intelligent, beautiful, funny, witty, and charming

young lady. Her only fault was that she was naive.

Statement by Eric C. Strain, M.D. on Behalf of the College on Problems of Drug Dependence

Food and Drug Administration

Peripheral and Central Nervous System Drug Advisory Committee

June 6, 2001

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 and I am a professor in the Department of Psychiatry and Behavioral Sciences at Johns Hopkins University School of Medicine. I am a Board Certified Psychiatrist with added Board Qualification 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 travel to today's meeting, and I have no relationship with Orphan or other pharmaceutical companies that make narcolepsy products.

There are two points 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 Drug Abuse Advisory Committee 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, 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 the Peripheral and Central Nervous System Drug Advisory Committee for allowing me to make these comments today. The hope of the College is that these comments will spur tangible demonstration of the 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.

Public Statement, Food And Drug Advisory Committee Meeting on the approval of Xyrem (gamma hydroxybutyrate)

My name is Dr. Deborah Zvosec. My research is in the area of gamma hydroxybutyrate (GHB) abuse, toxicity, addiction and withdrawal. Dr. Stephen Smith and I, with others, published a case series in Morbidity and Mortality Weekly Report in February 1999, describing adverse events due to ingestion of "dietary supplements" containing gamma butyrolactone (GBL). 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; toxicity episodes included 2 deaths that occurred with no co-intoxicants and no evidence of aspiration or asphyxiation or adulterants. Among the many health risks of GHB that I could describe to you today, I will focus on GHB addiction. In the course of our work, my name and Dr. Smith's name were listed on the Project GHB help site. We have received calls from over 40 addicted patients from 25 states and have treated an additional 5 cases of inpatient withdrawal at Hennepin County Medical Center in Minneapolis.

The majority of these addicted individuals began using GHB to treat insomnia, anxiety, depression, chemical dependence, or for bodybuilding purposes, as recommended by product marketers, web sites, and fringe pro-GHB physicians such as Dr. Ward Dean, author of "GHB, The Natural Mood Enhancer." Our patients began with small doses, often only at night, and discovered that it made them feel very good. They increased dosing frequency and, as tolerance developed, they needed more GHB in order to feel good; within months, they were taking GHB every 1-3 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; they lost their jobs; they acquired tremendous debt to support their habit; and they became comatose while driving and crashed their cars, frequently on multiple occasions, and often causing injury and sometimes death. They called us in absolute desperation. We helped with locating and consulting with a physician on their inpatient detoxification. Detoxification 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 detoxification and some also experienced muscle twitching and tremors. Of the over 40 patients we have worked with, only a handful have remained GHB-free, frequently despite chemical dependency treatment. Many have detoxified numerous times but continue to relapse, sometimes within hours of release from treatment. Unfortunately, many never lost faith in GHB and continued to be convinced that they could get back on G and use this wonder drug responsibly. They continue to argue its health benefits.

One of our patients was a 50-year-old businessman who used GHB for 5 years, initiating use to enhance bodybuilding and increasing to around the clock dosing within 2-3 months. His life was entirely controlled by the need to have GHB with him at all times. He had 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 of GHB users. It was only on the morning of his admission for withdrawal that she learned the truth. After 6 days of detoxification with diazepam, he was through the worst of the hallucinations and appeared to be on the road to recovery. A psychiatrist treated him with sleeping medications and antidepressants, but within 3 days, he began using GHB again to control profound anxiety attacks and depression.

It has been the same story over and over. Few who have ventured deep enough into GHB have been able to emerge again, and when they do, neither they nor their families emerge unscathed.

GHB is perhaps the most addictive drug ever abused. Experienced drug users describe a euphoria that surpasses that of any other drug. Availability by 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 Xyrem prescriptions for fake sleep disorders, and for insomnia, fibromyalgia, depression, anxiety, 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, which is determined by cost, perceived quality, ease of procurement, and legal status.

Clinical literature reports an addicted user who spent up to $200 per day for GHB (over $70,000 per year). Our patients have reported ingestion of up to a bottle of supplement/solvent product every 1-2 days, at $60-100 per bottle ($11,000-$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 cheap 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 to such users. We know that users are watching for the release of Xyrem. Recreational drug sites post links to narcolepsy sites and publications about Xyrem; hotyellow98.com, for example, instructed "click here to find out when GHB will be released under the trade name of Xyrem."

There is no systematic federal, state, or local data on the demographics, epidemiology, use patterns, or costs of GHB abuse or addiction. Adverse events are vastly underreported because: 1) we have no field test to detect GHB; 2) we have no routine hospital toxicology screening test for GHB; 3) most clinicians and toxicologists do not know to look for GHB and it is easily masked by or confused with other intoxications; and 4) we have no systematic reporting mechanism accessible to all practitioners. Furthermore, we have no data on chronic or long-term effects of frequent use and addiction. No federal or state funds have been spent on research, education, or prevention of GHB-related health risks in the general public. There are no treatment protocols that have been scientifically validated for either acute GHB toxicity or severe withdrawal, both of which are highly variable and extremely unpredictable.

The nature and course of the Xyrem approval process troubles me deeply. In contradiction to past procedures, the determination of Schedule III status for medically-used GHB occurred prior to discussion of scientific proof of safety and efficacy. Release of Xyrem for off-label prescription, at this time, to a distribution system that uses voluntary self-monitoring with no mandatory governmental oversight or regulation is madness. I urge you to maintain Xyrem/GHB under research status so that narcolepsy patients may receive their medications until an externally monitored and regulated prescription and distribution system may be established. Potential repercussions of ill-advised or premature action are profound. Precedent has already been broken with this split scheduling. It must be broken again if we hope to avoid learning from more tragic mistakes.

Deborah L. Zvosec, Ph.D.
Research Associate, Department of Emergency Medicine
Hennepin County Medical Center
Investigator, Minneapolis Medical Research Foundation
Minneapolis, Minnesota

FDA PCNS Committee Meeting (June 6, 2001)
Statement by Trinka Porrata
Drug Consultant (Retired Narcotics Officer)

There is no way to crush five years of intensity into five minutes. I have lived and breathed GHB issues since June 1996 when I was first assigned to handle it for LAPD. Four young men collapsed; two literally died and were brought back by paramedics. I was stunned that hardly anyone knew anything about this drug, but one thing was clear------people were dying from GHB and it was being missed due to lack of ability to test for it and lack of knowledge that it even exists.

I'm not a doctor or a chemist. I realize research is important, but I'm sickened when reality is brushed off with "Oh well, that wasn't a clinical study" or "You can't PROVE it was GHB versus an analog." In some cases we can prove it; meanwhile, no federal agency has made any systematic effort to make such identification possible. I live in a real world of suffering people that can't be captured by clinical studies. I see both immediate disasters and long-term aftermath of GHB. I'll try to cover as much as I can because I feel an obligation to victims of GHB worldwide.

I have read the research. I've talked to hundreds of GHB users/dealers plus patients/doctors in the narcolepsy/cataplexy research. I've reviewed or consulted on hundreds of sexual assault cases where GHB has been identified as the weapon or where symptoms point to GHB. I've helped more than 300 GHB addicts, each of whom can name dozens more just like them and many with 3-5 impaired driving incidents in just a few months. They are in virtually every state of this country and several foreign countries. They aren't whom you would expect; they are businessmen, bodybuilders, airline employees, athletes, exotic dancers, bodybuilders, computer wizards and more bodybuilders. Most of them believed they were taking a safe workout or sleep aid, but then it took over their bodies and souls. I have worked closely with several dedicated doctors during the 17 months we have operated the GHB addiction helpline via www.projectghb.org (aka www.ashesonthesea.com/ghb). We have learned so much about GHB from these previously unrecognized and still typically undertreated addiction cases. I have seen the pain of the families/friends of GHB death victims, the horror of overdoses. My addicts have lost relationships, jobs, fortunes, suffered ongoing disabling injuries. Some lost their lives to GHB, whether by overdose, traffic accident or suicide. The suicidal depression associated with GHB withdrawal is stunning. I have GHB addiction/withdrawal related suicides and/or currently suicidal people from New Zealand to Sweden. I have some "MIAs" who probably did end their lives. Grieving parents have told me their stories; my office wall bears the pictures they have sent me. It has been a heartbreaking five years, mixed with the privilege of learning more and teaching others to recognize the rape, OD and death cases or getting rape victims into treatment or convincing youngsters not to try GHB. It has also been very lonely at times when agencies who should care don't.

DEA has reviewed and documented 71 deaths related to GHB, but stopped counting once the drug was controlled. No one at FDA has ever expressed interest in actively identifying these cases. My database includes about 200 GHB-related deaths now. Robert McCormick of the FDA's orphan drug unit told me emphatically that he did not care how many people had died or were addicted to GHB, as he intended to approve it anyway. Something is wrong with this picture. This is truly the most horrid drug I have encountered in 25 years as a police officer. Much new info has come to light during the past two years, none of it good. Around the world, countries are now just awakening to their problems with GHB, and restrictions on it are tightening. New Zealand tried it as a prescription drug and now realize it was wrong. France is backing away. NIDA is releasing $2 million in research about this drug. This is clearly NOT a time to be pushing it forward on unsuspecting American citizens.

You are here today to approve GHB (disguised as sodium oxybate) for use with narcolepsy/cataplexy. Orphan's investors have been assured (according to their message board posts) that you will approve it (FYI--news reports said that Orphan stock dropped 30 percent when you canceled the previous meeting). But doing so would contribute to the internet-generated belief that real GHB is safe and would simply lead to a rush for the "good stuff." You have not seen my video tapes of the day-to-day struggle of GHB addicts, clearly showing that GHB gives previously healthy people symptoms that can only be described as

narcolepsy/cataplexy. They are destroying themselves with it; wives are terrified of their husbands and often have no idea what is happening to them; many are being locked into psych wards instead of being treated because ERs and doctors don't recognize GHB psychotic episodes and withdrawal syndrome; and they are killing themselves/others behind the wheel. I often hear, "GHB (withdrawal) leaves a hole in your soul." Many are suffering long-term anxiety and depression, Parkinson-like shakes, etc. even 18 months after detoxing. There are no answers for them yet, so how can it be approved, letting it cause similar damage to others?

I am deeply concerned about the "off label use" policy that would enable any doctor to prescribe this drug 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, for example, a condition with vague symptoms for which a drug seeker could easily get a prescription. And, I know that doctors won't realize that Xyrem (sodium oxybate) is GHB. I called an FDA doctor who had written about the dangers of GHB, but another person had taken over GHB issues. The assistant passed the info I gave her to this person, who then called and said that I must be nuts. She had looked on FDA's orphan drug list and didn't find GHB. And, she checked the Orphan website and found that they weren't researching GHB either. She clearly proved my point-----If an FDA employee assigned to know all about GHB can't figure it what sodium oxybate is, the vast majority of doctors around the country would not realize it was GHB! I see no significant talk on the legitimate narcolepsy websites about this impending new drug, but message boards where GHB addicts hang out are buzzing about it. In fact, one of the key figures in illegal GHB internet sales is behind the original posted website www.xyrem.com!

There is very little drug diversion enforcement in the US. Only a handful of agencies devote one iota of time to the diversion of prescription medications to abuse. It is a very small portion of DEA effort. Most state narcotics agencies are too busy with meth, cocaine, heroin, etc., to have anyone assigned to diversion. State pharmacy and medical boards aren't staffed adequately. A doctor, for example, testified before the California Legislature that he was illegally prescribing GHB to his narcolepsy patients (being illegally imported from Europe by a compounding pharmacy) and was untouched because no one had time to follow up. He has a narcolepsy practice and puts out a radical narcolepsy newsletter (which openly attacks the FDA and doesn't identify a publisher), and will undoubtedly be included on Orphan's list of approved doctors. Therefore, Orphan's proposed voluntary (keyword: voluntary) promises of careful controls are frightening. They are designed to put at ease those precious limited resources devoted to drug diversion so that no one will worry about taking time to look at them. And, there are no real penalties associated with failure to abide by their voluntary conditions! The drug can be taken off the market, but how long would that take? The FDA is a huge, cumbersome bureaucracy that has been incredibly slow in dealing with this drug. It took a legislative subcommittee on oversight to demand a scheduling report from FDA in response to DEA's proposal!

Orphan representatives and others have claimed that Xyrem will be too expensive for addicts. But that contradicts the facts. GHB addicts pay up to $100 per day or more for a 2 oz bottle that may be near 100 percent or a 32 oz bottle that may be watered down to even as little as 5 percent. GHB addicts often find themselves with all their credit cards maxed out by their GHB purchases (up to $30,000 in a year). GHB addicts will be diagnosed as narcoleptic/cataplectic because they essentially become that! A number reportedly have done so. I was once personally misdiagnosed as having narcolepsy once when in fact I merely had Epstein Barre virus.

More importantly, once in possession of that prescription and a bottle of Xyrem, the addict will be "home free." There is no "field test kit" for GHB at this time. Thus ALL investigations of GHB cases are difficult. Encountering a prescription (real or counterfeit) and Xyrem bottle, the officer would have absolutely no ability to determine if it contained the prescription product or had been refilled with street GHB or its analogs. NO POSSIBILITY at the street level. It would require elaborate circumstances (establishing a high level of "probable cause" to believe that the bottle contained something other than the legitimate product) to even think of justifying further lab testing. In an impaired driving case, it doesn't matter (in states with thorough DUI laws) since impairment is the issue, not illicit versus licit drugs. In terms of possession cases, few if any agencies will have or be willing to expend the resources to do a detailed analysis (assuming it's even possible to tell the difference). At this moment GHB rape cases go

undetected and/or unprosecuted due to lack of training and testing capabilities. Agencies dread investigating possession cases because of the lack of a test kit. They dread sales cases because of the complexity of analog issues and deceptive practices being used (hiding it as weight belt cleaner, plant food, ink jet cartridge cleaner, etc.). Few agencies are equipped to handle internet sales cases because of the deceptive practices and the difficulty in physically "finding" the internet companies.

To those who claim that "real" GHB is safe and that only the street stuff is dangerous, I say "poppycock." Addicts have used everything from European pharmaceutical grade GHB, carefully manufactured GHB to horribly tainted products, plus varying quality GBL, BD and a third analog. For every one of them who swears that he was "OK" when taking GHB but got in trouble when he took GBL (or BD), there is one who says the opposite. Besides, no matter which one you take, you urinate out GHB. Yes, there have been cases where the medical problems involved high pH (drain cleaner) product or contamination by other toxic solvents; these are rather obvious. The vast majority of incidents are clearly consistent with GHB-related problems. Let's stop ignoring reality.

The unprecedented split scheduling of GHB was an unwise decision, clearly impossible to enforce. Those of us involved in the federal legislation were forced to accept what we knew was an insane compromise or face no scheduling of the drug at all. I know because I flew to Washington, D.C., at my own expense for the privilege of attending a small, by-invitation-only meeting. There were no doctors or scientists, just two Legislators with differing legislation on the issue, a few of their staffers, and a PR representative from Orphan Medical, a representative from the Rare Disease Foundation and me. The agenda was clear. GHB would be Schedule III (second legislation introduced), with Orphan Medical offering their first draft of "voluntary controls," and the previously submitted Schedule I legislation would be killed. Undaunted by what I felt was an intimidation effort, I—and others-- fought like hell for Schedule I behind the scenes anyway and ended up with the split compromise. It was no small political victory just to bring it up to that.

It has been frustrating to watch a drug company dictating to various states how to word their legislation on GHB to meet the drug company's demands and in general calling all the shots. This hasn't been about science or medicine, but about politics. It has indeed been a slick PR operation by a company that clearly has inappropriate political clout (as even commented on by their own investors on their finance message board!) and that has played on the hopes of those with narcolepsy/cataplexy in their drive to make big bucks from a drug of devastation. I have never before seen drug companies openly paying people at forensic conferences to attend their presentations ($175 per person). Inexplicable amounts of money have been spent to "PR" this drug.

Meanwhile, I have lost all respect for one of the current narcolepsy trials doctors, who volunteered his concerns about this drug to me and then, two years later, recanted all of his statements suddenly, after I brought that info into the open. I must assume that his reversal was at the company's request. I have my doubts that narcolepsy/cataplexy trials are as successful and promising as we have been lead to believe. I do feel that those with narcolepsy/cataplexy need a longer-acting, safer "cousin," not GHB; an opinion also expressed by Dr. Mortimer Mamelak on prior occasions.

I can't stand by quietly and let this travesty occur. In my opinion, this would be the biggest mistake ever made by the FDA and the drug would have to be taken off the market in the near future but it won't be soon enough. The now known tragedies and the massive "unknowns" about GHB truly outweigh potential benefits. Please read the "viewers comments" section at www.projectghb.org and vote against approval of this drug at this time.

Testimony of the National Sleep Foundation

Presented to the

Peripheral and Central Nervous System Drugs Advisory Committee

Of the

U.S. Food and Drug Administration

June 6, 2001

By

Richard L. Gelula, MSW
Executive Director
National Sleep Foundation

Disclosure

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Finally, from a financial perspective, the Foundation has operated conservatively and has had budget surpluses for each of the past five years. Support from Orphan Medical did not contribute materially to NSF's maintenance or development. The absence of their contributions would not have differentially affected the Foundation's programs or its functioning.

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The National Sleep Foundation has been an advocate for people with narcolepsy for some time. In 1998, upon recommendation of its Research Committee, then chaired by Thomas Roth, Ph.D., editor of the journal Sleep, the NSF Board approved a comprehensive program titled, "Toward the Cause of Narcolepsy." This program has provided grant funding that supported the breakthrough research at Stanford University, which in 2000 led to the discovery of the canine narcolepsy gene and the subsequent finding that the recently discovered hypocretin peptide is almost or entirely missing in people with narcolepsy. Since 1996, NSF has also invested in another approach to the discovery of the pathophysiology of narcolepsy, the establishment of the National Narcolepsy Registry, a serum DNA and family history registry for narcoleptics and their family members. The National Narcolepsy Registry is housed at and managed by the Montefiore Medical Center in New York City and currently has registered nearly 700 patients and family members. The NNR has been a research resource in seven narcolepsy studies. This initiative was funded by private (non-corporate) donations and by NSF's general operating fund.

Through our Pickwick Post-doctoral Research Fellowship program, NSF is also now funding a two-year study at UCLA on the neurochemical control of muscle tone in sleep and cataplexy.

Additionally, NSF has also provided a significant number of resources to professional and public education about narcolepsy and cataplexy. Given the small number of people directly affected by narcolepsy and the debilitating character of the disease, these contributions to education have been important. We publish brochures about the disease and distribute them at public, patient and medical meetings, through sleep centers across the U.S., upon written request, and we also place them on our Web site, www.sleepfoundation.org. We provide a lot of coverage about narcolepsy in our quarterly news magazine, **sleep***matters*. And over the years, we have devoted a significant number of issues of *Sleep Medicine Alert* to issues related to narcolepsy and cataplexy. Our professional outreach includes attendance and exhibits at such meetings as those held by the Associated Professional Sleep Societies, American College of Physicians/American College of Internal Medicine, American Academy of Neurology, American Psychiatric Association, Academy of Family Practice, and others.

Finally, based on a perspective grounded in patient interests, NSF, under the leadership of its Government Affairs Chair, Dr. William C. Dement, took an active role in advocating against legislation that would have assigned Gamma Hydroxybutyrate (GHB) a Schedule I classification under the Controlled Substances Act, which would have jeopardized further investigation of its therapeutic benefits; and NSF supported the final bill authorizing bifurcated scheduling for this medication. Our advocacy activity was primarily carried out through NSF volunteers and its Advocacy Network, and to a limited degree by NSF's general operating fund.

Summary of NSF's Position on Sodium Oxybate

The National Sleep Foundation calls upon the Peripheral and Central Nervous System Drugs Advisory Committee 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. The National Sleep Foundation does not presume to second-guess the evidence that has been submitted about the safety and efficacy of this drug, but goes on record to say that such considerations should only pertain to affected patients and not other societal considerations: if safe and effective for people with narcolepsy, sodium oxybate should be made readily available to them; any concern for illicit use should be addressed 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, should 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 stabilize patients who usually first experience the dreadful effects of narcolepsy and cataplexy during their developmental years before the completion of education and development of a career.

Background and Key Issues

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 existence for almost all other humans – the alternating cycle of sleep and alertness – into something entirely different, an uncontrolled and 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.

Just imagine what it would be like to have a life where the predictability of alertness cannot be counted on, where you felt such overwhelming sleepiness during the day that you could not stay awake to read texts, listen to lectures, or have the simple pleasure of

going out with a friend or watching a movie, where the experience of extreme emotion, the most human of attributes, such as laughter, anger or surprise, must be guarded against to prevent the loss of control, collapse and embarrassment that comes with a cataplectic attack, where despite all of the sleepiness, you do not even get a good night's sleep and awaken unrefreshed, and where available treatments often are inappropriate and leave you jittery or with other adverse side-effects. And these are only some of the effects of untreated or inadequately treated narcolepsy.

My guess is that if this disease occurred to me or during the development of any person who is here today in a professional capacity, that the AFFLICTION of narcolepsy would have proved to be a sufficient barrier that none of us would have been able to compete at a level necessary to keep up with our unaffected peers or to complete educational and career development at a professional level -- such that, in fact, none of us would be here today.

With this AFFLICTION we are not just talking about "sleepiness," an annoyance, but a condition where no amount of sleep or behavioral intervention provides sustained relief.

And the debilitating characteristics of narcolepsy are compounded by the fact that it is a low prevalence, orphan disease and that its onset most often occurs in the second decade of life when psychological and emotional development is unfinished and when people have not yet completed their education or established a career. It should also be recognized that:

Narcolepsy is not well understood or accepted – this applies to individuals suffering from this affliction as well as their families, schools and universities, employers and including personnel such as teachers, counselors and physicians, as well as peers, classmates and co-workers – in other words, the patient's entire world!

People suffer a double blow because it is thought their sleepiness is volitional and a sign of laziness – a stigma that has a troubling personal effect.

Primary care physicians are not familiar with its signs or symptoms and are unlikely to ask the kinds of questions or order tests that would speed an accurate diagnosis. One report states that it takes narcoleptics 15 years and visits to five different physicians to obtain an accurate diagnosis and in his text on Sleep Medicine, the late neurologist Michael Aldrich states that in his practice, he saw five narcoleptic patients in their 70's who had never been accurately diagnosed with the disease.

People who suffer from narcolepsy usually suffer alone, without support and are confused about their own symptoms. Their numbers are insufficient to ensure the availability of support groups in most locations.

Most people with narcolepsy do NOT have a relative with the disease, thus, even within their family context, the disease is strange and unfamiliar.

Thus, it should come as no surprise that people with narcolepsy suffer from a high rate of depression (Aldrich, 1999; Daniels, E., et.al, 2001) and research has shown that people with narcolepsy have a health-related quality of life rating as bad or worse than persons with Parkinson's disease, epilepsy or suffering from chronic migraine headache (Beusterien, et.al, 1999). Worse is that a rating by health professionals found that they desired greater social distance from narcoleptics than a number of conditions that one might expect a higher ranking such as epileptics and colostomy patients (Cohen & Mudro, 1992).

But the good news is that one study on health-related quality of life found that appropriate medical treatment does improve the HQL for people with narcolepsy (Beusterien, et.al, 1999). At this time, there are no pharmacological treatments indicated for cataplexy and those used off-label such as tricyclic antidepressants have significant quality of life side-effects including suppression of libido.

The National Sleep Foundation believe that narcolepsy exacts an unusual and cruel toll on those who suffer from this AFFLICTION and that this is a patient population greatly in need of medications that would control their symptoms. Such medications would foster more timely and appropriate diagnosis and treatment and would restore a good measure of the confidence and capability otherwise impaired by this cruel disease. I think of my own teenage child and I know that if she developed narcolepsy, I would want her to have access to any medication that might control her symptoms regardless of its effects on other members of society. We ask this panel to do all that it can to help people with narcolepsy and to consider the safety and efficacy of this drug as it applies to patients suffering from this disease.

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Testimony of the National Sleep Foundation

Presented to the

Peripheral and Central Nervous System Drugs Advisory Committee

Of the

U.S. Food and Drug Administration

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###

Memorandum

DATE: May 31, 2001

TO: *Sandra Titus*

FROM: *Matt Speakman*

RE: FDA public advisory committee meeting

CC: [*Patty Engel, Orphan Medical*]

Sandra:

As a narcolepsy patient successfully treated with XYREM, the drug which is to be discussed at the upcoming public advisory meeting, I would like to be alotted no more than 5 minutes to make the following statement.

Six years ago, as I entered my senior year of high school, my grades were slipping, my attitude was negative (to say the least), and my efforts to receive an appointment to the United States Naval Academy were useless.

I had recently been diagnosed with the condition called narcolepsy, a sleep disorder that effects the brain and causes severe daytime sleepiness and cataplexy, a sudden and nearly complete loss of muscular control.

I quickly learned that narcolepsy is a very rare disorder, about which little is known, and for which there are few effective treatments. I spent my remaining year of high school sleeping through class (averaging about 16 to 18 hours of sleep a day), angering my teachers (who suspected drug abuse), and in a generally foul disposition which affected my friendships, relationships, family life, and academic efforts.

I struggled to make it through my first year of college at the University of Kentucky, finding it difficult to awake for classes on time, and to meet friends who would understand the strange behavior patterns that result from "passing out" every few hours.

Determined to find some way to better my condition, my mother searched to find a specialist who dealt with cases such as mine. She found such a specialist in nearby Cincinatti who promised a "wonder drug" and that my life would undoubtedly change for the better.

I was skeptical. I had dealt emotionally with my disorder and had come to a realization that I would live this way for the rest of my life. I had little hope for success in the future, as I wondered what kind of employer would hire such a person.

After my first week of trial medication of GHB, which is now called XYREM, I can not fully explain to you the changes that occurred. Instead of desperately trying to stay awake during the day, I was functioning at nearly 100%. Instead of fighting restlessly at night to maintain a constant sleep, I rested deeply and soundly. The cataplectic attacks (the real monster of narcolepsy) ceased almost completely. Over the past 4 years of using XYREM I have had 4 cataplectic episodes (and only because I failed to take the medication while pulling all-night study sessions). This number is reduced from the 6 to 8 cataplectic episodes a WEEK that I experienced before treatment.

Two weeks ago, I graduated from West Virginia University (cum laude) with a Fine Art degree in graphic design. This week I will send resume's and portfolio all over the country. My ambition and energy (characteristics for which I have always been known) are restored along with my confidence of success in the future. I have built strong friendships and relationships. I have established professional contacts and experience within the field of graphic design.

THE MESSAGE: None of this would be possible without effective treatment for my sleep disorder. My experience with XYREM has been without side effects. YES, without side effects (unless you consider happiness, hope, and confidence to be side effects). I understand and agree with concerns regarding the abuse and misuse of GHB...or any drug for that matter. That is why I ask for a solution to this matter to be resolved as quickly as possible. There are thousands of other narcoleptics who need this treatment, and there are thousands of victims from abuse and misuse of this drug. Please approve the medication for those who need it, regulate it appropriately, and penalize those who abuse it.

Thank you.

-Matt Speakman

724.413.7778

National Association of Drug Diversion Investigators, Inc.
P. O. Box 42015 • Baltimore, MD 21284-2015

Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration

Established in 1987, the National Association of Drug Diversion Investigators (NADDI), 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's principal activities comprise:
(1) Cooperative education and training in the specifics of pharmaceutical drug diversion, investigation and prevention;
(2) The sharing of investigative information and communication with a wide variety of interested parties with regard to the nature, scope and impact of pharmaceutical drug diversion, and;
(3) The development of stronger effective measures to combat the problem.

NADDI supports the safety and efficacy of the new drug application (NDA) 21-196, XYREM® (sodium oxybate), proposed to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness for persons with narcolepsy.

NADDI is aware that in many reported cases, use of GHB has changed from homemade GHB to ingesting of industrial chemicals that convert to GHB in the body. There are no known cases which involve 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.

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 for consideration of this written submission. I would also be willing to provide oral submission of behalf of the organization.

Sincerely,

Charles F. Cichon
President

MICHAEL'S MESSAGE FOUNDATION, INC

My name is Debbie Alumbaugh. 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 or (Gamma Hydroxybutyrate) Toxicity.

Michael was a sophomore at Westwood High School in Ft. Pierce, Fl. He was a black belt in karate, and was also an instructor. He had won several academic awards for reading, music, mathematics and spelling. He was on the honor roll.

On October 1, 1998, Michael came home from school, and asked if he could go to the show with some friends, this was unusual for a school night, as we usually did not allow him out during the school week. We also required Michael to bring home a weekly progress report. That evening, he had brought it home and was doing well making A's & B's. Before he left, a friend came to the house; they went directly to Michael's room. His friend was only in our home for 5 minutes. This is when Michael was given the GHB.

We found out 18 months after Michael died, that when they left our home for the movie, they stopped at the local park to shoot some hoops. Michael had the ball and went for a lay-up and when he came down, he passed out. He lay there unconscious for several minutes. This should have been a red flag to his friends that something was wrong. They giggled and laughed and scooped my son up and put him in the car and onto the movie they went. We understand that Michael didn't see the first five minutes of the movie, he passed out again. When they returned home from the show, Michael's father looked at our son and asked "Are you on something son? Did you take something?" He replied no dad. After continuous questioning, he finally admitted that they had smoked some pot. Brad decided not to lecture Michael this late, he would talk to him tomorrow. Brad never got that chance.

P. O. Box 690453 Vero Beach, Florida 32969
561/464-7612

Michael died that night; in his safest place of all places, alone in his bed.

The next morning Brad went to wake Michael for school. He could hear Michael's alarm blaring. Michael did have intentions of getting up. When he opened the door, he knew our son was dead. He thought his head was going to explode, thought he was going to have a heart attack. Brad's instinct was to close our son's door and run from the house. The scene was horrendous. Our son was on his back, eyes wide open, glassy. His mouth hung open, his tongue so swollen, his father couldn't close his mouth. He had dried vomit running down his chin into a puddle in his collarbone. His hands were in a clawed position, where he had tried to roll himself over but couldn't, because the drug had paralyzed him and taken away his gag reflexes. Because we didn't know why our son had died, there had to be an autopsy. It took twelve weeks for us to learn why our son had died none of his friends would come forward. **GHB** leaves the body very quickly. They took our sons brain; that is where they found this drug. There is no antidote for **GHB** Overdose.

In the last three years, we have lost 174 young people to these designer drugs in Florida alone. That is 173 tragedies just like ours.

After several months, Michael came to his father in a dream. He said "Dad it is wrong to destroy the body the way I did. I need you and Mother to tell my friends, my generation; my story, our tragedy." "You don't have a clue about the drugs they are faced with daily. This put a burden on Michael's father and I until one day we gathered up enough courage and strength to make the first call.

I tell the students what took our sons life, and then tell them a little about Michael. I tell them he was not only a great son, but also a loving son. June 1st, Michael would have celebrated his 18th birthday, and enjoyed the pleasure of graduating on that same day. We missed prom and graduation because of this deadly drug. Since our son's death, our family has not been able to have any celebrations.

We are here to have our voices heard. This is a dangerous and deadly drug. It has taken many lives; not only in death, but in addiction also. Addiction to GHB is as serious as dying from it. What kind of life can there be when you have to have this drug every 2 hours, and without it you go into withdrawal. Detoxification from GHB is very difficult. It cannot be done in 3-5 day period. There must be professional help that knows what to do to save your life. We have devoted our lives to this. We have chosen to take our tragedy and educate our nation. We have turned our grief into

something positive and constructive.

We travel to schools from 6th grade to 12th, and on into college sharing our son's story. Our goal is to take Michael's Message Nationwide; in the hopes of saving another family the heartache and devastation this drug has caused our family. We have shared our message with just over 35,000 students in our first year. Our children are our future. Students inform us after hearing our story that they didn't know, they thought it was safe. That's what the Internet says. They tell us with tears streaming down their faces, that they worry about friends who are taking GHB. We feel that parents and grandparents should hear Michael's Message also. Because it is a relatively new drug, most parents are unaware that it even exists. They must be educated to the signs and symptoms of GHB use and abuse. Education plays a key role, not only informing the kids that it is wrong, but death is a consequence of this activity. Michael's voice must be heard.

I am here today, with the hope that GHB will not be made available legally.

P. O. Box 690453 Vero Beach, Florida 32969
561/464-7612

Attention: Sandra Titus
FDA Center for Drug Evaluation and Research (HFD-1)
Peripheral and Central Nervous System Advisory Committee
5600 Fishers Lane
Rockville MD 20857
NDA 21-196, Xyrem (sodium oxybate, Orphan Medical Inc.)

Presenter: Brian A. Hunter
Young Adults With Narcolepsy – YAWN

Dear Sandra:

I am requesting time to make a formal oral presentation on my views regarding the NDA 21-196 application being held before the Peripheral and Central Nervous System Advisory Committee meeting on June 6, 2001. I will require approximately four (4) minutes to present my views for consideration by the committee concerning risk management issues pertaining to the safety and efficacy of Xyrem (sodium oxybate, Orphan Medical Inc.) I have attached my intended comments for your review.

Young Adults With Narcolepsy, YAWN is an online organization working to support, advocate, and advance public awareness of narcolepsy, on behalf of young adults their families, peers, coworkers, employers, teachers, and others whose lives are affect by this often debilitating sleep disorder. By working at the grassroots level, YAWN is able to make an immediate impact on the lives of our younger generation by coordinating local support groups, involving other non-profit services in providing access to rehabilitative services and social service agencies and by educating teaching professionals from junior high school counselors to University professors.

Thank you for your kind consideration of this request.

Sincerely,

Brian A. Hunter
Director
Young Adults With Narcolepsy – YAWN
3209 Dupont Avenue South
Minneaplis, MN 55408
huntoo38@tc.umn.edu
612-396-9268

I feel it is important to preface my comments today by disclosing that my organization, Young Adults with Narcolepsy (YAWN) has received a $5000 grant from Orphan Medical to underwrite the developmental expenses for our website and have provided a scholarship for my travel and accommodations to attend this meeting.

As founder of YAWN, the first online youth-focused patient support and advocacy organization, and a person with narcolepsy and cataplexy, I believe that 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 a large number of young adults with narcolepsy who have, or would like to have, participated in clinical trials for Xyrem, I am compelled to present my views on risk management issues pertaining to the safety and efficacy of Xyrem (sodium oxybate, Orphan Medical Inc.).

YAWN works to support, advocate, and advance public awareness of narcolepsy on behalf of young adults, their families, employers, teachers, and others whose lives are affected by this often-debilitating sleep disorder. By working at the grassroots level, YAWN is able to make an immediate impact on the lives of these young adults by coordinating local support groups and involving other nonprofit services in providing access to rehabilitative services and social service agencies.

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 social, interpersonal, and educational development of these young adults at a critical point in their development. It has been well documented that the cataplexy and excessive sleepiness of narcolepsy has multiple effects on these individuals and their families. This disease has a significant negative impact on education, interpersonal relationships, gainful employment, motivation, and marital life. I submit that the risk for experiencing the negative impact of untreated cataplexy on the potential of 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% young adults with narcolepsy who suffer with cataplexy. Other therapies including tricyclic antidepressants such as Prozac are only minimally effective in controlling symptoms of cataplexy in this patient population. Xyrem has been shown to be an effective therapy in limiting the cataplexy episodes that result from sudden surges of emotion, including surprise, anger and happiness.

We must recognize the consequences of failing to approve Xyrem to treat the 1:1000 people suffering with narcolepsy, an incidence equal to multiple sclerosis. For example, three months after founding YAWN, I was contacted by the parents of a sixteen-year-old boy living in a small town three hours away from the nearest city. This young man was bright, did well in school, and was active in his community until his twelfth 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 is forced to spend five days a week in a nursing home. What are the costs of providing nursing home care in a public institution for a sixteen-year-old for the next 60-70 years? By not adequately controlling his cataplexy, what are his chances for becoming a contributing member of society?

Unfortunately, this young 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, doesn't have to be the case. In fact, a brighter future has been achieved by the lucky few who have participated in GHB clinical trials. They have become success stories. To these young adults with narcolepsy, GHB 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, by earning their PhDs, by becoming successful artists, entrepreneurs, lawyers, teachers, doctors, politicians, Olympic athletes, or simply by being good parents.

These and the thousands of other talented and capable young adults who have not yet had a chance to fulfill their dreams are the reason I formed YAWN and why I am here testifying before you today. It is my responsibility to protect their right to pursue a happy and productive life by having access to medications that will effectively treat their disease. 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.

Thank you for allowing me to present these remarks to you today. I urge you to approve the NDA 21-196 for Xyrem. There are lives at stake.

Statement Regarding GHB (Xyrem) Approval

Joe Spillane, Pharm.D., ABAT
June 2001

My name is Joe Spillane. I am a pharmacist and a clinical toxicologist. I work as an associate professor at Nova Southeastern University College of Pharmacy and as a clinical coordinator at Broward General Medical Center in Fort Lauderdale, Florida. I also serve on the Broward County Commission on Substance Abuse and coauthor a twice-annual report on substance abuse trends in Broward County, Florida. I am not representing any organization and I have had no affiliation with Orphan Medical. I would like to voice some reservations that I have to the approval and scheduling of gamma hydroxybutyrate GHB (Xyrem) , but I would first like to mention the basis for my concerns.

I'd like to underscore the immense and rapidly growing popularity, highly addictive nature, and lethality of GHB and its precursors.

Overdoses & Drug Rape

In our emergency department alone, which treats approximately 70,000 patients per year, we had 48 GHB or GHB precursor overdoses in 1999. That number rose by approximately 60% to 77 cases in 2000. Most of these patients are brought in by rescue because of decreased level of responsiveness. All require monitoring and many require airway management including intubation and ventilation. Vomiting is particularly common with the abuse of this drug, which can have the potentially fatal consequence of aspiration in an individual with central nervous system depression. Most of our GHB abusers were young people (average age of 26.3yrs old) who were using the drug recreationally often while coingesting alcohol, ecstasy, cocaine, and/or marijuana.

We have had numerous patients say that someone must have given this drug to them without their knowledge, perhaps to facilitate robbery or sexual assault. There have been educational campaigns instructing people not to accept a drink from anyone but the bartender. However, we treated one of the local bartenders for GHB overdose recently who claimed that many of those employed in the local beverage industry are also using GHB and/or its precursors.

Withdrawal

We have treated 5 known cases of GHB or GHB precursor withdrawal in our facility. The sudden cessation of this drug results in physical withdrawal which is prolonged, impressive to observe, and very difficult to treat. Clinical manifestations of withdrawal have included tachycardia, sleeplessness, severe agitation, tremulousness, and hallucinations. Two of these patients experienced two separate withdrawal episodes. I submit that there are probably numerous other withdrawal cases at our institution and throughout the country that go unrecognized and are treated as psychosis.

Withdrawal is extremely difficult to treat and the long-term effects of multiple withdrawal episodes remains unclear.

Deaths

From 1996 through December 31, 2000, there have been nine fatalities in Broward County (a county of 1.6 million people) where GHB was considered one of the proximate causes of death. In most cases the drug was being used recreationally, in combination with alcohol and/or other central nervous system depressants. However, in July of 2000, a 25-yr. old white male was doing "capfuls of GHB all night long". Some friends left him briefly to rent a movie, and found him dead upon their return. On autopsy, his GHB level was very high, his alcohol level was zero, and no other drug was detected.

This is an important case to refute the common misperception that the drug is not lethal unless taken with other CNS depressants such as alcohol, and that the only treatment necessary for GHB toxicity alone is to "sleep it off".

Concerns

It is because of this experience in South Florida that I feel compelled to voice concerns over the scheduling and the proposed distribution system of Xyrem.

First, it is concerning to me that the entire system of distribution is voluntary and that there appears to be very little governmental/regulatory oversight. The proposed distribution system as I understand it, appears to be a fairly closed system where one pharmacy would store the drug and would be responsible for mailing the drug directly to customers. An exception to this would be made if third party payors insisted on the drug being sent to a pharmacy for dispensing. It certainly appears that the system is flexible and accommodating when profit margins might be affected. This is concerning because of the voluntary nature of the system and the understandable commitment of the company to maximize profits for their shareholders.

I also have concerns with the voluntary and proprietary nature of the data on GHB sales and distribution/diversion. Are there any guarantees of the availability of that data to governmental agencies? Again, it appears that all of this hinges upon voluntary action on the part of Orphan and the specialty pharmacy. What happens when the financial interests of the company conflict with the voluntary collection/submission of this information or indeed with the continuation of this closed loop system?

Given the addictive potential of this drug, I wonder what will happen to the patient who can no longer afford the medication or when the patient's insurance no longer covers this medication. What provisions would be made in these instances? What resources are available to treat the withdrawal? How will Orphan participate/contribute to those resources?

I think the potential for accidental pediatric poisoning should be addressed (and possibly already has been). This is a potentially lethal anesthetic/respiratory depressant that may be in a readily accessible container at a patient's bedside while they sleep.

Finally, deep and careful consideration should be given to the future impact of this "bifurcated scheduling" not just for GHB but for future medications. Couldn't any future manufacturer of an addictive/ or potentially abused medication claim that they designed a revolutionary system for distribution? Couldn't they then suggest it be made a schedule III or IV when used for "legitimate medical purposes" and schedule I when diverted? There would certainly be financial incentive on the part of the manufacturer to improve accessibility and cut the costs and potential obstacles of government regulation and oversight by doing so. Any future company could look confidently to the Xyrem decision as an applicable precedent.

Summary

In summary, I wanted to underscore the increasing abuse of GHB and its precursors, its use to facilitate sexual assault and robbery, its highly lethal and addictive properties, and its propensity to precipitate physical withdrawal. I strongly suggest that it would not be prudent to rely on a voluntarily closed system with very little regulation, very little oversight, and no guaranteed access to data to prevent its diversion. Further, the proposed bifurcated scheduling, while economically appealing to the manufacturer, is fraught with potential problems which could lead to increased diversion of GHB and a dangerous precedent for the future. I commend Orphan for their ingenuity and creativity, and for their commitment to bringing this medication to those who could benefit from it. Stricter control, with additional oversight, and verification would certainly enhance the possibility of attaining another one of Orphan's stated goals of reducing abuse and diversion. Thank you for a chance to participate in this important process.

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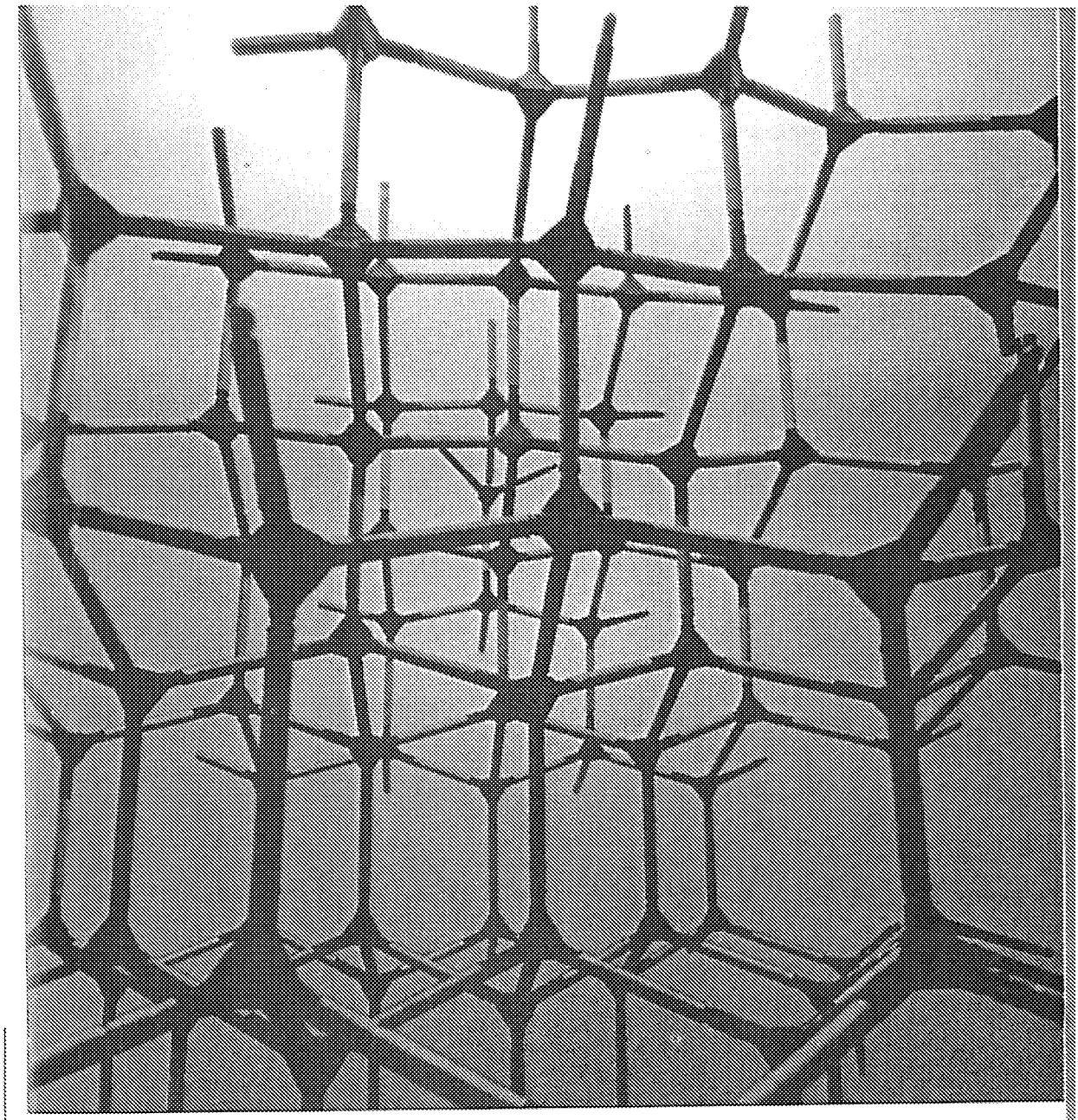

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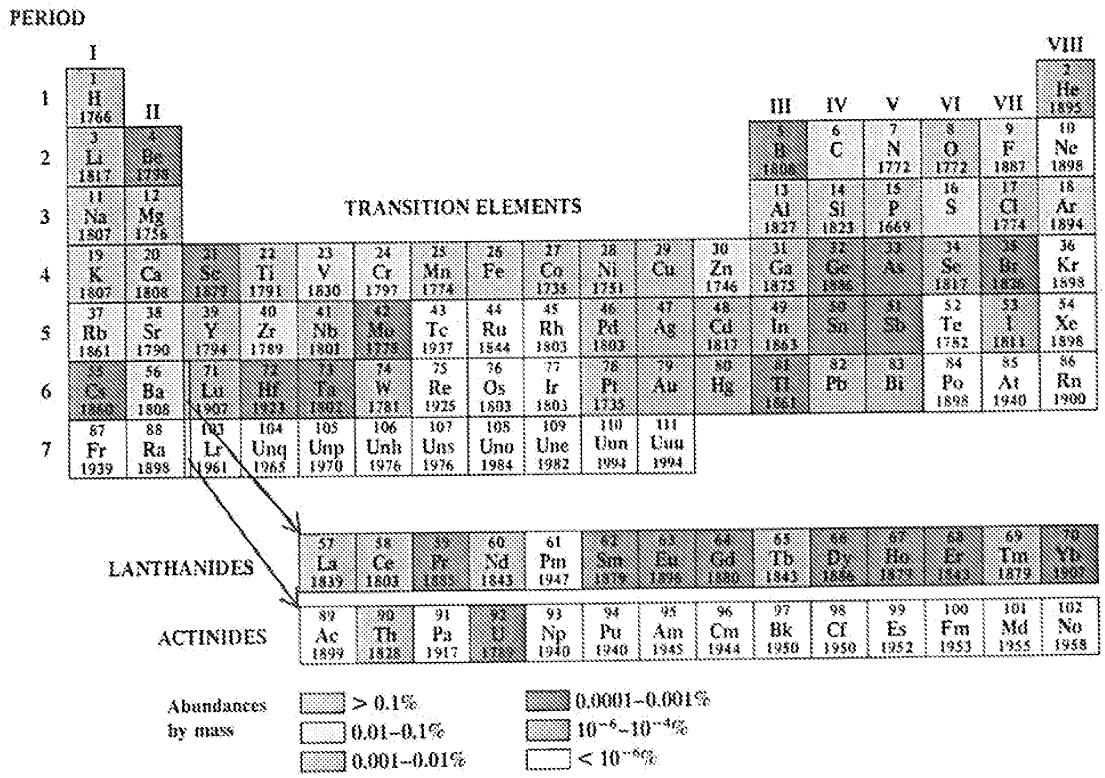


Figure 2-7

The modern periodic table of the elements. Below each symbol is the element's year of discovery; elements with no dates have been known since ancient times. Above each symbol is the atomic number. The color coding indicates the relative abundance by mass of the elements in the world (the atmosphere, oceans and freshwater bodies, and the earth's crust to a depth of 40 km). Oxygen alone comprises almost 50% of this mass, and silicon comprises more than 25%.

division between metallic and nonmetallic elements (see inside the front cover of this book). One of the major accomplishments of modern chemistry is its ability to account for these systematic variations (and many individual exceptions as well) both qualitatively and quantitatively.

2-2 IONS AND IONIC COMPOUNDS

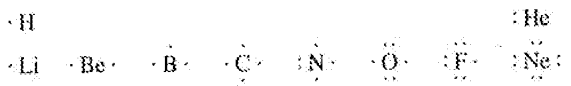
The periodic table is a useful way to describe systematically the properties of the elements, and we shall return to it frequently. Chapter 13 will show how the structure of the periodic table arises from the application of quantum mechanics to the electronic structures of atoms. Here we confine our discussion to a simple and helpful model called the **Lewis electron-dot model.** It was proposed by the Ameri-

can chemist G. N. Lewis in 1916, well before modern quantum mechanics was fully developed. It works equally well for ions and ionic compounds and for the compounds we shall shortly identify as covalent.

The Lewis model begins by recognizing that not all the electrons in an atom participate in chemical bonding. Electrons appear to occupy a set of **shells** surrounding the nucleus, and those in inner shells (called **core electrons**) are not significantly involved in the formation of bonds between atoms. The outermost, partially filled shell (called the **valence shell**) contains the electrons that need to be included in most descriptions of chemical bonding, the **valence electrons**. A filled shell possesses great chemical stability. Progress through the elements in order of increasing atomic number reveals a filled shell whenever a noble-gas element such as helium, neon, or argon is reached. The additional electron in atoms of the first element past a noble-gas element (that is, the outermost electron in an alkali-metal atom) is the first occupant of a new shell, so an alkali-metal atom has one valence electron. With the exception of helium, the number of valence electrons in a neutral atom of a main-group element (those in Groups I through VIII) is equal to the element's group number in the periodic table.

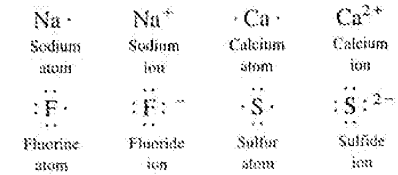
The main-group elements that follow a series of transition-metal elements require some special attention. Atoms of bromine, for example, have 17 more electrons than atoms of argon, the preceding noble gas. We still say that bromine has 7 valence electrons (like chlorine), not 17. The reason is that in the fourth, fifth, and sixth periods the ten electrons added in the course of the transition-metal series (although they are very important for the bonding of those elements) have become *core* electrons by the time the end of the transition-metal series is reached. The bonding properties of an element such as bromine resemble those of the lighter elements in its group.

The Lewis model represents valence electrons with dots; core electrons are not shown. The first four dots are displayed singly around the four sides of the symbol of the element. If there are more than four valence electrons, their dots are paired with those already present. The result is a **Lewis dot symbol** for that atom. The Lewis notation for the elements of the first two periods is



The Formation of Ionic Compounds

A positively charged **ion** (called a **cation**) forms when an atom loses one or more electrons, and a negatively charged ion (called an **anion**) forms when an atom adds electrons. The creation of ions is indicated by removing dots from or adding them to the Lewis dot symbol and also by writing the net electric charge of the ion as a right superscript. For example:



Special stability results when an atom, by either losing or gaining electrons, forms an ion whose outermost shell has the same number of electrons as the outermost shell of a noble-gas atom. Except for hydrogen and helium, whose valence shells are completed with two electrons, atoms of the first few periods of the periodic table have a maximum of eight electrons in their valence shells. We say that a chlorine ion ($:\ddot{\underset{\cdot\cdot}{\text{Cl}}}:^-$) or an argon atom ($:\ddot{\underset{\cdot\cdot}{\text{Ar}}}:$) has a completed **octet** in its valence shell.

The tendency of atoms to achieve valence octets describes much chemical reactivity. Atoms of elements in Groups I and II achieve an octet by losing electrons to form cations; atoms of elements in Groups VI and VII do so by gaining electrons to form anions. Reactions of the metallic elements on the left side of the periodic table with the nonmetallic elements on the right side always transfer just enough electrons to form ions with completed octets. The following equations, in which e^- stands for an electron, use Lewis symbols to show the formation first of a cation and an anion and then of an **ionic compound.**

$$\text{Na}\cdot \longrightarrow \text{Na}^+ + e^- \qquad \text{Loss of a valence electron}$$

$$e^- + :\ddot{\underset{\cdot\cdot}{\text{Cl}}}\cdot \longrightarrow :\ddot{\underset{\cdot\cdot}{\text{Cl}}}:^- \qquad \text{Gain of a valence electron}$$

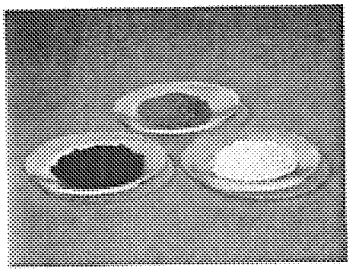
$$\text{Na}^+ + :\ddot{\underset{\cdot\cdot}{\text{Cl}}}:^- \longrightarrow \text{Na}^+\ :\ddot{\underset{\cdot\cdot}{\text{Cl}}}:^- \qquad \text{Combination to form the compound NaCl}$$

Another example is the formation of $CaBr_2$:

$$\underset{\text{Neutral atoms not having octets}}{\cdot\text{Ca}\cdot + 2\ :\ddot{\underset{\cdot\cdot}{\text{Br}}}\cdot} \longrightarrow \underset{\text{Positive ion with octet}}{\text{Ca}^{2+}} + \underset{\text{Negative ions with octets}}{2\ :\ddot{\underset{\cdot\cdot}{\text{Br}}}:^-} \longrightarrow \underset{\text{Ionic compound}}{\text{Ca}^{2+}(\text{Br}^-)_2}$$

The model predicts a 1:1 compound between Na and Cl and a 1:2 compound between Ca and Br, in agreement with experiment.

Ionic compounds, except those with OH^- as the anion, are often called **salts** by analogy with NaCl, common table salt. They are solids at room conditions and generally have high melting and boiling points (for example, NaCl melts at 801°C and boils at 1413°C). Solid ionic compounds usually conduct electricity poorly, but their melts (the molten liquids) conduct well.



Three compounds of lead and oxygen. Lead dioxide (PbO_2, *left*) contains Pb^{4+} ions; litharge (PbO, *right*) contains Pb^{2+} ions; minium (Pb_3O_4, *top*) contains both Pb^{2+} and Pb^{4+} ions. (Leon Lewandowski)

Names and Formulas of Ionic Compounds

The combination of cations with anions results in ionic compounds. Each one's name consists of the name of the cation followed by that of the anion. Ions can be either monatomic or polyatomic; the latter are also referred to as molecular ions.

A monatomic cation bears the name of the parent element. We have already encountered such examples as the sodium ion (Na^+) and the calcium ion (Ca^{2+}); ions of the other elements in Groups I and II are named in the same way. The transition metals and the metallic elements of Groups III, IV, and V differ from the Group I and II metals in that they often form several stable ions in compounds and in solution. Although calcium compounds never contain Ca^{3+} ions (always Ca^{2+}), the element iron forms both the Fe^{2+} and Fe^{3+} ions, and thallium forms both the Tl^+ and Tl^{3+} ions. When a metal forms ions of more than one charge, we distinguish them by placing a Roman numeral in parentheses after the name of the metal:

Cu^+	copper(I) ion	Fe^{2+}	iron(II) ion	Sn^{2+}	tin(II) ion
Cu^{2+}	copper(II) ion	Fe^{3+}	iron(III) ion	Sn^{4+}	tin(IV) ion

An earlier method for distinguishing between such pairs of ions used the suffixes *-ous* and *-ic* added to the root of the (usually Latin) name of the metal to indicate the ions of lower and higher charge, respectively. Thus, Fe^{2+} was called the ferrous ion and Fe^{3+} the ferric ion. This method, although still sometimes used, is not recommended for systematic nomenclature and will not appear again in this book.

A few polyatomic cations are of importance in inorganic chemistry. These include the ammonium ion, NH_4^+ (obtained by adding H^+ to ammonia); the hydronium ion, H_3O^+ (obtained by adding H^+ to water); and the particularly interesting molecular ion formed by mercury: Hg_2^{2+}, the mercury(I) ion. This species must be carefully distinguished from Hg^{2+}, the mercury(II) ion. The Roman numeral I in parentheses means in this case that the average charge on each of the two mercury atoms is +1. Compounds with the empirical formulas HgCl and HgBr correspond to Hg_2Cl_2 and Hg_2Br_2.

A monatomic anion is named by adding the suffix *-ide* to the first portion of the name of the element. Thus, chlor*ine* becomes the chlor*ide* ion, and oxy*gen* becomes the ox*ide* ion. The other monatomic anions of Groups V, VI, and VII are named similarly. Many polyatomic anions exist, and the naming of these species is more complex. The names of the oxoanions (each contains oxygen in combination with a second element) are derived by adding the ending *-ate* to the stem of the name of that second element. Some elements form two oxoanions. The *-ate* ending is then used for the oxoanion with the larger number of oxygen atoms (e.g., NO_3^-, nitr*ate*), and the ending *-ite* is added for the name of the anion with the smaller number (e.g., NO_2^-, nitr*ite*). For elements such as chlorine, which form more than two oxoanions, we use the additional prefixes *per-* (largest number of oxygen atoms) and *hypo-* (smallest number of oxygen atoms). An oxoanion containing hydrogen as a third element includes that word in its name. The HCO_3^- oxoanion, for example, is called the hydrogen carbonate ion in preference to its common (nonsystematic) name, "bicarbonate ion," and HSO_4^-, often called "bisulfate ion," is better designated as the hydrogen sulfate ion. Table 2-2 lists some of the most important anions. It is

Table 2-2 Formulas and Names of Some Common Anions

F^-	fluoride	CO_3^{2-}	carbonate
Cl^-	chloride	HCO_3^-	hydrogen carbonate
Br^-	bromide	NO_2^-	nitrite
I^-	iodide	NO_3^-	nitrate
H^-	hydride	SiO_4^{4-}	silicate
O^{2-}	oxide	PO_4^{3-}	phosphate
S^{2-}	sulfide	HPO_4^{2-}	hydrogen phosphate
O_2^{2-}	peroxide	$H_2PO_4^-$	dihydrogen phosphate
O_2^-	superoxide	SO_3^{2-}	sulfite
OH^-	hydroxide	SO_4^{2-}	sulfate
CN^-	cyanide	HSO_4^-	hydrogen sulfate
CNO^-	cyanate	ClO^-	hypochlorite
SCN^-	thiocyanate	ClO_2^-	chlorite
MnO_4^-	permanganate	ClO_3^-	chlorate
CrO_4^{2-}	chromate	ClO_4^-	perchlorate
$Cr_2O_7^{2-}$	dichromate		

important to be able to recognize and name the ions from that table, bearing in mind that the electric charge is an essential part of the formula.

The composition of an ionic compound is determined by overall charge neutrality: the total positive charge on the cations must exactly balance the total negative charge on the anions. The following names and formulas of ionic compounds illustrate this point.

Tin(II) bromide	One 2+ cation, two 1− anions	$SnBr_2$
Potassium permanganate	One 1+ cation, one 1− anion	$KMnO_4$
Ammonium sulfate	Two 1+ cations, one 2− anion	$(NH_4)_2SO_4$
Iron(II) dihydrogen phosphate	One 2+ cation, two 1− anions	$Fe(H_2PO_4)_2$

Example 2-1

Give the chemical formulas of (a) calcium cyanide and (b) copper(II) phosphate.

Solution

(a) Calcium cyanide is composed of Ca^{2+} and CN^- ions. For the overall charge to be 0, there must be two CN^- ions for each Ca^{2+} ion. Thus, the chemical formula of calcium cyanide is $Ca(CN)_2$.
(b) The ions present in this compound are Cu^{2+} and PO_4^{3-}. To ensure charge neutrality, there must be three Cu^{2+} ions (total charge +6) and two PO_4^{3-} ions (total charge −6) per formula unit. Thus, the chemical formula of copper(II) phosphate is $Cu_3(PO_4)_2$.

Related Problems: 11, 12

2-3 COVALENT COMPOUNDS AND THEIR LEWIS STRUCTURES

Elements in Groups III through V of the periodic table (especially in the first two periods) have a lesser tendency to form ions than those at the left and right sides of the table. Consider the simplest stable compound of carbon and hydrogen: methane (CH_4). Unlike ionic compounds, this substance is a gas at room temperature, not a solid. Cooling methane to low temperatures condenses it to a solid in which the CH_4 molecules retain their identities. Methane dissolves in water to a slight extent, but it does not ionize. Thus, it is not useful to think of methane as an ionic substance made up of C^{4-} and H^+ ions (or C^{4+} and H^- ions). It is a nonionic compound.

The Lewis electron-dot model can describe the bonding in molecules of nonionic substances as well as in ionic compounds. Electrons are not transferred from one atom to another in a nonionic compound, but are *shared* between atoms to form **covalent bonds.** Hydrogen and chlorine combine, for example, to form the **covalent compound** hydrogen chloride. This can be indicated with a **Lewis structure** for the molecule of the product, in which the valence electrons from each atom are redistributed so that one electron from the hydrogen atom and one from the chlorine atom are now shared by the two atoms. The two dots representing this electron pair are placed between the symbols for the two elements:

$$H\cdot + \cdot\ddot{\underset{\cdot\cdot}{Cl}}: \longrightarrow H:\ddot{\underset{\cdot\cdot}{Cl}}:$$

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.:	107632	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 (7).

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.: 107632

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

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $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).			
☐ 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	

APPLICATION AS AMENDED – PART II

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	12/31/2013						
	Total (37 CFR 1.16(i))	* 28	Minus	** 30	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

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

LIE
/DIANA BATES/

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	13/592,202	REARDAN ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 12/31/13	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

2/Tds approved.

Lawana Hixon

U.S. Patent and Trademark Office

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 371-2140 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402--0938
(612) 371-2140

Date January 7, 2014

By / /
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:	Lena Najarian	Group Art Unit:	3686
Customer No.:	107632	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 Statement (2 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.: 107632

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

Electronic Acknowledgement Receipt

EFS ID:	17848141
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:	107632
Filer:	Gregory M. Stark/John Gustav-Wrathall
Filer Authorized By:	Gregory M. Stark
Attorney Docket Number:	101.031US9
Receipt Date:	08-JAN-2014
Filing Date:	22-AUG-2012
Time Stamp:	09:31:11
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_sups_010814.pdf	80554 1b3bbe6fd299dd3e4e2f88410d531285920 30194	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Miscellaneous Incoming Letter	1	1
	Supplemental Response or Supplemental Amendment	2	3
Warnings:			
Information:			
	Total Files Size (in bytes):	80554	

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.

EXPEDITED PROCEDURE-EXAMINING GROUP 3686

S/N 13/592,202 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Dayton T. Reardan Ph.D et al.	Examiner: Lena Najarian
Serial No.:	13/592,202	Group Art Unit: 3686
Filed:	August 22, 2012	Docket No.: 101.031US9
Customer No.:	107632	Confirmation No.: 5805
Title:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD	

SUPPLEMENTAL STATEMENT

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

Applicant respectfully submits that it neglected to state in its response of December 31, 2013 that it respectfully disagrees with the rejection of the claims as unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Talk About Sleep ("An Interview with Orphan Medical about Xyrem"), and further in view of Rosenblum (US 2003/0050731 A1). Applicant reserves the right to pursue the rejected subject matter in a later-filed continuation application.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L5	2	"7970622".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/01/06 15:09
L6	10	("20020042723" | "20020042725" | "20020052760" | "20030050799" | "20030050802" | "20030074225" | "5737539" | "5790409" | "6687676" | "6859780").PN. OR ("7970622").URPN.	US-PGPUB; USPAT; USOCR	OR	ON	2014/01/06 15:09
L7	4469	((705/3) or (707/803)).CCLS.	US-PGPUB	OR	OFF	2014/01/06 15:10
L8	3	((database or data adj1 base) AND (abus$ or fraud$ or misus$ or diver$) AND narcolep$ AND cash).CLM.	US-PGPUB	OR	ON	2014/01/06 15:12

1/6/2014 3:12:48 PM
C:\Users\lnajarian2\Documents\EAST\Workspaces\13592202.wsp

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BIB DATA SHEET

CONFIRMATION NO. 5805

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/592,202	08/22/2012 RULE	705	3686	101.031US9

APPLICANTS

INVENTORS

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

**** CONTINUING DATA ***************************

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 ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

08/31/2012

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /LENA NAJARIAN/ Examiner's Signature	☐ Met after Allowance LN Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		MN	16	26	3

ADDRESS

Schwegman Lundberg & Woessner/Jazz Pharmaceutical
P.O. Box 2938
Minneapolis, MN 55402
UNITED STATES

TITLE

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

FILING FEE RECEIVED		
2390	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13592202	REARDAN ET AL.
	Examiner	**Art Unit**
	LENA NAJARIAN	3686

CPC		
Symbol	**Type**	**Version**

CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 28	
/LENA NAJARIAN/ Primary Examiner.Art Unit 3686 01/06/2014 (Primary Examiner) (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 2B

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13592202	REARDAN ET AL.
	Examiner	**Art Unit**
	LENA NAJARIAN	3686

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION												
CLASS	SUBCLASS	CLAIMED									NON-CLAIMED					
705	2	G	0	6	Q	10 / 00 (2012.01.01)										
CROSS REFERENCE(S)																
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)															
705	3															
707	803															

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 28	
/LENA NAJARIAN/ Primary Examiner.Art Unit 3686 (Primary Examiner)	01/06/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 2B

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13592202	REARDAN ET AL.
	Examiner	**Art Unit**
	LENA NAJARIAN	3686

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	15	17	27	33										
	2	16	18	28	34										
	3	17	19												
2	4	18	20												
3	5	19	21												
4	6	20	22												
5	7		23												
6	8		24												
7	9		25												
8	10		26												
9	11	21	27												
10	12	22	28												
11	13	23	29												
12	14	24	30												
13	15	25	31												
14	16	26	32												

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 28	
/LENA NAJARIAN/ Primary Examiner.Art Unit 3686 (Primary Examiner)	01/06/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 2B

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NOTICE OF ALLOWANCE AND FEE(S) DUE

107632 7590 01/15/2014

Schwegman Lundberg & Woessner/Jazz Pharmaceutical
P.O. Box 2938
Minneapolis, MN 55402

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

DATE MAILED: 01/15/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/592,202	08/22/2012	Dayton T. Reardan	101.031US9	5805

TITLE OF INVENTION: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	04/15/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE 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.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

107632 7590 01/15/2014
Schwegman Lundberg & Woessner/Jazz Pharmaceutical
P.O. Box 2938
Minneapolis, MN 55402

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/592,202	08/22/2012	Dayton T. Reardan	101.031US9	5805

TITLE OF INVENTION: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	04/15/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
NAJARIAN, LENA	3686	705-002000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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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

107632 7590 01/15/2014

Schwegman Lundberg & Woessner/Jazz Pharmaceutical
P.O. Box 2938
Minneapolis, MN 55402

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

DATE MAILED: 01/15/2014

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 0 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 0 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.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. 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.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 13/592,202	Applicant(s) REARDAN ET AL.	
	Examiner LENA NAJARIAN	Art Unit 3686	AIA (First Inventor to File) Status No

-- 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 *12/31/13*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ 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.
3. ☒ The allowed claim(s) is/are *1,4-22 and 27-34*. As a result of the allowed claim(s), 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 .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   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.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ 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. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 20131231
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/LENA NAJARIAN/
Primary Examiner, Art Unit 3686

IN THE CLAIMS

Please amend the claims as follows:

1. (Currently Amended) 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 configured to:

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

reconcile inventory of the prescription drug before the shipments for a day or other time period are sent by using said database query to identify information in the prescription fields and patient fields;

wherein the data processor is configured to process a second database query that identifies that 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 that the narcoleptic patient is a cash payer 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.

2. (Canceled).

3. (Canceled).

4. (Currently Amended) The system of claim 1 [[3]], wherein the data processor selectively blocks shipment of the prescription drug to the patient based upon said identifying by the database query.

5. (Currently Amended) The system of claim 1 [[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. (Currently Amended) 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 is ~~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. (Currently Amended) The system of claim 1, wherein the single computer database is distributed among multiple computers and ~~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. (Currently Amended) The system of claim 1, wherein the data processor is configured to process a third ~~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. (Previously Presented) 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. (Previously Presented) 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.

29. (Currently Amended) 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, wherein an inventory reconciliation is performed where current inventory is counted and reconciled with database quantities before shipments for a day or other time period are sent, and wherein the data processor is configured to selectively block shipment of the prescription drug based on the inventory reconciliation;

wherein the data processor is configured to process a second database query that identifies that 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 that the narcoleptic patient is a cash payer 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.

30. (Currently Amended) A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug, comprising:

one or more computer memories for storing a central computer database of the company that obtained approval for distribution of the prescription drug, for receiving prescriptions from any and all patients being prescribed the company's prescription drug, said central computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said central computer database being distributed over multiple computers;

said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion;

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 any and all physicians or other prescribers of the company's prescription drug and information to show that the physicians or other prescribers are authorized to prescribe the company's prescription drug;

one or more data processors for processing one or more database queries that operate over data related to the prescription fields, prescriber fields, and patient fields for the prescription drug;

said one or more database queries checking for abuse within the central computer database, wherein the filling of the prescriptions is authorized for the company's prescription drug only if there is no record of incidents that indicate abuse, misuse, or diversion by the narcoleptic patient and prescriber and if there is a record of such incidents, the central computer database indicates that such incidents have been investigated, and the central computer database indicates that such incidents do not involve abuse, misuse or diversion.

31. (Previously Presented) The system of claim 30, wherein the one or more database queries are processed by the one or more data processors for identifying: that 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 that the narcoleptic patient is a cash payer 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.

32. (Previously Presented) The system of claim 30, where the central computer database is distributed among multiple computers, and where the one or more database queries operate over all data relating to said prescription fields, prescriber fields, and patient fields for the prescription drug.

33. (Previously Presented) The system of claim 30, wherein the central 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.

34. (Previously Presented) The system of claim 30, wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent.

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	05/30/2013	10/23/2013	01/06/2014					
	1	÷	✓	✓	=					
	2	÷	✓	=	-					
	3	÷	✓	✓	-					
	4	÷	✓	✓	=					
	5	÷	✓	✓	=					
	6	÷	✓	✓	=					
	7	÷	✓	✓	=					
	8	÷	✓	✓	=					
	9	÷	✓	✓	=					
	10	÷	✓	✓	=					
	11	÷	✓	✓	=					
	12	÷	✓	✓	=					
	13	÷	✓	✓	=					
	14	÷	✓	✓	=					
	15	÷	✓	✓	=					
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	22	÷	✓	✓	=					
	23	÷	N	-	-					
	24	÷	N	-	-					
	25	÷	N	-	-					
	26	÷	N	-	-					
	27		✓	✓	=					
	28		✓	✓	=					
	29			✓	=					
	30			✓	=					
	31			✓	=					
	32			✓	=					
	33			✓	=					
	34			✓	=					

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-8,589,182	11/19/2013	Reardan, Dayton T, et al.

FOREIGN PATENT DOCUMENTS

Examiner Initial *	Foreign Document Number	Publication Date	Name of Patentee or Applicant of cited Document	T 1
	EP-0527027A1	2/10/1993	Poole, Neil	

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
	"Civil Action No. 2:13-cv-00391-ES-SCM (consolidated)", Defendant Amneal Pharmaceuticals, LLC's Preliminary Invalidity Contentions (United States District Court of New Jersey), 182 pgs 11/7/13	
	"Final Minutes: Peripheral and Central Nervous System Drugs Advisory Committee", [Online]. Retrieved from the Internet: <URL: http://www.fda.gov/ohrms/dockets/ac/01/minutes/3754m1.htm>, (Jun. 6, 2001), 6 pgs.	
	"Notice of Paragraph IV Certification", Detailed Statement of the Factual and Legal Bases for Par's Paragraph IV Patent Certification and Offer of Confidential Access, (11/20/13), 190 pgs	
	"Orphan Medical Slides: Xyrem (sodium oxybate) oral solution", Peripheral and Central Nervous System Drugs Advisory Committee Meeting, [Online]. Retrieved from the Internet: <URL: http://www.fda.gov/ohrms/dockets/ac/01/slides/3754s1_01_orphanmedical/index.htm>, (Jun. 6, 2001), 167 pgs.	
	"Slides: Pediatric Subcommittee of the Peripheral and Central Nervous system Drugs Advisory Committee", [Online]. Retrieved from the Internet: <URL: http://www.fda.gov/ohrms/dockets/ac/01/slides/3754s1.htm>, (Jun. 6, 2001), 86 pgs.	
	OXTOBY, DAVID W, et al., "", Principles of Modern Chemistry, Fort Worth : Saunders College Pub., (1996), 52-56	

EXAMINER /Lena Najarian/ **DATE CONSIDERED** 01/08/2014

* 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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /L.N./

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13592202	REARDAN ET AL.
	Examiner	Art Unit
	LENA NAJARIAN	3686

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
707	803	5/29/13	LN
705	2, 3	5/29/13	LN

SEARCH NOTES		
Search Notes	Date	Examiner
East	5/28/13	LN
East	10/22/13	LN
East	10/23/13	LN
forward/backward citation search	1/6/14	LN
Google	1/6/14	LN

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
705	3	1/6/14	LN
707	803	1/6/14	LN
	PGPUB text search	1/6/14	LN

REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL		
	Application Number	13/592,202
	Filing Date	August 22, 2012
	First Named Inventor	Dayton T. Reardan Ph.D
	Confirmation Number	5805
	Group Art Unit	3686
	Examiner Name	Lena Najarian
	Attorney Docket Number	101.031US9
	Customer No.	107632

This is a Request for Continued Examination (RCE) under 37 C.F.R § 1.114 of the above-identified application entitled SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

1. Submission required under 37 C.F.R. § 1.114:

   X Amendment and Response Under 37 C.F.R § 1.116 (10 pages) is enclosed.

   X Information Disclosure Statement (2 pages), Form 1449 (2 pages), and copies of cited documents (12).

2. Fees

   X Authorization to charge deposit account 19-0743 in the amount of $1200.00 to pay the RCE filing fee required under 37 C.F.R. § 1.17(e).

The Commissioner is hereby authorized to charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

SCHWEGMAN, LUNDBERG & WOESSNER, P.A. By: / /

David D'Zurilla
Reg. No. 36,776

REMARKS

This communication responds to the Final Office Action dated October 31, 2013.

Applicant gratefully acknowledges the entering of its amendment to the claims dated December 31, 2013, and the subsequent notice of allowance of January 15, 2014.

In this current communication, no claims are currently amended; claims 2, 3, and 23-26 are canceled; and no claims are added; as a result, claims 1, 4-22, and 27-34 are now pending and subject to examination in this application.

Examiner Interview Summary

Applicant expresses its gratitude to Examiner Lena Najarian for the courtesies extended to its representative, Mr. David D'Zurilla, during a telephonic interview on January 8, 2014.

Mr. D'Zurilla initiated the interview with a telephone call to Examiner Najarian. Mr. D'Zurilla informed Examiner Najarian that Applicant had filed a response on December 31, 2013 to the Final Office Action of October 31, 2013. Mr. D'Zurilla also informed Examiner Najarian that Applicant believed the response has put the claims into a condition for allowance since allowable subject matter was incorporated into the independent claims. Mr. D'Zurilla further informed Examiner Najarian that, notwithstanding Applicant's belief that the response put the claims into a condition for allowance, Applicant would be filing a Request for Continued Examination (RCE). The RCE would permit Examiner Najarian to consider material that has recently been filed in a U.S. District Court in connection with one of the litigations involving the family of patents to which this current application belongs.

In response, Examiner Najarian informed Mr. D'Zurilla that she has already considered Applicant's response of December 31, 2013, and has already allowed the claims in light of Applicant's response.

Applicant gratefully acknowledges the indication from Examiner Najarian regarding the allowed claims.

Mr. D'Zurilla reiterated to Examiner Najarian that, notwithstanding the allowance of the claims, Applicant would file an RCE so that she could consider the recent litigation material.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 371-2140 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402--0938
(612) 371-2140

Date January 16, 2014

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

IN THE CLAIMS

The pending claims are as follows.

1. (Previously Presented) 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 configured to:

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

reconcile inventory of the prescription drug before the shipments for a day or other time period are sent by using said database query to identify information in the prescription fields and patient fields;

wherein the data processor is configured to process a second database query that identifies that 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 that the narcoleptic patient is a cash payer 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.

2. (Canceled).

3. (Canceled).

4. (Previously Presented) The system of claim 1, wherein the data processor selectively blocks shipment of the prescription drug to the patient based upon said identifying by the database query.

5. (Previously Presented) The system of claim 1, wherein the prescription drug is shipped to the narcoleptic patient if no potential misuse, abuse or diversion is found for the narcoleptic patient.

6. (Previously Presented) 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 is 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. (Previously Presented) The system of claim 1, wherein the single computer database is distributed among multiple computers and the database query 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. (Previously Presented) The system of claim 1, wherein the data processor is configured to process a third 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. (Previously Presented) 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. (Previously Presented) 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.

29. (Previously Presented) 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, wherein an inventory reconciliation is performed where current inventory is counted and reconciled with database quantities before shipments for a day or other time period are sent, and wherein the data processor is configured to selectively block shipment of the prescription drug based on the inventory reconciliation;

wherein the data processor is configured to process a second database query that identifies that 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 that the narcoleptic patient is a cash payer 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.

30. (Previously Presented) A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug, comprising:

one or more computer memories for storing a central computer database of the company that obtained approval for distribution of the prescription drug, and for receiving prescriptions from any and all patients being prescribed the company's prescription drug, said central computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said central computer database being distributed over multiple computers;

said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion;

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 any and all physicians or other prescribers of the company's prescription drug and information to show that the physicians or other prescribers are authorized to prescribe the company's prescription drug;

one or more data processors for processing one or more database queries that operate over data related to the prescription fields, prescriber fields, and patient fields for the prescription drug;

said one or more database queries checking for abuse within the central computer database, wherein the filling of the prescriptions is authorized for the company's prescription drug only if there is no record of incidents that indicate abuse, misuse, or diversion by the narcoleptic patient and prescriber and if there is a record of such incidents, the central computer database indicates that such incidents have been investigated, and the central computer database indicates that such incidents do not involve abuse, misuse or diversion.

31. (Previously Presented) The system of claim 30, wherein the one or more database queries are processed by the one or more data processors for identifying: that 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 that the narcoleptic patient is a cash payer 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.

32. (Previously Presented) The system of claim 30, where the central computer database is distributed among multiple computers, and where the one or more database queries operate over all data relating to said prescription fields, prescriber fields, and patient fields for the prescription drug.

33. (Previously Presented) The system of claim 30, wherein the central 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.

34. (Previously Presented) The system of claim 30, wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent.

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.:	107632	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, Applicants request that a copy of the PTO 1449 Form, initialed as being considered by the Examiner, be returned to the Applicants 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 January 16, 2014 By /David D'Zurilla/

David D'Zurilla
Reg. No. 36,776

DDZ:vam

EXPEDITED PROCEDURE-EXAMINING GROUP 3686

S/N 13/592,202 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Dayton T. Reardan Ph.D et al.	Examiner: Lena Najarian
Serial No.:	13/592,202	Group Art Unit: 3686
Filed:	August 22, 2012	Docket No.: 101.031US9
Customer No.:	107632	Confirmation No.: 5805
Title:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD	

SUPPLEMENTAL AMENDMENT & RESPONSE UNDER 37 C.F.R. 1.116

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

In response to the Final Office Action dated October 31, 2013, please consider the following.

This response is accompanied by a Request for Continued Examination (RCE).

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845-425-7100
fax 845-573-5795
www.parpharm.com

CONFIDENTIAL

November 20, 2013

Jazz Pharmaceuticals, Inc.
3180 Porter Drive
Palo Alto, California 94304

Jazz Pharmaceuticals International Limited
2 Church Street
Hamilton HM 11
Bermuda

EUSA Pharma (USA), Inc.
1717 Langhorne Newtown Rd #201
Langhorne, PA 19047-1085

EUSA Pharma (Europe), Ltd.
The Magdalen Centre
Oxford Science Park
Oxford OX4 4GA
England

Re: Sodium Oxybate 500 mg/ml Oral Solution (XYREM®)
United States Patent Nos. 6,780,889; 7,262,219; 7,668,730; 7,765,106; 7,765,107; 7,851,506; 7,895,059; 8,263,650; 8,324,275; and 8,457,988
Notice of Paragraph IV Certification

Dear Sirs:

This is a notice of certification letter on behalf of Par Pharmaceutical, Inc., ("Par") pursuant to § 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act ("the Act") and 21 U.S.C. § 355(j)(2)(B)(ii) and § 314.95 of Title 21 of the Code of Federal Regulations:

1. An Abbreviated New Drug Application ("ANDA") containing any required bioavailability or bioequivalence data or information has been submitted under § 505(j) of the Act for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration date of United States Patent Nos. 6,780,889; 7,262,219; 7,668,730; 7,765,106; 7,765,107; 7,851,506; 7,895,059; 8,263,650; 8,324,275; and 8,457,988, listed in the *Approved Drug Products with Therapeutic Equivalence*

Evaluations (the "Orange Book"). The Food and Drug Administration ("FDA") has received this ANDA for substantive review.

2. The ANDA number is 205403.

3. The established name of Par's proposed drug product is: Sodium Oxybate Oral Solution.

4. The active ingredient, strength, and dosage form of the proposed drug product is 500 mg/ml of sodium oxybate. The dosage form is an oral solution.

5. The Orange Book lists the following U.S. Patents for XYREM® tablets: (1) U.S. Patent No. 6,780,889 ("the '889 patent"), which is listed as expiring on July 4, 2020; (2) U.S. Patent No. 7,262,219 ("the '219 patent"), which is listed as expiring on July 4, 2020; (3) U.S. Patent No. 7,668,730 ("the '730 patent"), which is listed as expiring on June 16, 2024; (4) U.S. Patent No. 7,765,106 ("the '106 patent"), which is listed as expiring on June 16, 2024; (5) U.S. Patent No. 7,765,107 ("the '107 patent"), which is listed as expiring on June 16, 2024; (6) U.S. Patent No. 7,851,506 ("the '506 patent") which is listed as expiring on December 22, 2019; (7) U.S. Patent No. 7,895,059 ("the '059 patent") which is listed as expiring on December 17, 2022; (8) U.S. Patent No. 8,263,650 ("the '650 patent") which is listed as expiring on December 22, 2019; (9) U.S. Patent No. 8,324,275 ("the '275 patent") which is listed as expiring on December 22, 2019; and (10) U.S. Patent No. 8,457,988 ("the '988 patent") which is listed as expiring on December 17, 2022. The ANDA indicates that Par intends to market the product before the expiration of the '889, '219, '730, '106, '107, '506, '059, '650, '275, and '988 patents, and contains a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that in Par's opinion, these patents are invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of the product for which the application is submitted.

6. An Offer of Confidential Access to the ANDA, pursuant to § 505(j)(5)(C)(i)(III) of the Act accompanies this notice as a separate enclosure.

Attached is a detailed statement of the factual and legal bases of Par's patent certification. This information is supplied for the sole purpose of complying with the above-referenced statutes and regulations. Neither Par nor its attorneys waive any attorney-client privilege or work-product immunity concerning the subject matter of this communication.

Sincerely,

Michelle Bonomi-Huvala

Michelle Bonomi-Huvala
Senior Vice President Corporate Regulatory Affairs
Par Pharmaceutical, Inc.

Encl.: Detailed Statement of the Factual and Legal Bases for Par's Paragraph IV Patent Certification and Offer of Confidential Access

Duplicate with enclosure via FEDEX

OFFER OF CONFIDENTIAL ACCESS
PURSUANT TO 21 U.S.C. § 355(j)(5)(C)(i)(III)

WHEREAS Par Pharmaceutical, Inc. ("Par") has provided notice to Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals International Limited (collectively, "Jazz") that Par has filed with the U.S. Food and Drug Administration ("FDA") Abbreviated New Drug Application ("ANDA") No. 205403 to obtain approval to engage in the commercial manufacture, use, or sale of Sodium Oxybate Oral Solution, 500 mg/ml, along with a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to 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; 8,263,650; 8,324,275; and 8,457,988 (the "Patents") which are listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") for XYREM®.

WHEREAS Par offers to provide Jazz confidential access to certain information from its proprietary and confidential ANDA, subject to the restrictions and terms set forth below, and this offer accompanies Par's Detailed Statement as to the Patents.

NOW, THEREFORE, pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III):

1. Par hereby provides Jazz this Offer of Confidential Access ("Offer") to its ANDA No. 205403 ("Par's ANDA") for the sole purpose of determining whether an action referred to in 21 U.S.C. § 355(j)(5)(B)(iii) should be brought.

2. This Offer is subject to the following restrictions:

A. Accessible information: A copy of Par's ANDA, redacted to remove information of no relevance to any issue of Patent infringement (the "Information").

B. Persons entitled to access: Two outside counsel and two in-house counsel, who shall be identified in writing to Par before the Information is provided to Jazz and provided that outside counsel does not engage in any Patent prosecution for Jazz (the "Authorized Persons").

C. Use of information accessed: The Authorized Persons shall review the Information for the sole and limited purpose of evaluating whether Jazz will bring suit against Par alleging infringement of the Patents and for no other purpose. The Authorized Persons shall not disclose the Information to any person not authorized to access the Information, except that the Authorized Persons shall be permitted to advise Jazz as to whether an action referred to in 21 U.S.C. § 355(j)(5)(B)(iii) should be brought.

D. Disposition of information accessed:

i. If Jazz does not file an action against Par alleging infringement of the Patents within 45 days of receiving Par's Detailed Statement as to the Patents (the "45-day period"), Jazz shall cause the Authorized Persons to destroy or return to Par the Information, including any and all notes or other documents containing

any portion of the Information, within 30 days after expiration of the 45 days, and Jazz shall promptly notify Par that this has been done.

ii. If Jazz files an action against Par alleging infringement of the Patents within the 45-day period, (a) Jazz shall not include any portion of the Information in any pleadings or other documents that would be publicly available; (b) while the action is pending, Jazz shall treat the Information, including any and all notes or other documents containing any portion of the Information, under the highest level of confidentiality designated in protective orders entered in the action; and (c) Jazz shall cause the Authorized Persons to destroy or return to Par the Information, including any and all notes or other documents containing any portion of the Information, within 30 days after the final determination of the action, and Jazz shall promptly notify Par that this has been done.

3. In the event of any inadvertent or unauthorized disclosure of the Information, Jazz shall promptly notify Par of the content and extent of disclosure, the individuals to whom such disclosure was made, and the actions taken to ensure that the Information is not further disseminated.

4. The terms of this Offer shall be considered terms of an enforceable contract, and Jazz acknowledges that any violation of the terms of this Offer will cause irreparable injury to Par and entitle Par to injunctive relief, in addition to any other remedies available at law or in equity and including any and all costs, expenses, and reasonable attorneys fees.

5. In the event that a provision of this Offer is found by a court of competent jurisdiction to be invalid or unenforceable, the remaining provisions shall continue in full force and effect.

6. Nothing in this Offer shall be construed as a representation by Par of the accuracy or relevance of the Information with respect to any issues relating to the Patents, including validity, enforceability, and/or infringement.

7. Jazz may accept this Offer and request access to the Information by executing a copy of this Offer and returning the executed copy, within the 45-day period, to: Richard J. Berman, Esq., Arent Fox LLP, 1717 K Street, NW, Washington, DC 20036.

8. Upon Jazz's acceptance, this Offer shall constitute the entire agreement of the Parties with respect to the subject matter herein (the "Agreement") and may not be amended or modified except in writing signed by both Parties.

9. The Offer and the Agreement shall be construed in accordance with the laws of the State of New York, without regard to its conflict of laws principles.

[signature page follows]

PAR PHARMACEUTICALS, INC.

By: Michelle Bonomi-Huvala

Name: Michelle Bonomi-Huvala

Title: Senior Vice President Corporate Regulatory Affairs

Date: November 20, 2013

JAZZ PHARMACEUTICALS, INC.

By: _____

Name: _____

Title: _____

Date: _____

JAZZ PHARMACEUTICALS INTERNATIONAL LIMITED

By: _____

Name: _____

Title: _____

Date: _____

DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASES FOR THE OPINION OF PAR PHARMACEUTICAL, INC. ("PAR") THAT UNITED STATES PATENT NOS. 6,780,889; 7,262,219; 7,668,730; 7,765,106; 7,765,107; 7,851,506; 7,895,059; 8,263,650; 8,324,275; AND 8,457,988 ARE INVALID AND/OR NOT INFRINGED

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I. EXECUTIVE SUMMARY

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"), 7,765,107 ("the '107 patent"), 7,851,506 ("the '506 patent"), 7,895,059 ("the '059 patent"), 8,263,650 ("the '650 patent"), 8,324,275 ("the '275 patent"), and 8,457,988 ("the '988 patent") are invalid.

Additionally, at least claim 1 of the '889 patent, claims 1-4 of the '219 patent, claim 1 of the '506 patent, claims 1-18 of the '650 patent, claims 1-4 of the '275 patent, claims 1-11 of the '730 patent, claims 1-8 of '106, claims 1-7 of the '107 patent, claims 1-16 of the '059 patent, and claims 1-15 of the '988 patent are not infringed.

II. BASES FOR ANALYSIS

The conclusions in this detailed Statement are based on a review of the following:

1. the claims and specifications of the '889, '219, '506, '275, '650, '730, '106, '107, '059, and '988 patents;
2. the prosecution history of the '889, '219, '506, '275, '650, '730, '106, '107, '059, and '988 patents;
3. the relevant U.S. law; and
4. the prior art.

III. PAR'S PROPOSED SODIUM OXYBATE PRODUCT AND USE THEREOF

Par proposed to make, obtain FDA approval for, and market an oral solution of sodium oxybate (500 mg/mL) ("Par's Sodium Oxybate Solution"). Par's proposed product also contains sodium benzoate. The pH of the solution is 8.2 +/- 0.30.

IV. LEGAL STANDARDS

A. INVALIDITY

A patent is presumed valid under 35 U.S.C. § 282. However, a patent may be invalidated for anticipation by prior art, obviousness in light of prior art, or failure to meet the requirements of written description, enablement, best mode, and definiteness. *See* 35 U.S.C. §§ 102, 103, and 112.

B. ANTICIPATION

A claimed invention is not new, and thus is invalid as anticipated, if it was known or used by others in the U.S., or patented or described in a printed publication, before the date of invention by the applicant (35 U.S.C. § 102(a)), or was patented or described in a printed publication, or in public use or on sale in the U.S., more than one year before the filing date of the application (35 U.S.C. § 102(b)). In order to anticipate, a prior art reference must describe

every limitation of a claim. *See*, e.g., *Crown Operations, Int'l Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1375 (Fed. Cir. 2002) ("A patent is invalid for anticipation when the same device or method, having all of the elements contained in the claim limitations, is described in a single prior art reference."); *Schumer v. Laboratory Computer Sys., Inc.*, 308 F.3d 1304, 1309 n.3 (Fed. Cir. 2002) ("[A] method claim will be anticipated by an earlier device performing all of the operative steps of the methods."). A patent or printed publication anticipates a claimed invention if it expressly describes the claimed invention or if the claimed invention is necessarily inherent in the patent or printed disclosure. *See Hughes Aircraft Co. v. U.S.*, 15 Cl. Ct. 267, 271 (1988) ("The mere fact that a prior art reference failed to mention something that undeniably existed is of no consequence, for the element must have been there."), *dismissed in part, aff'd in part, without op.*, 862 F.2d 320 (Fed. Cir. 1988); *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) ("[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patently new to the discoverer."); *EMI Group N. Am., Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1349-50 (Fed. Cir. 2001) (same, quoting *Atlas Powder*).

C. OBVIOUSNESS

The claimed invention must be nonobvious over the prior art to a person of ordinary skill in the art of the invention. 35 U.S.C. § 103. Under § 103(a):

> A patent may not be obtained ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains ....

If one of ordinary skill in the art could have implemented a predictable variation of the prior art, such variation was obvious, and § 103 likely bars patentability. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1738 (2007). The ultimate determination of obviousness does not require absolute predictability of success, only a "reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Factors to consider in assessing obviousness include: (a) the scope and content of prior art; (b) the differences between the prior art and the claims at issue; (c) the level of ordinary skill in the art; and (d) whatever objective evidence may be present. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

When evaluating the scope and content of the prior art, the question under § 103 is not merely what the references expressly teach, but what they would have suggested to one of ordinary skill in the art at the time the invention was made. *Merck & Co. v. Biocraft Labs.*, Inc., 874 F.2d 804, 807 (Fed. Cir. 1989). However, the "obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents." *KSR*, 127 S. Ct. at 1741 (discussing the "TSM" approach).

In the pharmaceutical arts, "[t]he TSM test, flexibly applied, merely assures that the obviousness test proceeds on the basis of evidence—teachings, suggestions (a tellingly broad term), or motivations (an equally broad term)—that arise before the time of invention as the

statute requires. As KSR requires, those teachings, suggestions, or motivations need not always be written references but may be found within the knowledge and creativity of ordinarily skilled artisans." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.,* 520 F.3d 1358, 1365 (Fed. Cir. 2008).

For chemical compounds in particular, their structure and properties are important considerations in the obviousness determination. *See In re Sullivan*, 498 F.3d 1345, 1353 (Fed. Cir. 2007). Obviousness may depend on whether the prior art provided a suggestion or reason to choose a specific lead compound for modification or to make the specific modification of the compound at issue. *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). The teaching, suggestion, or motivation may come from the knowledge of those skilled in the art, the prior art reference itself, or the nature of the problem to be solved. *Sibia Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000).

Other secondary considerations that may be helpful in determining obviousness include evidence of commercial success, long-felt but unsolved need, prior failure of others, initial skepticism of experts, praise from experts, copying by an infringer, near simultaneous invention by others, and licenses under the examined patent. *Graham*, 383 U.S. at 17.

D. INFRINGEMENT

Under 35 U.S.C. § 271(e)(2)(A), it is "an act of infringement to submit [] an application under § 505(j) of the Federal Food, Drug, and Cosmetic Act or described in § 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent." § 271(e)(2) "provides an 'artificial' act of infringement that creates case-or-controversy jurisdiction to enable the resolution of an infringement dispute before the ANDA applicant has actually made or marketed the product." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003). Once jurisdiction is established, the substantive determination of whether actual infringement will take place is determined by traditional patent infringement analysis. *Id.*

The analysis of patent infringement is a two-step process. *Dolly, Inc. v. Spalding & Evenflo Cos.*, 16 F.3d 394, 397 (Fed. Cir. 1994). First, the scope of the claims must be determined. Determining claim scope—claim interpretation—is an issue of law. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 372 (1996) ("*Markman II*"); *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1453 (Fed. Cir. 1998) (en banc). Second, the properly construed claims must be compared to the accused product or method to determine whether all of the claim limitations are present in the accused device, either literally or by a substantial equivalent. *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 988 (Fed. Cir. 1999); *Cybor*, 138 F.3d at 1453. This is a factual determination of whether the claims "read on" the accused product or method. *Markman II*, 517 U.S. at 385 (citing *Winans v. Denmead*, 56 U.S. 330, 338 (1854)); *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1562 (Fed. Cir. 1990), cert. dismissed, 499 U.S. 955 (1991). Infringement may be direct, as in literal infringement or infringement under the "doctrine of equivalents." 35 U.S.C. § 271(a). Infringement may also be indirect, by inducement or contribution to infringement. 35 U.S.C. § 271(b) and (c).

1. Claim Interpretation

Claim interpretation involves consideration of the language of the patent claim itself, the specification, other claims, the prosecution history, and extrinsic evidence, if necessary. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979-80 (Fed. Cir. 1995), *aff'd en banc*, 517 U.S. 370 (1996) ("*Markman I*"); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Generally, claims are given their ordinary and customary meaning to a person skilled in the art at the time of invention. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). However, "the claims of [a] patent cannot be given a construction broader than the teachings expressed in the patent." *Studiengesellschaft Kohle GmbH v. Eastman Kodak, Inc.*, 616 F.2d 1315, 1324 (5th Cir. 1980), cert. denied, 449 U.S. 1014 (1980).

The specification is usually dispositive of the meaning of a term and has been called "the single best guide to the meaning of a disputed term." *Vitronics*, 90 F.3d at 1582. The specification may act as a "dictionary" that explains the claimed subject matter and defines terms used in the claims. *Markman I*, 52 F.3d at 979; *CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1153 (Fed. Cir. 1997), *reh'g denied*, 120 F.3d 1260 (Fed. Cir. 1997), cert. denied, 522 U.S. 1109 (1998). Where the specification contains nothing to indicate that terms are to be given anything other than their ordinary meanings, those are the meanings the court must give them. *Enercon GmbH v. Int'l Trade Comm'n*, 151 F.3d 1376, 1384 (Fed. Cir. 1998) (citing *Vitronics*, 90 F.3d at 1582); *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 759 (Fed. Cir. 1984). For example, a technical term used in a patent is given the same meaning that it would be given by persons experienced in the field of the patent, unless it is apparent from the patent and prosecution history that the patentee used the term with a different meaning. *CVI/Beta Ventures*, 112 F.3d at 1153 (quoting *Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1578 (Fed. Cir. 1996)).

Extrinsic evidence is any evidence external to the patent and prosecution history, such as expert testimony, inventor testimony, dictionaries, and technical treatises and articles. *Vitronics*, 90 F.3d at 1584. Courts may admit extrinsic evidence during claim interpretation if necessary, as long as the extrinsic evidence is consistent with the intrinsic record. *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 996 (Fed. Cir. 2006).

2. Literal Infringement

Under 35 U.S.C. § 271(a), "whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States, or imports into the United States any patented invention during the term of the patent therefor, infringes the patent." "Literal infringement requires that each and every claim limitation be present in the accused product." *Abraxis Bioscience, Inc. v. Mayne Pharma Inc.*, 467 F.3d 1370, 1378 (Fed. Cir. 2006); *Townsend Eng'g Co. v. Hitec Co.*, 829 F.2d 1086, 1090 (Fed. Cir. 1987). "Each element contained in a patent claim is deemed material to defining the scope of the patented invention." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29 (1997). Thus, the allegedly infringing product or method must embody every element of the asserted claims. *Dolly*, 16 F.3d at 397. "If even one limitation is missing or not met as claimed, there is no literal infringement." *Mas-Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998).

3. Infringement Under the "Doctrine of Equivalents"

Even if a product or method does not literally infringe, the court may find infringement if there is "equivalence" between the elements of the accused product or method and the elements of the asserted patent claims. *Warner-Jenkinson*, 520 U.S. at 21 (citing *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 609 (1950)); *We Care, Inc. v. Ultra-Mark Int'l Corp.*, 930 F.2d 1567, 1571 n. 3 (Fed. Cir. 1991). To establish equivalence, the patentee must prove that the accused product "differs from what is literally claimed only insubstantially, and [that] it performs substantially the same function in substantially the same way to achieve substantially the same result." *Wright Med. Tech., Inc. v. Osteonics Corp.*, 122 F.3d 1440, 1444 (Fed. Cir. 1997); *Texas Instruments, Inc. v. Cypress Semiconductor Corp.*, 62 F.3d 1558, 1567 (Fed. Cir. 1996). The nature of the differences is assessed according to whether a person with ordinary skill in the relevant art would find the differences to be substantial. *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1518 (Fed. Cir. 1995), *rev'd on other grounds*, 520 U.S. 17 (1997) (affirming the viability of the "insubstantial differences" test).

However, there can be no infringement under the doctrine of equivalents if a claim limitation is entirely missing from the accused product or method. *London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1539 (Fed. Cir. 1991). That is, "each element contained in a patent claim is deemed material to defining the scope of the patented invention, and thus the doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole." *Warner-Jenkinson*, 520 U.S. at 29. "The doctrine of equivalents is not a license to ignore claim limitations ... [and a] court cannot convert a multilimitation claim to one with fewer limitations to support a finding of equivalency." *Dolly*, 16 F.3d at 398-99.

Prosecution history estoppel and prior art also limit the range of equivalents. *Haynes Int'l, Inc. v. Jessop Steel Co.*, 8 F.3d 1573, 1579 (Fed. Cir. 1993), clarified on other grounds, 15 F.3d 1076 (Fed. Cir. 1994); *Pennwalt Corp. v. Durand-Wayland, Inc.*, 833 F.2d 931, 934 n. 1 (Fed. Cir. 1987) (en banc). Prosecution history estoppel arises when the applicant surrenders subject matter by either amendment or argument. Amendments made during prosecution to satisfy any requirement of the Patent Act or to avoid prior art may give rise to an estoppel. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 736-37 (2002).

In addition, arguments made during prosecution, even without amendment, to obtain allowance of the claims at issue, give rise to estoppel when such assertions clearly and unmistakably surrender subject matter, even when such arguments were not necessary to distinguish prior art. *See Sextant Avionique, S.A. v. Analog Devices, Inc.*, 172 F.3d 817, 828 n. 3 (Fed. Cir. 1999) (citing *Hoganas AB v. Dresser Indus., Inc.*, 9 F.3d 948, 952 (Fed. Cir. 1993)); *Litton Sys., Inc. v. Honeywell, Inc.*, 140 F.3d 1449, 1458 (Fed. Cir. 1998); *Texas Instruments, Inc. v. Int'l Trade Comm'n*, 988 F.2d 1165, 1174-75 (Fed. Cir. 1993).

Furthermore, arguments emphasizing the criticality of a claim element may give rise to estoppel in the form of a surrender of all competitive products that do not contain the critical element. *See Pharmacia & Upjohn Co. v. Mylan Pharm., Inc.*, 170 F.3d 1373, 1378-79 (Fed. Cir. 1999) (finding that all compositions not containing a component described as critical during prosecution and interpreted as indispensable were surrendered during prosecution).

Prior art may limit the doctrine of equivalents because "[t]here can be no infringement if the asserted scope of equivalency of what is literally claimed would encompass the prior art." *Wilson Sporting Goods Co. v. David Geoffrey & Assoc.*, 904 F.2d 677, 683 (Fed. Cir. 1990). Thus, "[a] patentee should not be able to obtain, under the doctrine of equivalents, coverage which he could not lawfully have obtained from the [Patent Office] by literal claims." *Id.* at 684. Under this limit to the doctrine, the claim must not "ensnare the prior art." *Id.* at 685.

4. Inducement of Infringement

Induced infringement under 35 U.S.C. § 271(b) is predicated on direct infringement of the claims by users of the infringing product or method. *C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc.*, 911 F.2d 670, 673 (Fed. Cir. 1990); *see also Sage Prods., Inc. v. Devon Indus., Inc.*, 45 F.3d 1575, 1577 (Fed. Cir. 1995). Thus, if there is no direct infringement of the patent by any party, there cannot be induced infringement.

To succeed on a theory of inducing infringement of a patent, "a plaintiff must prove that the defendants' actions induced infringing acts and that [they] knew or should have known [their] actions would induce actual infringement." *Warner-Lambert*, 316 F.3d at 1363 (quoting *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990)) (internal quotation marks omitted) (alteration in original). However, the mere knowledge of possible infringement by others is insufficient to prove inducement. *See DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1305 (Fed. Cir. 2006); *Manville*, 917 F.2d at 554. The accused infringer must have "knowingly aided and abetted another's direct infringement of the patent." *Warner-Lambert*, 316 F.3d at 1363 (quoting *Rodime PLC v. Seagate Tech., Inc.*, 174 F.3d 1294, 1306 (Fed. Cir. 1999)) (internal quotation marks omitted). For a finding of inducing infringement, "specific intent and action to induce infringement must be proven.'" *DSU Med.*, 471 F.3d at 1305; *Warner-Lambert*, 316 F.3d at 1363; *Manville*, 917 F.2d at 554.

5. Contributory Infringement

Contributory infringement must also be predicated on finding direct infringement of the claims by users of the infringing product or method. *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 341 (1961). Under 35 U.S.C. § 271(c), contributory infringement involves supplying a material component of the patented invention where that component is not "suitable for substantial noninfringing use." Like inducement of infringement, "contributory infringement [] also requires a mens rea." *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1381 (Fed. Cir. 2007). No contributory infringement can be found unless the accused contributory infringer knew of another's direct infringement and also knew of the patent. *Hewlett-Packard Co. v. Bausch & Lomb, Inc.*, 909 F.2d 1464, 1469 n. 4 (Fed. Cir. 1990).

V. THE '889 PATENT

A. OVERVIEW OF THE '889 PATENT

1. Specification of the '889 Patent

U.S. Patent No. 6,780,889 is directed, *inter alia*, to a pharmaceutical composition consisting essentially of an aqueous solution of gamma-hydroxybutyrate salt for treatment of

narcolepsy. The '889 patent is titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," and is assigned on its face to Orphan Medical, Inc., but has subsequently been assigned to Jazz. The patent lists five inventors on its face: Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad, and Dayton Reardan.

According to the '889 patent, the "invention particularly relates to the field of pharmaceutical production of microbiologically resistant and chemically stable preparations or solutions of gamma-hydroxybutyrate (GHB), also known as 4-hydroxybutyrate, and the sodium salt of GHB (sodium oxybate) and other salts such as magnesium, ammonium and calcium. . . ." The '889 patent concedes that GHB was known to be useful in the treatment of narcolepsy when administered as an oral solution. ('889 patent, col. 1, lines 51-61).

According to the '889 patent, organic salts of GHB were known, including magnesium and calcium salts: "Organic salts and amides of GHB have been produced to reduce the physiological side effects of GHB (U.S. Pat. No. 5,380,937). Magnesium and calcium salt have been produced to reduce the hygroscopic nature of GHB or powdered forms (U.S. Pat. No. 4,393,236; British Patent No. 922,029)." ('889 patent, col. 2, lines 43-47).

The '889 patent indicates that the main problem with existing solutions of GHB was degradation and contamination.

> However, problems with the storage of GHB solutions still exist. GHB degrades into gamma-butyrolactone (GBL) and possibly other degradants in solution depending upon the pH and other factors. Also, the contamination by microorganisms in GHB solutions rapidly surpass acceptable limits, and preservatives can adversely affect the pH and thus, GHB's stability. As a chronically used product which requires high levels of drug, the volume of a non-concentrated product creates cost and handling issues. Thus, there is an immediate need for effective solutions of GHB that are stable to biological or chemical degradation.

('889 patent, col. 2, lines 47-58).

According to the '889 patent, they solved the contamination and stability problems using a pH adjusted solution resistant to microbial growth without compromising stability. ('889 patent, col. 2, line 60 – col. 3, line 15).

2. Prosecution History of the '889 Patent

The '889 patent issued from U.S. Application No. 10/194,021 ("the '021 application"), filed July 11, 2002, claiming priority to U.S. Provisional No. 60/113,745, filed December 23, 1998.

On July 11, 2002, the applicants filed their original '021 application as a divisional of the application leading to U.S. Patent No. 6,472,431. The original application contained 64 claims, including the following by way of example:

> 1. A pharmaceutical composition, comprising gamma-hydroxybutyrate in an aqueous medium rendered chemically stable and resistant to microbial growth.
>
> 62. A pharmaceutical composition, consisting essentially of an aqueous solution of 500 mg/mL sodium gamma-hydroxybutyrate 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.
>
> 63. A pharmaceutical composition, consisting essentially of an aqueous solution of 500 mg/mL sodium gamma-hydroxybutyrate, 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.
>
> 64. A set for the treatment of a condition responsive to gamma-hydroxybutyrate, comprising: (A) water; (B) malic acid as a pH adjusting agent; and (C) sodium gamma-hydroxybutyrate; wherein components (A), (B), and (C) are packaged separately, in a suitable storage means, and wherein (A), (B) and (C) when combined yield a solution having a concentration of 500 mg/mL of sodium gamma-hydroxy butyrate and a pH of about 7.5.

('889 patent application, Jul. 11, 2002, Claims). In a preliminary amendment, the applicants canceled claims 1-61, leaving claims 62-64. (*Id.*).

On March 17, 2004, the examiner interviewed the applicants, wherein the applicants authorized the examiner to cancel claims 62 and 64, leaving only claim 63. ('889 patent application, Mar. 17, 2004, Examiner Interview Summary).

On March 24, 2004, the examiner issued a notice of allowance, with the following reasons for allowance:

> The following is an examiner's statement of reasons for allowance: In examiner's opinion, the advantage of claimed aqueous solution containing 500 mg/mL sodium gammahydroxybutyrate and malic acid at a pH of about 7.5 in rendering the aqueous solution resistant to microbial growth in free of preservative is not taught or recognized by the prior art.

('889 patent application, Mar. 24, 2004, Notice of Allowance).

On August 24, 2004, the '889 patent issued with a single claim.

3. Claim of the '889 Patent

The '889 patent issued with the following claim:

#	Claim of the '889 Patent
1	A pharmaceutical composition, consisting essentially of an aqueous solution of 500 mg/mL sodium gamma-hydroxybutyrate, 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.

B. LEVEL OF SKILL IN THE ART OF THE '889 PATENT

The subject matter of the '889 patent falls within the field of pharmaceutical compositions, and in particular, aqueous solutions designed to resist microbial growth. Depending on the claim, the person of ordinary skill in this field would be a pharmacist, formulator, chemist, organic chemist, process chemist, physical chemist, or medicinal chemist. Such an individual would have a Masters or Ph.D. degree and several years of experience in the field, the amount of post-graduate experience depending upon the level of formal education. *E.I. DuPont de Nemours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), *aff'd*, 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein and would have the capability to draw inferences from them.

C. CLAIM CONSTRUCTION OF THE '889 PATENT

One of ordinary skill in the art and a court would interpret the claims of the '889 patent according to their plain and ordinary meaning unless otherwise specified herein. On September 14, 2012, the U.S. District Court for the District of New Jersey issued a claim construction order for some of the terms in the '889 patent in *Jazz Pharmaceuticals. Inc. v. Roxane Laboratories, Inc.,* No. 10-6108, D.I. 151 (D.N.J. Sep. 14, 2012). The district court's constructions for several relevant terms are briefly discussed below. Par includes these constructions for informational purposes only and reserves its right to challenge these constructions.

a. "resistant to microbial growth"

The term "resistant to microbial growth" was construed by the district court in the *Jazz* litigation as follows: "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 Pharms. Inc. v. Roxane Labs., Inc.,* No. 10-6108, D.I. 151, at *6-8 (D.N.J. Sep. 14, 2012). The court's construction was based on the definition from the patent. (*See, e.g.*, '431 patent, col. 3, lines 23-32). The '431 patent is the parent of the '889 patent.

b. "about"

In the *Jazz* litigation, the parties disputed the meaning of the term "about," but the district court found that no construction was necessary. *Jazz Pharms. Inc. v. Roxane Labs., Inc.,* No. 10-6108, D.I. 151, at *14-16 (D.N.J. Sep. 14, 2012). See further discussion of this term below.

c. "preservative"

The term "preservative" was construed by the district court in the *Jazz* litigation to mean: "a substance or substances added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action." *Jazz Pharms. Inc. v. Roxane Labs. Inc.,* No. 10-6108, D.I. 151, at *10-16 (D.N.J. Sep. 14, 2012). 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, col. 7, lines 42-46).

d. "pH-adjusting agent"

The parties disputed the meaning of the term "pH-adjusting agent" in the *Jazz* litigation, which the district court construed to mean: "compositions that achieve a desired pH."

> 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's construction reflects the plain meaning of the term in the context of the '431 patent family.

Jazz Pharms. Inc. v. Roxane Labs. Inc., No. 10-6108, D.I. 151, at *19-21 (D.N.J. Sept. 14, 2012).

D. NONINFRINGEMENT OF THE '889 PATENT

1. Par's Sodium Oxybate Solution Does Not Infringe Claim 1 Because It is Not Free of Preservatives

Par's Sodium Oxybate Solution does not literally infringe claim 1 because Par's product is not "free of preservatives." Par's product contains sodium benzoate, which is described as a "preservative" by the '889 patent.

> In certain embodiments, the pharmaceutical composition may contain a preservative. 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**, methylparaben, . . .

('889 patent, col. 7, lines 40-63 (bold emphasis added)). Par's Sodium Oxybate Solution would not infringe under the doctrine of equivalents. Because the '889 patent specification describes "sodium benzoate" as a preservative, and claim 1 specifically precludes preservatives, Jazz should not be able to expand claim 1 to cover a composition that includes sodium benzoate. When a patentee discloses, but does not specifically claim, a particular embodiment, the doctrine of equivalents cannot be used to expand a claim to cover that non-claimed embodiment. *See Johnson & Johnston Assocs. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002).

2. Par's Sodium Oxybate Solution Does Not Infringe Claim 1 Because It Does Not Have a pH of "about 7.5"

Par's Sodium Oxybate Solution does not literally infringe claim 1 because Par's product does not consist essentially of a composition which "has a pH of about 7.5." A person of ordinary skill in the art would interpret "about 7.5" to mean 7.5 +/- 0.1, which does not cover the pH of Par's proposed solution which is 8.2 +/- 0.30.

The word "about" means "approximately," which means that the upper 7.5 limit is not confined to 7.5 exactly. In the *Jazz* case, the district court did not construe the term "about." *Jazz Pharm., Inc. v. Roxane Labs., Inc.*, No. 10-6108 (ES) (D.N.J. Sept. 14, 2012).[1] The language "about 7.5" does not cover pHs of 8.2 +/- 0.30 for at least the following reasons. The reasons relate to the fact that the "about" modifies pH, as opposed to, for example, a concentration.

First, the district court specifically rejected the construction that about means 10-20%. *Id.* The patent states that the term "about" generally means 10-20%, and Roxane proposed that "about" means "20% of the number modified in the appropriate direction(s)." ('889 patent, col.

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[1] *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.") The issue concerns the numerical limit that the word "about" imparts to the limitation "6.8" in the context of the claimed invention. *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.).

4, lines 9-10). The court rejected the proposal. Through the specification, the patent indicates an upper pH of 10.3, and the court observed that accepting Roxane's proposed construction would put the claimed range far outside the disclosed upper limit. *See Jazz Pharm., Inc. v. Roxane Labs., Inc.*, No. 10-6108 (ES) (D.N.J. Sept. 14, 2012).

Second, because a person of ordinary skill in the art would understand that pH is logarithmic, such a person would interpret "about 7.5" to mean 7.5 +/- 0.1. The expressions "pH" and "pOH" are defined as the negative logarithms of the hydrogen ion and the hydroxide ion concentrations, respectively.

$$pH = - \log[H^+] = \log (1/[H^+])$$

$$pOH = - \log[OH^-] = \log (1/[OH^-])$$

The pH of pure water is about 7 at 25 °C, where $[H^+] = 1 \times 10^{-7}$.[2] Because pH is a logarithmic scale, a difference of one pH unit is equivalent to a tenfold difference in hydrogen ion concentration.[3] *See* John Bailar, Jr. et al., CHEMISTRY, 3d ed. (1989) at 509. "For example, a solution of pH 1 has ten times the concentration of hydrogen ion of a solution of pH 2, not twice the concentration. A solution of pH 12 has 100 times the concentration of hydroxide ion of a solution of pH 10." *Id.* Because the '889 patent lists the pH range to a significant figure of tenths for claim 1 (7.5), a person of ordinary skill in the art would interpret "about" as not encompassing wholesale changes to the pH, e.g., "about 7.5" cannot encompass 8.5. Even though +/- 0.1 is a 1.3% change for 7.5, it is significantly greater for the hydrogen ion concentration— more than a 20% difference in hydrogen ion concentration.[4]

Par's Sodium Oxybate Solution would not infringe under the doctrine of equivalents. Because the '889 patent specification describes other pHs, including 8.2, and claim 1 specifically claims "about 7.5," Jazz should not be able to expand claim 1 to cover a composition that includes a pH of 8.2. When a patentee discloses, but does not specifically claim, a particular embodiment, the doctrine of equivalents cannot be used to expand a claim to cover that non-claimed embodiment. *See Johnson & Johnston Assocs. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002).

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2 Most measured pH values lie between 0 to 14. When an acid is dissolved in water, the pH will be less than that of pure water, and a strong acid, e.g., hydrochloric acid, at a high concentration provides a pH of 0. When a base, or alkali, is dissolved in water, the pH will be greater than that of pure water, and a strong base, e.g., sodium hydroxide, at a high concentration provides a pH of 14.

3 *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, at n.1 (1997) ("The pH, or power (exponent) of Hydrogen, of a solution is a measure of its acidity or alkalinity. A pH of 7.0 is neutral; a pH below 7.0 is acidic; and a pH above 7.0 is alkaline. Although measurement of pH is on a logarithmic scale, with each whole number difference representing a tenfold difference in acidity, the practical significance of any such difference will often depend on the context. Pure water, for example, has a neutral pH of 7.0, whereas carbonated water has an acidic pH of 3.0, and concentrated hydrochloric acid has a pH approaching 0.0. On the other end of the scale, milk of magnesia has a pH of 10.0, whereas household ammonia has a pH of 11.9. 21 Encyclopedia Americana 844 (Int'l ed. 1990).").

4 Hydrogen ion concentration at pH 7.5 is 3.1622×10^{-8} mol/L (i.e., $10^{-7.5}$), whereas the hydrogen ion concentration at pH 7.6 is 2.5119×10^{-8} mol/L (i.e., $10^{-7.6}$). The percent difference in the hydrogen ion concentration is more than 20%.

E. OBVIOUSNESS OF THE '889 PATENT

1. The Scope and Content of the Prior Art

The earliest effective U.S. filing date for the '889 patent is December 23, 1998, based on the filing date for U.S. Provisional Application 60/113,745.

a. Gamma-Hydroxybutyric acid (GHB)

Gamma-hydroxybutyric acid (GHB) was first studied in 1960 by Laborit and his co-workers as an isostere of gamma-amino-butyric acid (GABA) able to cross the blood-brain barrier and was proposed as an hypnotic and general anesthetic. Laborit, H.; Jouany, J., Gerard, J., Fabiani, P. *Neuro-Psycho-pharmacol., Proc.* 1961, 2, 490. The drug is sold in Italy as Alcover®, France as Gamma OH, Germany as Somsanit, and Xyrem in the U.S., EU, and Canada. In 1990, the FDA declared GHB unsafe.

b. U.S. Patent No. 4,983,632

U.S. Patent No. 4,983,632 ("the '632 patent") is prior art to the '889 patent under 35 U.S.C. § 102(b) based on its January 8, 1991, issuance. The '632 patent is listed on the face of the '889 patent and was disclosed in an IDS during prosecution.

The '632 patent teaches the use of gamma-hydroxybutyric acid in various dosage forms including solution, tablet, sachet, powder and injectable vials for treating ethyl alcohol dependency, wherein citric acid and sodium bicarbonate are utilized as a secondary agent in NaGHB composition. ('632 patent, Examples 1-2 disclose 302.5mg/mL NaGHB in solution whereas Example 5 discloses about 740 mg/mL NaGHB in jelly form). The '632 patent contemplates formulations of gamma-hydroxybutyrate that are mixtures of solids (Examples 3 and 4) and a jelly (Example 5), as well as liquid solutions (Examples 1 and 2) and an injectable preparation (Example 6).

- Example 1 teaches a syrup bottle containing 140 mL of solution, which is 42.35 g of "gamma-hydroxy butyric acid, sodium salt," in an aqueous syrup solution of 140 mL, which is a concentration of 302.5 mg/mL.
- Example 2 teaches 6.05 g of "gamma-hydroxy butyric acid, sodium salt," in an aqueous solution of 20 mL, which is a concentration of 302.5 mg/mL. Example 2 also includes methylparaoxybenzoate and propylparaoxybenzoate.
- Example 5 discloses a "jelly" containing 30.25 g of GHB in 40.75 g of water, a 74.2% solution of GHB in water.

The '632 patent teaches that "suitable gamma hydroxy butyric acid salts include the sodium salt, potassium salt, calcium salt and magnesium salt" (col. 7, lines 32-34); "the choice of excipient depends not only on the chemical and physical characteristics of the active principle and the required physiology, but also on the type of composition desired" (col. 7, lines 37-40); and "the dosage of individual components of the administration obviously varies in accordance with the body weight of the patient and his clinical condition" (*see* col. 7, lines 40-43).

The '632 patent discloses that "[t]he typical dosage for a GHB salt is from 0.025 to 0.10 g/kg, the preferred GHB salt dosage being 0.05 g/kg in a single daily dose." ('632 patent, col. 7, lines 44-47). The patent teaches oral administration of a solution of sodium gamma hydroxybutyrate, particularly a solution comprising 42.35 g sodium gamma hydroxybutyrate in 140 mL water, and a solution comprising 6.05 g sodium gamma hydroxybutyrate in 20 mL water (Examples 1 and 2, p. 8). The solutions taught by the '632 patent have a concentration of approximately 300 mg/mL.[5]

c. U.S. Patent No. 5,210,083

U.S. Patent No. 5,210,083 ("the '083 patent") is prior art to the '889 patent under 35 U.S.C. § 102(b) based on its November 24, 1998, issuance. The '083 patent was not considered by the examiner. The pH of blood is usually slightly basic with a value of pH 7.365. This value is often referred to as physiological pH in biology and medicine. The '083 patent is titled "Pharmaceutical Compositions," and is directed to an aqueous solutions, and indicates that pH of them can be adjusted to obtain physiological pH, and prefers use of malic acids, acetic, or lactic acid, which is metabolisable. ('083 patent, col. 4, lines 23-32). *See also* U.S. Patent No. 4,460,605.

d. U.S. Patent No. 5,840,331

U.S. Patent No. 5,840,331 ("the '331 patent") is prior art to the '889 patent under 35 U.S.C. § 102(b) based on its November 24, 1998, issuance. The '331 patent is listed on the face of the '889 patent and was disclosed in an IDS during prosecution. The '331 patent teaches pharmaceutical compositions containing gamma hydroxybutyrate, including the following:

- they can further comprise "physiologically acceptable carriers, buffers, or other excipients" ('331 patent, col. 7, lines 13-17);
- "pharmaceutical compositions may be administered in the form of injectable compositions either as liquid solutions of suspensions" ('331 patent, col. 7, lines 17 -18);
- " ... acceptable carriers include aqueous solutions, non toxic excipients, including slats preservatives, buffers . . ." ('331 patent, col. 7, lines 25-27);
- "preservatives include antimicrobial agents, anti-oxidants and chelating agents . . ." ('331 patent, col 7, lines 35-36); and
- "the pH and exact concentration of the various components the pharmaceutical composition are adjusted according to well known parameters" ('331 patent, col. 7, lines 36-38).

e. Broughton 1979

Broughton et al. ("The Treatment of Narcolepsy-Cataplexy with Nocturnal Gamma-Hydroxybutyrate," CAN.J.NEUROL. SCI., 1979, vol. 6, no. 1, pp. 1-6) ("Broughton"), is prior art

[5] Columbo, "High Sensitivity to gamma-hydroxybutyric acid in ethaniol-preferring sP rates," Alcohol & Alcoholism, Vol. 33, No. 2, pp. 121-125, 1998 . This article describes administering GHB sodium salt dissolved in distilled water (3.4% w/v), which is 34 mg/mL.

to the '889 patent under 35 U.S.C. § 102(b) based on its 1979 publication. Broughton is listed on the face of the '889 patent. Broughton discloses a method for the treatment of narcolepsy and cataplexy, comprising diluting a solution of gamma-hydroxybutyrate, administering a first dosage of gamma-hydroxybutyrate orally before bedtime, and administering a second dosage of gamma-hydroxybutyrate no less than 2.5 hours after bedtime. (Broughton at p. 2, col. 1, ¶ 3). The dose was 1.5-2.25 gm administered orally at bedtime, followed by one or two further 1.0-1.5 gm doses during the night (Abstract). Broughton states,

> Since each sleep inducing oral dose of GHB lasts only two or three hours ... and because our aim was to maximize the duration of sleep produced by the drug while minimizing its anesthetic effects, multiple doses were used. The usual initial dose was 1.5-2.25 gm (10-15 mL) hs, followed by further multiple 1.0-1.5 gm doses during the night with each major reawakening, if at least 2.5 hours had passed since the previous dose. Usually only 2 or 3 doses per night were necessary. Each dose was about 30 mg/kg, but the total quantity of GHB given each night ranged from 3.75 to 6.25 gms, corresponding to approximately 50 mg/kg" (page 2, column 3, paragraph 2).[6]

The GHB was prepared from a syrup form, which was diluted in milk or juice in order to reduce gastrointestinal upset (p. 2, col. 3, ¶ 4 - p. 3, col. 1, ¶ 1). The diluted solution also retarded GHB's rate of absorption such that sleep induction was gradual and more normal. Apart from one patient, who took only a single bedtime dose, "the subjective quality of night sleep improved in all patients and the number of irresistible daytime attacks of sleep and cataplexy diminished" according to the publication (Abstract).

f. Scrima 1990

Scrima et al. (Sleep, vol. 13, No. 6, 1990, pp. 479-490) ("Scrima"), is prior art to the '889 patent under 35 U.S.C. § 102(b) based on its 1990 publication. Scrima 1990 is listed on the face of the '889 patent. Scrima teaches the use of gamma hydroxybutyrate for the treatment of sleep disorder such as narcolepsy patient wherein said gamma-hydroxybutyrate is administered to the patient in orally 25 mg/kg dosage (approximately 1.5-2.8 gm based on body weight disclosed in Table 1) at bedtime and followed by 25 mg/kg (approximately 1.5-2.8 gm) 3 hours later (abstract; p. 480, ¶ 3-4; Results). It appears that the dose was administered as a solution mixture of sterile, distilled water and syrup of orange. (Scrima at 482, second full paragraph).

Scrima teaches that "[h]igher doses of GHB, or longer treatment periods than were used in the present experiment may be needed to cause a more pronounced and subjectively noticeable decrease in sleepiness in narcolepsy patients." (Scrima at p. 488, first full paragraph). Scrima recognizes that long-term trials of higher doses of GHB in narcolepsy patients have revealed that the number of subjective sleep attacks were reduced throughout GHB treatment periods (p. 488, ¶ 1, last sentence) and that "GHB has been found to cause only minor side effects . . . . Tolerance to GHB has not been found to develop. . . . (p. 489, second paragraph).

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[6] 2.25 gm is 10 mL is 225 mg/mL.

g. Scharf 1998

Scharf, Martin, Allen Lai, Barb Branigan, Robin Stover, David Berkotwiz, "Pharmacokinetics of Gammahydroxybutyrate (GHB) in Narcolpetic Patients," Sleep [1998, 21(5):507-514] ("Scharf 1998") is prior art to the '889 patent under 35 U.S.C. § 102(a) based on its August 1998 publication. It appears that this reference was never considered by the examiner during prosecution of the '889 patent.

This paper describes a study evaluating the pharmacokinetics of GHB, given twice in one night to six narcoleptic patients who had been chronically taking GHB nightly on a similar basis. GHB elimination appears to be capacity-limited in some patients when administered at a fixed dose of 3 g twice nightly at a 4-hour interval: "The objective of this study was to assess the pharmacokinetics of GHB after oral administration of two consecutive single doses of GHB (3 g/dose, 4 hours apart) to narcoleptic patients who have been chronically maintained on a similar regimen of nightly GHB use." *Id.* at 508. The dose administered was 3 g (3,000 mg) dissolved in 2 ounces of water. 1 ounce of water is 29.5735 milliliters, for a concentration of 50 mg/mL.

> Patients ate their dinner at the clinical research unit soon after arrival and fasted until breakfast next morning. The investigator or his designee prepared the oral solution for dosing within 30 minutes prior to the first oral administration to individual patients. The contents of one twin-pouch containing 3 g of GHB in powder and excipient form was emptied into a dosing cup (provided by the sponsor) to which 2 ounces of water was added. After replacing the lid of the dosing cup (also provided by the sponsor), the dosing cup was gently shaken to dissolve the GHB and excipient in water. The GHB solution was ingested in its entirety. Likewise, the second GHB dosing solution was prepared in the same manner and was ingested in entirety 4 hours after the first GHB dose.

Id.

2. Application of the Prior Art

Claim 1 is directed to a particular preservative free composition of sodium gamma-hydroxybutyrate—which is an old compound—consisting essentially of an aqueous solution with malic acid to adjust the pH to 7.5. This would have been obvious in December 1998, because aqueous solutions of sodium gamma-hydroxybutyrate were known ('632 patent), and it was known that pharmaceutical solutions are normally at physiological pH, where malic acid is preferred (along with a small class of other acids) to adjust the pH because it is metabolizable ('083 patent). The claimed features, wherein the claimed composition is chemically stable and resistant to microbial growth, are inherent properties of an obvious composition.

Claim 1 of the '889 Patent	'632 patent + '083 patent
A pharmaceutical composition, consisting essentially	The '632 patent teaches a pharmaceutical composition.

of an aqueous solution of 500 mg/mL sodium gamma-hydroxybutyrate, and malic acid as a pH adjusting agent,	Example 2 of the '632 patent teaches 6.05 g of "gamma-hydroxy butyric acid, sodium salt," in an aqueous solution of 20 mL, which is a concentration of 302.5 mg/mL. Because concentrated oral solutions were known, if the target concentration of NaGHB was 302.5 mg/mL, then in a concentrated solution for later dilution, would naturally be even higher. The '083 patent teaches a pharmaceutical aqueous solution (not of gamma-hydroxy butyric acid) where the pH is adjusted using malic acid, acetic acid, or lactic acid, each of which is metabolisable.[7] ('083 patent, col. 4, lines 23-32).
wherein the composition has a pH of about 7.5, and	The '083 patent teaches obtaining a solution with a physiological pH, which is 7.365, and "about 7.5" is obvious over 7.365.
wherein the composition is chemically stable and resistant to microbial growth, and	Both the chemical stability and resistance to microbial growth of the resulting composition of 302.5 mg/mL with a pH of about 7.5 using malic acid as a pH adjusting agent are inherent properties of the composition.
wherein the composition is free of preservatives.	The '632 patent does not require preservatives, and it would have been obvious to create, or try, a preservative free composition.

The claimed 500 mg/mL concentration is obvious over the prior art 302.5 mg/mL concentration in the '632 patent. There is no indication that the specified 500 mg/mL concentration itself was novel, and the dose administrated to patients is more relevant than the concentration for the purpose of using the claimed pharmaceutical composition. Furthermore, because concentrated oral solutions were known, if the target concentration of NaGHB is around 300 mg/mL, then in a concentrated solution for later dilution, would naturally be even higher.[8] The '889 patent states that concentrations above 150 mg/mL are "suitably resistant to microbial contamination" at pH ranges of 7.5. ('889 patent, col. 12, lines 27-34). Furthermore, the '083 patent teaches a pharmaceutical aqueous solution (not of gamma-hydroxy butyric acid) where the pH is adjusted using malic acid, acetic acid, or lactic acid, each of which is metabolisable. ('083 patent, col. 4, lines 23-32).[9] The '083 patent teaches obtaining a pharmaceutical solution with a physiological pH, which is 7.365.

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7 Malic acid is a general-purpose acidulant, and listed as a GRAS ("Generally Recognized as Safe") substance by the FDA.

8 The "oral solution" is a common dosage form for drugs. "Oral solutions may be formulated for direct oral administration to the patient or they may be dispensed in a more concentrated form that must be diluted prior to administration." USP <1151>.

9 Compositions containing malic acid were known. *See, e.g.*, U.S. Patent 4,183,916 (claim 1).

The examiner allowed claim 1 because "the advantage of claimed aqueous solution containing 500 mg/mL sodium gammahydroxybutyrate and malic acid at a pH of about 7.5 in rendering the aqueous solution resistant to microbial growth in free of preservative is not taught or recognized by the prior art." ('889 patent application, Mar. 24, 2004, Notice of Allowance). It appears that the examiner found that, even if the particular claimed solution of 500 mg/mL sodium gammahydroxybutyrate and malic acid at a pH of about 7.5 was *prima facie* obvious, the applicants' observation that this solution was "resistant to microbial growth" without preservatives created novelty. Laws of nature are not patentable. *Mayo Collaborative Serv. v. Prometheus Labs., Inc.*, 132 S.Ct. 1289 (2012) (citing *Diamond v. Diehr*, 450 U. S. 175, 185 (1981)); *see also Bilski v. Kappos*, 130 S.Ct. 3218, 3238 (2010).

The resistance to microbes and chemical stability of the composition of aqueous solution of 500 mg/mL sodium gamma-hydroxybutyrate, and malic acid as a pH adjusting agent, with a pH of 7.5 are inherent properties of the composition, which is obvious in view of the prior art.[10] By the patentees' own admission, concentrations of GHB above 150 mg/mL are resistant to microbial contamination, and the '632 patent teaches a solution at 302.5 mg/mL. Based on this fact, there is no motivation to add a preservative to the solution.[11]

Furthermore, the pH and formulation for the sodium oxybate solution was the result of routine formulation work, which is described in the '889 patent itself, see Example 4. When a person of ordinary skill is faced with "a finite number of identified, predictable solutions" to a problem and pursues "the known options within his or her technical grasp," the resulting discovery "is likely the product not of innovation but of ordinary skill and common sense." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 127 S. Ct. 1727, 1742 (2007). "Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress." *Id.* at 1741. *See, e.g., Pfizer v. Apotex*, 408 F.3d 1348 (Fed. Cir. 2007) (selection of the phosphate salt from a small, well-defined set of possible candidates was obvious because it was merely the routine optimization of a single variable using techniques common in the pharmaceutical sciences).

The '889 patent provides no specific evidence of secondary considerations of non-obviousness, and the applicants did not rely on evidence of unexpected results to rebut a charge of obviousness during prosecution. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359–60 (Fed. Cir. 2007) ("[O]nce a challenger has presented a *prima facie* case of invalidity, the patentee has the burden of going forward with rebuttal evidence.") It is the patentee's obligation to present

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10 *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); *see also Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320 (Fed. Cir. 2004)("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention.").

11 There was a motivation in December 1998 not to use preservatives. *See, e.g.*, Kabara, Jon, "Preservative-Free and Self-Preserving Comsetic and Drug: Principle and Practice," Marcel Dekker, Inc. (1997), is prior art to the '889 patent under 35 U.S.C. § 102(b) based on its 1990 publication. Chapter 11, "Preservative-Free and Self-Preserving Cosmetic and Drug Products: The Future," explains that "preservative-free and self-preserving cosmetic and drug products "are not new."

evidence of secondary considerations, if any, to rebut a *prima facie* case of obviousness. The problem presented by the inventors was finding a way to formulate a solution of sodium oxybate in a way that maintained chemical stability and sterility. Even if the use of preservatives in an oral pharmaceutical solution was obvious, not using preservatives was also obvious. The patentees have not established that any need was met by, nor commercial success attributable to, the claimed subject matter, rather than the compound of the prior art disclosure of a sodium oxybate in an aqueous solution.

Claim 1 is additionally obvious over the combination of '632 patent, '083 patent, and the '331 patent. Whereas the '632 patent discloses oral solutions of NaGHB and the '083 patent teaches the use of malic acid, the '331 patent teaches pharmaceutical compositions containing gamma hydroxybutyrate, including the following "pharmaceutical compositions may be administered in the form of injectable compositions either as liquid solutions of suspensions" ('331 patent, col. 7, lines 17 -18). The '331 patent specifies that "the pH and exact concentration of the various components the pharmaceutical composition are adjusted according to well known parameters." ('331 patent, col. 7, lines 36-38).

F. CONCLUSION

For the reasons stated above, claim 1 of the '889 patent is not infringed, either literally or under the doctrine of equivalents, and claim 1 of the '889 patent is obvious over the prior art. Par reserves the right to develop additional grounds, reasons, and authorities that any or all of the claims of these patents are invalid, unenforceable or not infringed.

VI. THE '219 PATENT

A. OVERVIEW OF THE '219 PATENT

1. Specification of the '219 Patent

U.S. Patent No. 7,262,219 is directed, *inter alia*, to a pharmaceutical composition consisting essentially of an aqueous solution of gamma-hydroxybutyrate salt for treatment of narcolepsy. The '219 patent is titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," and is assigned on its face to Orphan Medical, Inc., but has subsequently been assigned to Jazz. The patent lists five inventors on its face: Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad, and Dayton Reardan.

According to the '219 patent, the "invention particularly relates to the field of pharmaceutical production of microbiologically resistant and chemically stable preparations or solutions of gamma-hydroxybutyrate (GHB), also known as 4-hydroxybutyrate, and the sodium salt of GHB (sodium oxybate) and other salts such as magnesium, ammonium and calcium. . . ." ('219 patent).

According to the '219 patent, GHB was known to be useful in the treatment of narcolepsy when administered as an oral solution. ('889 patent, col. 1, lines 56 - col. 2, line 34).

According to the '219 patent, organic salts of GHB were known, including magnesium and calcium salts: "Organic salts and amides of GHB have been produced to reduce the physiological side effects of GHB (U.S. Pat. No. 5,380,937). Magnesium and calcium salt have been produced to reduce the hygroscopic nature of GHB or powdered forms (U.S. Pat. No. 4,393,236; British Patent No. 922,029)." ('219 patent, col. 2, lines 55-60).

The '219 patent indicates that the main problem with existing solutions of GHB was degradation and contamination.

> However, problems with the storage of GHB solutions still exist. GHB degrades into gamma-butyrolactone (GBL) and possibly other degradants in solution depending upon the pH and other factors. Also, the contamination by microorganisms in GHB solutions rapidly surpass acceptable limits, and preservatives can adversely affect the pH and thus, GHB's stability. As a chronically used product which requires high levels of drug, the volume of a non-concentrated product creates cost and handling issues. Thus, there is an immediate need for effective solutions of GHB that are stable to biological or chemical degradation.

('219 patent, col. 2, line 60 – col. 3, line 5).

According to the '219 patent, they solved the contamination and stability problems using a pH adjusted solution resistant to microbial growth without compromising stability. ('219 patent, col. 3, lines 8 – 31).

2. Prosecution History of the '219 Patent

The '219 patent issued from U.S. Application No. 10/841,709 ("the '709 application"), filed May 7, 2004, claiming priority to U.S. Provisional No. 60/113,745, filed December 23, 1998.

On May 7, 2004, the applicants filed their original '709 application as a divisional of the application leading to U.S. Patent No. 6,780,889. The original application contained 64 claims, including the following by way of example:

> 1. A pharmaceutical composition, comprising gamma-hydroxybutyrate in an aqueous medium rendered chemically stable and resistant to microbial growth.
>
> 62. A pharmaceutical composition, consisting essentially of an aqueous solution of 500 mg/mL sodium gamma-hydroxybutyrate 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.
>
> 63. A pharmaceutical composition, consisting essentially of an aqueous solution of 500 mg/mL sodium gamma-hydroxybutyrate, 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.
>
> 64. A set for the treatment of a condition responsive to gamma-hydroxybutyrate, comprising: (A) water; (B) malic acid as a pH adjusting agent; and (C) sodium gamma-hydroxybutyrate; wherein components (A), (B), and (C) are packaged separately, in a suitable storage means, and wherein (A), (B) and (C) when combined yield a solution having a concentration of 500 mg/mL of sodium gamma-hydroxy butyrate and a pH of about 7.5.

('219 patent application, May 5, 2007, Claims). In a preliminary amendment, the applicants canceled claims 1-64, adding claims 65-71. *Id.*

On November 30, 2006, the examiner issued a non-final rejection. Claims 65, and 67-71 were rejected under 35 U.S.C. § 112. The claims were also rejected under 35 U.S.C. § 103. Claims 65-71 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Gessa et al. (U.S. Patent No. 4,983,632) in view of Van Cauter et al. (U.S. Patent No. 5,840,331) and the admitted prior art (p. 12, lines 3-8 of the instant specification). The examiner also rejected the claims for obviousness-type double patenting: "Claim 65-71 is rejected under the judicially created doctrine of double patenting over claim 1 of U.S. Patent No. 6,780,889 and further in view of Gessa et al. (US 4983632) or Cacciaglia (US 6436998)." ('219 patent application, Nov. 30, 2006, Office Action). The applicants overcame the double patenting rejection by filing a terminal disclaimer. ('219 patent application, Feb. 21, 2007, Terminal Disclaimer).

On February 21, 2007, the applicants amended the claims to deal with the § 112 rejection, and responded to the obviousness rejection. ('219 patent application, Feb. 21, 2007, Amendment and Response).

On April 27, 2007, the examiner interviewed the applicants, at which the applicants authorized the examiner to amend claim 65, cancel claims 67-71, and add claims 72 and 73. ('219 patent application, May 25, 2007, Examiner-Initiated Interview Summary).

On May 25, 2007, the examiner issued a notice of allowance without reasons for allowance. The claims were amended as follows:

> In claim 65, line 3, add – wherein the pH adjusting agent is malic acid, citric acid, acetic acid, lactic acid, carbonic acid, formic acid, propionic acid or tartaric acid, -- before "wherein the composition has a pH of about 6-7.5."
>
> Add new claims 72 and 73.
>
> 72. (New) The pharmaceutical composition of claim 65, wherein the pH adjusting agent is malic acid.
>
> 73. (New) 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 hydrochloric acid, phosphoric acid, sulphuric acid, boric acid or nitric 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.

Claims 67-71 are cancelled.

On August 28, 2007, the '219 patent issued with 4 claims.

3. Claims of the '219 Patent

The '219 patent issued with the following claims:

#	Claims from the '219 Patent
1	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.
2	The pharmaceutical composition of claim 1 wherein the aqueous solution contains about 400-650 mg/mL of sodium gamma-hydroxybutyrate.
3	The pharmaceutical composition of claim 1, wherein the pH adjusting agent is malic acid.
4	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 hydrochloric acid, phosphoric acid, sulphuric acid, boric acid or nitric 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.

B. LEVEL OF SKILL IN THE ART

The subject matter of the '219 patent falls within the field of pharmaceutical compositions, and in particular, aqueous solutions designed to resist microbial growth. Depending on the claim, the person of ordinary skill in this field would be a pharmacist, formulator, chemist, organic chemist, process chemist, physical chemist, or medicinal chemist. Such an individual would have a Masters or Ph.D. degree and several years of experience in the field, the amount of post-graduate experience depending upon the level of formal education. *E.I. DuPont de Nemours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), *aff'd*, 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein and would have the capability to draw inferences from them.

C. CLAIM CONSTRUCTION OF THE '219 PATENT

One of ordinary skill in the art and a court would interpret the claims of the '219 patent according to their plain and ordinary meaning unless otherwise specified herein. On September

14, 2012, the U.S. District Court for the District of New Jersey issued an claim construction order for terms in the '219 patent in the case of *Jazz Pharm. Inc. v. Roxane Labs, Inc.,* No. 10-6108, D.I. 151 (D.N.J. Sept. 14, 2012) . The district court's constructions for several relevant terms are briefly discussed in section V(C), above. Par includes these constructions for informational purposes only and reserves its right to challenge these constructions.

D. NONINFRINGEMENT OF THE '219 PATENT

1. Par's Sodium Oxybate Solution Does Not Infringe Claims 1-4 Because It Is Not Free of Preservative

Par's Sodium Oxybate Solution does not literally infringe claims 1 or 4 because Par's product is not "free of preservatives." Par's product contains sodium benzoate, which is described as a "preservative" by the '219 patent.

> In certain embodiments, the pharmaceutical composition may contain a preservative. 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**, methylparaben, ...

('219 patent, col. 8, lines 21-44 (emphasis added)). Further, Par's Sodium Oxybate Solution does not infringe under the doctrine of equivalents. Because the '219 patent specification describes "sodium benzoate" as a preservative, and claims 1 and 4 specifically preclude preservatives, Jazz should not be able to expand claims 1 and 4 to cover a composition that includes sodium benzoate. When a patentee discloses, but does not specifically claim, a particular embodiment, the doctrine of equivalents cannot be used to expand a claim to cover that non-claimed embodiment. *See Johnson & Johnston Assocs. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002).

Claims 2 – 3 depend from claim 1. Because independent claim 1 is not infringed literally or under the doctrine of equivalents, claims 2 – 3 cannot be infringed literally or under the doctrine of equivalents. *Wahpeton Canvas*, 870 F.2d at 1553.

2. Par's Sodium Oxybate Solution Does Not Infringe Claims 1-4 Because the Solution Does Not Have a pH of "About 6 - 7.5"

Par's Sodium Oxybate Solution does not literally infringe claim 1 or 4 because Par's product does not comprise a composition which has a "pH of about 6-7.5." A person of ordinary skill in the art would interpret "about 6-7.5" to mean 7.5 +/- 0.1 at the high range, which does not cover the pH of Par's proposed solution is 8.2 +/- 0.30.

The word "about" means "approximately," which means that the upper 7.5 limit is not confined to 7.5 exactly, as discussed above. Par's Sodium Oxybate Solution would not infringe under the doctrine of equivalents. Because the '219 patent specification describes other pHs, including 8.2, and claim 1 specifically claims "about 6-7.5," Jazz should not be able to expand claim 1 to cover a composition that includes a pH of 8.2. When a patentee discloses, but does not specifically claim, a particular embodiment, the doctrine of equivalents cannot be used to

expand a claim to cover that non-claimed embodiment. *See Johnson & Johnston Assocs. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002).

Claims 2 – 3 depend from claim 1. Because independent claim 1 is not infringed literally or under the doctrine of equivalents, claims 2 – 3 cannot be infringed literally or under the doctrine of equivalents. *Wahpeton Canvas*, 870 F.2d at 1553.

3. Additional Noninfringement of Claim 4

Par's Sodium Oxybate Solution does not literally infringe claim 4 for the separate reason that Par's product does not consist essentially of an aqueous solution wherein the pH adjusting agent is "hydrochloric acid, phosphoric acid, sulphuric acid, boric acid or nitric acid." Par's Sodium Oxybate Solution contains no hydrochloric acid, phosphoric acid, sulphuric acid, boric acid or nitric acid. Par's Sodium Oxybate Solution would not infringe under the doctrine of equivalents because Par's product contains no equivalent to hydrochloric acid, phosphoric acid, sulphuric acid, boric acid or nitric acid in Par's Sodium Oxybate Solution. The original claims were broader (e.g., did not even require a pH adjusting agent), and narrowed pursuant to a preliminary amendment. Voluntary amendments, including preliminary amendments are treated the similarly to amendments required by the examiner. *See, e.g., Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1313 (Fed. Cir. 2006). Because the '219 patent applicants narrowed the claims, the doctrine of prosecution history estoppel precludes any range of equivalents to a pH adjusting agent. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 493 F.3d 1368, 1376 (Fed. Cir. 2007); *see also Litton Sys., Inc. v. Honeywell, Inc.*, 140 F.3d 1449, 1458 (Fed. Cir. 1998).

E. OBVIOUSNESS OF THE '219 PATENT

1. The Scope and Content of the Prior Art

The earliest effective U.S. filing date for the '219 patent is December 23, 1998, based on the filing date for U.S. Provisional Application 60/113,745. This date is the same as that of the '889 patent. A description of the prior art can be found in section V(E)(1), above.

2. Application of the Prior Art

Sodium gamma-hydroxybutyrate is an old compound. Claim 1 is directed to a particular preservative free aqueous solution of sodium gamma-hydroxybutyrate at a concentration of about 350-750 mg/mL, where the pH is adjusted to 6-7.5 using particular acids. This would have been obvious in December 1998, because aqueous solutions of sodium gamma-hydroxybutyrate were known ('632 patent), and it was known that pharmaceutical solutions are normally at physiological pH, where malic acid is preferred (along with a small class of other acids) to adjust the pH because malic acid is metabolizable ('083 patent). The claimed features, wherein the claimed composition is chemically stable and resistant to microbial growth, are inherent properties of an obvious composition.

Claim 1 of the '219 Patent	'632 patent + '083 patent
A pharmaceutical composition,	The '632 patent teaches a pharmaceutical composition.

consisting essentially of an aqueous solution of about 350-750 mg/mL sodium gamma-hydroxybutyrate, and	Example 2 of the '632 patent teaches 6.05 g of "gamma-hydroxy butyric acid, sodium salt," in an aqueous solution of 20 mL, which is a concentration of 302.5 mg/mL.
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,	The '083 patent teaches a pharmaceutical aqueous solution (not of gamma-hydroxy butyric acid) where the pH is adjusted using malic acid, acetic acid, or lactic acid, each of which is metabolisable.[12] ('083 patent, col. 4, lines 23-32).
wherein the composition has a pH of about 6-7.5, and	The '083 patent teaches obtaining a solution with a physiological pH, which is 7.365, and which is also the same as "about 7.5."[13]
wherein the composition is chemically stable and resistant to microbial growth, and	Both the chemical stability and resistance to microbial growth of the resulting composition of 302.5 mg/mL with a pH of about 7.5 using malic acid as a pH adjusting agent are an inherent properties of the composition.
wherein the composition is free of preservatives.	The '632 patent does not require preservatives, and it would have been obvious to create, or try, a preservative free composition.

The claimed "about" 350-750 mg/mL concentration is obvious over the prior art 302.5 mg/mL concentration in the '632 patent.

Although the New Jersey District Court in the *Jazz* case decided not to construe the term "about," the patent states: "As used herein, the term 'about' generally means within about 10-20%." ('219 patent, col. 4, lines 8-9) Focusing on the claimed low end of 350 mg/mL, a 10% decrease results in 315 mg/mL and a 20 mg/mL decrease results in 280 mg/mL. The 302.5 mg/mL taught by the '632 patent falls within the claimed range when "about" is interpreted as 10-20% in the context of the API concentration.

Even if the term "about" means "approximately," the claimed range of 350-750 mg/mL would be obvious over the prior art concentration of 302.5 mg/mL. There is no indication that the specified 350-750 mg/mL concentration range itself was novel, and the dose administrated to patients is more relevant than the concentration for the purpose of using the claimed pharmaceutical composition. Furthermore, because concentrated oral solutions were known—i.e., a concentrated liquid dosage form to be diluted before administration were known—, if the target concentration of NaGHB is around 302.5 mg/mL, then in a concentrated solution for later dilution, would naturally be even higher.[14]

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12 Malic acid is a general-purpose acidulant, and listed as a GRAS ("Generally Recognized as Safe") substance by the FDA.

13 As indicated above, the '083 patent teaches a pharmaceutical aqueous solution (not of gamma-hydroxy butyric acid) where the pH is adjusted using malic a*cid.*, acetic acid, or lactic acid, each of which is metabolisable. ('083 patent, col. 4, lines 23-32.) The '083 patent teaches obtaining a solution with a physiological pH, which is 7.365.

14 The "oral solution" is a common dosage form for drugs. "Oral solutions may be formulated for direct oral administration to the patient or they may be dispensed in a more concentrated form that must be diluted prior to administration." USP <1151>.

The examiner allowed claim 1 without providing reasons for allowance. In response to an obviousness rejection during prosecution of the '219 patent, the applicants argued that even if the composition was prima facie obvious, the self-sterilization of the composition at the claimed concentrations was "unexpected."

> Even if, assuming arguendo, that the present solutions are prima Jacie obvious in view of the cited art, the Examiner is requested to consider that the ability of aqueous GRB solutions to "self-sterilize" at those concentrations and pH's to yield solutions that are chemically stable and resistant to microbial growth is an unexpected result which is sufficient to rebut any prima facie case of obviousness established by the invention. Examiner Fay and the present Examiner recognized this unexpected and beneficial property of GRB when they allowed the claims of parent application Ser. No. 09/497,570 which issued as U.S. Patent No. 6,472,431 (copy enclosed). Therefore, withdrawal of this rejection is appropriate and is respectfully requested.

('219 patent application, Feb. 21, 2007, Amendment and Response). The applicants' observation that higher concentrations of sodium oxybate are "resistant to microbial growth" without preservatives cannot create novelty. This observation is not patentable: Laws of nature are not patentable. *Mayo Collaborative Serv. v. Prometheus Labs., Inc.*, 132 S.Ct. 1289 (2012) (citing *Diamond v. Diehr*, 450 U. S. 175, 185 (1981)); *see also Bilski v. Kappos*, 130 S.Ct. 3218, 3238 (2010).

The resistance to microbes and chemical stability of the composition of aqueous solution of 350-750 mg/mL sodium gamma-hydroxybutyrate, and malic acid, citric acid, acetic acid, lactic acid, carbonic acid, formic acid, propionic acid or tartaric acid, as a pH adjusting agent, with a pH of 6-7.5 are inherent properties of the composition, which itself is obvious in view of the prior art. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); *see also Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."). By the patentees' own admission, concentrations of GHB above 150 mg/mL are resistant to microbial contamination, and the '632 patent teaches a solution at 302.5 mg/mL. Based on this fact, there is no motivation to add a preservative to the solution.[15]

Furthermore, the pH and formulation for the sodium oxybate solution was the result of routine formulation work, which is described in the '219 patent itself, see Example 4. When a

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[15] In fact, there was a motivation in December 1998 not to use preservatives. *See, e.g.,* Kabara, Jon, "Preservative-Free and Self-Preserving Comsetic and Drug: Principle and Practice," Marcel Dekker, Inc. (1997), is prior art to the '889 patent under 35 U.S.C. § 102(b) based on its 1990 publication. Chapter 11, "Preservative-Free and Self-Preserving Cosmetic and Drug Products: The Future," explains that "preservative-free and self-preserving cosmetic and drug products "are now new."

person of ordinary skill is faced with "a finite number of identified, predictable solutions" to a problem and pursues "the known options within his or her technical grasp," the resulting discovery "is likely the product not of innovation but of ordinary skill and common sense." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 127 S. Ct. 1727, 1742 (2007). "Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress." *Id.* at 1741. *See, e.g., Pfizer v. Apotex*, 408 F.3d 1348 (Fed. Cir. 2007) (selection of the phosphate salt from a small, well-defined set of possible candidates was obvious because it was merely the routine optimization of a single variable using techniques common in the pharmaceutical sciences).

The '219 patent provides no specific evidence of secondary considerations of non-obviousness, and the applicants only mentioned the unexpected observation that higher concentration solutions of sodium oxybate self-sterilize during prosecution. It is the patentee's obligation to present evidence of secondary considerations, if any, to rebut a *prima facie* case of obviousness. The problem presented by the inventors was finding a way to formulate a solution of sodium oxybate in a way that maintained chemical stability and sterility. Even if the use of preservatives in an oral pharmaceutical solution was obvious, not using preservatives was also obvious. The patentees have not established that any need was met by, nor commercial success attributable to, the claimed subject matter, rather than the compound of the prior art disclosure of a sodium oxybate in an aqueous solution.

Claim 2 is directed to the pharmaceutical composition of claim 1 "wherein the aqueous solution contains about 400-650 mg/mL of sodium gamma-hydroxybutyrate." This claim narrows the range of claimed concentrations from 350-750 to 400-650, and is obvious for the same reasons claim 1 is obvious. As indicated above, the prior art '632 patent teaches 302.5 mg/mL, and there is no indication that the concentration itself was novel. The dose administrated to patients is more relevant than the concentration for the purpose of using the claimed pharmaceutical composition. The '219 patent states that concentrations above 150 mg/mL are "suitably resistant to microbial contamination" at pH ranges of 7.5. ('219 patent, col. 13, lines 38-44).

Claim 2 is directed to the pharmaceutical composition of claim 1 "wherein the pH adjusting agent is malic acid." This claim is narrows the pH adjusting agents to just malic acid, and is obvious for the same reasons claim 1 is obvious. As indicated above, the '083 patent teaches a pharmaceutical aqueous solution (not of gamma-hydroxy butyric acid) where the pH is adjusted using malic acid, acetic acid, or lactic acid, each of which is metabolisable. ('083 patent, col. 4, lines 23-32).

Claim 4 is almost identical to claim 1, but instead provides different pH adjusting agents. Instead of "malic acid, citric acid, acetic acid, lactic acid, carbonic acid, formic acid, propionic acid or tartaric acid" (claim 1), it lists "hydrochloric acid, phosphoric acid, sulphuric acid, boric acid or nitric acid" (claim 4). It would be obvious to adjust the pH of the sodium oxybate solution to a physiological pH using the claimed acids.

F. CONCLUSION

For the reasons stated above, claims 1-4 of the '219 patent are not infringed, either literally or under the doctrine of equivalents, and claims 1-4 of the '219 patent are obvious over the prior art. Par reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these patents are invalid, unenforceable or not infringed.

VII. THE '506 PATENT

A. OVERVIEW OF THE '506 PATENT

1. Specification of the '506 Patent

U.S. Patent No. 7,851,506 is directed, *inter alia*, to a method of treating various conditions responsive to gamma-hydroxybutyrate, including narcolepsy, by administering an aqueous composition of the compound on a particular schedule. The '506 patent is titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," and is assigned on its face to Jazz. The patent lists five inventors on its face: Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad, and Dayton Reardan.

According to the '506 patent, the "invention particularly relates to the field of pharmaceutical production of microbiologically resistant and chemically stable preparations or solutions of gamma-hydroxybutyrate (GHB), also known as 4-hydroxybutyrate, and the sodium salt of GHB (sodium oxybate) and other salts such as magnesium, ammonium and calcium. . . ." ('506 patent).

According to the '506 patent, GHB was known to be useful in the treatment of narcolepsy when administered as an oral solution. ('506 patent, col. 1, lines 53 - col. 2, line 24). According to the '506 patent, organic salts of GHB were known, including magnesium and calcium salts: "Organic salts and amides of GHB have been produced to reduce the physiological side effects of GHB (U.S. Pat. No. 5,380,937). Magnesium and calcium salt have been produced to reduce the hygroscopic nature of GHB or powdered forms (U.S. Pat. No. 4,393,236; British Patent No. 922,029)." ('506 patent, col. 2, lines 44-59).

The '506 patent indicates that the main problem with existing solutions of GHB was degradation and contamination.

> However, problems with the storage of GHB solutions still exist. GHB degrades into gamma-butyrolactone (GBL) and possibly other degradants in solution depending upon the pH and other factors. Also, the contamination by microorganisms in GHB solutions rapidly surpass acceptable limits, and preservatives can adversely affect the pH and thus, GHB's stability. As a chronically used product which requires high levels of drug, the volume of a non-concentrated product creates cost and handling issues. Thus, there is an immediate need for effective solutions of GHB that are stable to biological or chemical degradation.

('506 patent, col. 2, lines 48-59).

According to the '506 patent, they solved the contamination and stability problems using a pH adjusted solution resistant to microbial growth without compromising stability. ('506 patent, col. 2, line 63 – col. 3, line 16).

2. Prosecution History of the '506 Patent

The '506 patent issued from U.S. Application No. 11/777,877 ("the '877 application"), filed July 13, 2007, claiming priority to U.S. Provisional No. 60/113,745, filed December 23, 1998.

On July 13, 2007, the applicants filed their original '877 application as a divisional of the application leading to U.S. Patent No. 7,262,219. The original application contained 22 claims, including the following by way of example:

> 1. A method of treating a condition responsive to sodium gammahydroxybutyrate,
>
> comprising administering to a patient afflicted with the condition an aqueous composition comprising about 350-750 mg/mL sodium gamma-hydroxybutyrate, wherein the administrating comprises the patient taking a first dosage of about 0.1 to about 10 grams of sodium gammahydroxybutyrate.

('506 patent application, Jul. 13, 2007, Claims).

On July 14, 2008, the examiner issued a restriction requirement, stating: "This application contains claims directed to the following patentably distinct species: a) a sleep disorder, b) a drug consumption disorder, c) a reduced growth hormone level disorder and d) an increase level of intracranial pressure disorder." ('506 patent application, Jul. 14, 2008, Office Action).

On July 31, 2008, the applicants requested reconsideration of the examiner's restriction requirement, but elected claims 1-5, 8-19, and 22. ('506 patent application, Jul. 31, 2008, Response to Election/Restriction Filed).

On November 6, 2008, the examiner issued an office action, rejecting the claims under 35 U.S.C. § 112:

> Claims 1-2,8-16 and 22 are rejected under 35 U.S.c. 112, first paragraph, because the specification, while being enabling for treating the specific condition responsive to sodium gamma-hydroxybutyrate (i.e., apnea, sleep time disturbances, narcolepsy, catalepsy, etc ...) with the administration of sodium gamma-hydroxybutyrate, does not reasonably provide enablement for "treating a condition responsive to sodium gamma-hydroxybutyrate" with the administration of gamma-hydroxybutyrate. The specification does not enable any person skilled in the art to which it pertains, or with which

> it is most nearly connected, to practice the invention commensurate in scope with these claims.

('506 patent application, Nov. 6, 2008, Non-final Rejection). The examiner also rejected the claims § 103(a): "Claims 1-5,8-19 and 22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gessa et al. (US 4,983,632) in view of Scrima et al. (Sleep, vol. 13, No. 6, 1990, pp. 479-490)." *Id.*

On April 6, 2009, the applicants amended its claims and responded. ('506 patent application, Apr. 6, 2009, Response).

> 14. (Currently Amended) A method of treating a condition responsive to sodium gammahydroxybutyrate, comprising orally administering to a patient afflicted with the condition an aqueous composition comprising a first dose of [0.1] J. to 10 grams of sodium gammahydroxybutyrate within an hour prior to initial sleep onset and an aqueous composition comprising a second dose of [0.1] 3 to 10 grams within 2 to 5 hours following initial sleep onset, 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 applicants amended their claims to avoid the lack of enablement rejection. The applicants traversed the obviousness rejection, stating: "The basis of the presently claimed method is the discovery that sodium gammahydroxybutyrate can be administered orally, in two doses of 3-10 grams each, to effectively treat a patient afflicted with said conditions responsive to sodium gamma-hydroxybutyrate treatment." ('506 patent application, Apr. 6, 2009, Response).

On July 10, 2009, the examiner issued a final rejection. ('506 patent application, Jul. 10, 2009, Final Rejection). The examiner asserted that the pending claims were obvious: "Claims 1-5,8-19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gessa et al. (US 4983632) in view of Scrim a et al. (Sleep, vol. 13, No.6, 1990, pp. 479-490)." *Id.*

On January 11, 2010, the applicants responded to the final rejection. ('506 patent application, Jan. 11, 2010, Response).

> 14. (Currently Amended) A method of treating a condition responsive to sodium gammahydroxybutyrate, comprising orally administering to a patient afflicted with the condition an aqueous composition comprising a first dose of about 4.5 [[3]] 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 [[3]] to about 10 grams within 2 to 5 hours following initial sleep onset, 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.

('506 patent application, Jan. 11, 2010, Amendment). The applicants also filed a request for continued examination.

On February 3, 2010, the examiner issued a non-final rejection. ('506 patent application, Feb. 3, 2003, Non-final Rejection). The examiner rejected the claims as obvious: "Claims 14 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gessa et al. (US 4983632) in view of Scrim a et al. (Sleep, vol. 13, No.6, 1990, pp. 479-490)." *Id.*

On July 28, 2010, the applicants amended their claims and responded. ('506 patent application, Jul. 28, 2010, Amendment after Non-final Rejection).

> 14. (Currently Amended) A method of treating a condition responsive to sodium gammahydroxybutyrate, 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, cataplexy, sleep paralysis, hypnagogic hallucination, sleep arousal, insomnia, and nocturnal myoclonus.

According to the applicant, the new recitation of the dose concentration distinguished the prior art.

> Applicants respectfully traverse the rejection, but to facilitate prosecution, Applicants amend claim 14 to recite a concentration of sodium gamma-hydroxybutyrate (NaGHB) in the first and the second aqueous composition as being greater than about 500 mg/mL of NaGHB. Applicants believe that claims 14 and 19 are now in condition for allowance.
>
> In the Office Action dated Feb. 3, 2010, the Examiner states (page 4) that Scrima discloses compositions comprising about 302.5 mg/mL in Examples 1-2, and about 740 mg/mL NaGHB in jelly form in Example 5. Applicants respectfully draw the Examiner's attention to an error he has made in calculating the concentration of N aGHB in Example 5. While Examples 1 and 2 specify "purified water to make up to", Example 5 specifies 100 gm of jelly including 30.25 gm of gamma-hydroxy butyric acid, sodium salt and 40.75 gm of purified water. The amount of water (40.74 gm) specified in Example 5 is not the total volume of the jelly, but is the actual amount of water that is added to the composition which comprises 100 gm (about 100 mL) of jelly. Thus, the NaGHB content of the jelly of Scrima's Example 5 is about 300 mg/mL, not 740 mg/mL.

> Applicants believe that the Examiner's miscalculation likely arose through the incorrect assumption that 40.75 gm was the total quantity of jelly including the 30.25 gm of NaGHB.
>
> This being the case, Scrima nowhere discloses a composition comprising more than about 500 mg/mL NaGHB. Furthermore Gessa, while not specifying any concentrations, states that doses of GHB are given in an orange-flavored drink, not in any concentrated form. Thus, neither cited document discloses the use of a concentration of NaGHB in water of greater than about 500 mg/mL for use in treatment of any condition. Also, neither document suggests the use of higher concentrations of NaGHB to provide stability to the solution or for any other purpose. Gessa suggests only the use of relatively large volumes of a flavored fluid for administration of a relatively dilute solution of GHB, and Scrima does not disclose or suggest any concentration of GHB salt content of greater than 50% by weight (500 mg/mL).
>
> Applicants believe that the use of the highly concentrated solutions of NaGHB is both novel and inventive for the treatment of malconditions including narcolepsy. The higher concentrations are well-suited for storage of the medicinal composition by patients, the compositions not being susceptible to bacterial growth as might occur over prolonged storage in a home medicine cabinet. It is expected that narcolepsy sufferers would need regular access to this medication, and that it would be prescribed for home administration. Neither Scrima nor Gessa address this issue, and neither perceives the advantages identified to by the present inventor to use of the inventive method herein. Therefore, it would not be obvious to the person of ordinary skill to use a composition such as is claimed herein for treatment of malconditions such as narcolepsy.

('506 patent application, Jul. 28, 2010, Response).

On October 8, 2010, the examiner issued a notice of allowance, with the following reasons for allowance:

> The present claims, claims 14, 19 and 20, are directed to, in general, a method for treating a condition responsive to sodium gamma-hydroxybutyrate, such as narcolepsy, which includes the administration of aqueous compositions comprising concentrations of sodium gammahydroxybutyrate of greater than about 500 mg/ml., (e.g., *see* claim 14). Support for this concentration may be found in the present specification at page 6 of the present specification, lines 8+ where concentrations of gamma hydroxybutyrate of greater than 500 mg/mL is disclosed. While the sodium salt is not specifically disclosed there, the concept that the sodium salt may be employed for the base compound may be found throughout the specification, (e.g., page 9 of the present specification, lines 29+).

> In the art of record applied under 35 U.S.C. § 103, there simply is no suggestion or teaching or common sense dictate for employing sodium gamma-hydroxybutyrate may be found. Thus, one or ordinary skill in the art would not have found it to have been obvious to employ sodium gamma-hydroxybutyrate in the amount claims and thus the present claims reciting such concentration, i.e., claims 14, 19 and 20, are in condition for allowance.

('506 patent application, Oct. 8, 2010, Response).

On December 14, 2010, the '506 patent issued with 3 claims.

3. Claims of the '506 Patent

The '506 patent issued with the following claims:

#	Claims of the '506 Patent
1	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, cataplexy, sleep paralysis, hypnagogic hallucination, sleep arousal, insomnia, and nocturnal myoclonus.
2	The method of claim 1, wherein the condition is narcolepsy.
3	The method of claim 1, wherein the condition is a cataplexy.[16]

B. LEVEL OF SKILL IN THE ART OF THE '506 PATENT

The subject matter of the '506 patent falls within the field of pharmaceutical compositions and methods for treating narcolepsy and cataplexy using sodium oxybate. Depending on the claim, the person of ordinary skill in this field would be a pharmacist, formulator, chemist, organic chemist, process chemist, physical chemist, or medicinal chemist. Such an individual would have a Masters or Ph.D. degree and several years of experience in the field, the amount of post-graduate experience depending upon the level of formal education. *E.I. DuPont de Nemours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), *aff'd*, 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein and would have the capability to draw inferences from them.

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16 This claim was corrected, wherein the "cataplexy" replaced "catalepsy."

C. CLAIM CONSTRUCTION OF THE '506 PATENT

One of ordinary skill in the art and a court would interpret the claims of the '506 patent according to their plain and ordinary meaning unless otherwise specified herein. On September 14, 2012, the U.S. District Court for the District of New Jersey issued an claim construction order for terms in the '506 patent in the case of *Jazz Pharm. Inc. v. Roxane Labs, Inc.*, No. 10-6108, D.I. 151 (D.N.J. Sept. 14, 2012). The district court's constructions for several relevant terms are briefly discussed below. Par includes these constructions for informational purposes only and reserves its right to challenge these constructions.

In the *Jazz* case, the parties disputed the meaning of the terms "about" and "dose" in the *Jazz* litigation, but the district court found that no construction of either term was necessary. *Jazz Pharm. Inc. v. Roxane Labs, Inc.*, No. 10-6108, D.I. 151, at *14-16, *22-24 (D.N.J. Sept. 14, 2012).

D. NONINFRINGEMENT OF THE '506 PATENT

Par's Sodium Oxybate Solution does not literally infringe claim 1 of the '506 patent because Par does not treat any condition with a dose of aqueous solution with a concentration of 500 mg/mL. Claim 1 is directed to treating a condition with two doses of aqueous composition of sodium gamma-hydroxybutryate, each of which has a concentration "of greater than about 500 mg/mL." There is no mention in the claims of diluting the 500 mg/mL before administration. Par's label, on the other hand, requires dilution of the 500 mg/mL before administration.

> **2.2 Important Administration Instructions**
>
> Take the first dose of Xyrem at least 2 hours after eating because food significantly reduces the bioavailability of sodium oxybate.
>
> Prepare both doses of Xyrem prior to bedtime. Prior to ingestion, each dose of Xyrem should be diluted with approximately ¼ cup (approximately 60 mL) of water in the empty pharmacy vials provided. Patients should take Xyrem while in bed and lie down immediately after dosing as Xyrem may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking Xyrem, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night. Rarely, patients may take up to 2 hours to fall asleep. Therefore, patients should remain in bed following ingestion of the first dose, and should not take the second dose until 2.5 to 4 hours later. Patients may need to set an alarm to awaken for the second dose.

Because Par's proposed product label instructs to dilute the solution before administration, the 500 mg/mL itself is not administered or used to treat the claimed conditions. Furthermore, there is no infringement under the doctrine of equivalents because the '506 patent applicants included the 500 mg/mL limitation to avoid the prior art during prosecution. The doctrine of prosecution history estoppel precludes *Jazz* from claiming any range of equivalents to diluting the 500 mg/mL solution. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*,

493 F.3d 1368, 1376 (Fed. Cir. 2007); *see also Litton Sys., Inc. v. Honeywell, Inc.*, 140 F.3d 1449, 1458 (Fed. Cir. 1998) ("This court has acknowledged that even arguments made during prosecution without amendments to claim language – if sufficient to evince a clear and unmistakable surrender of subject matter – may estop an applicant from recapturing that surrendered matter under the doctrine of equivalents.").

Par does not induce infringement. 35 U.S.C. § 271(b). Claim 1 of the '506 patent at most covers a minimum dosing regimen of 9 g per night, e.g., 4.5 g at bedtime and 4.5 g taken 2.4-4 hours later (both of which are the lowest claimed doses). Claim 1 cannot cover the 4.5, 6, or 7.5 g nightly doses. Inducement requires direct infringement by the third party, actual or constructive knowledge by Par of the patent infringed, and the intent to induce the third party to infringe that patent. There are non-infringing uses of Par's Sodium Oxybate Solution that do not induce infringement, including the 4.5, 6, and 7g nightly doses.

E. OBVIOUSNESS OF THE '506 PATENT

1. The Scope and Content of the Prior Art

The earliest effective U.S. filing date for the '506 patent is December 23, 1998, based on the filing date for U.S. Provisional Application 60/113,745. This date is the same as that of the '889 patent. A description of the prior art can be found in section V(E)(1), above. In addition, the following reference is also prior art.

a. Mamalek 1986

Mamalek, Mortimer, Martin Scharf, Marcia Wood, "Treatment of Narcolepsy with gamma-Hydroxybutyrate. A Review of Clinical and Sleep Laboratory Findings," Sleep, Vol. 9, No. 1 (1986) at 287 ("Mamalek"), is prior art to the '506 patent under 35 U.S.C. § 102(b) based on its 1986 publication. This reference was not considered by the examiner.

> The cases of 48 patients who have been taking GHB for 6 months to 9 years are now being followed in Toronto. The cases of other patients who were started on this treatment in Toronto are being followed by their physicians in other parts of Canada and the United States. These patients, 21 men and 27 women, range in age from 17 to 71 years. All combine stimulants during the day with GHB at night. **The commonest schedule is GHB about 30 mg/kg or 2.25-3 g twice each night** and a single long-acting 15 mg dexedrine dospan in the morning. Patients are encouraged to nap late in the afternoon when the dexedrine is wearing off to produce a more alert evening, but many do not do so regularly. **The use of GHB in this patient series ranges from 4.5 to 9 g/night**.

Id. at 287.

2. Application of the Prior Art

Claim 1 is directed to a method of treating conditions (including narcolepsy) using two doses of 4.5-10 grams of sodium gamma-hydroxybutyrate—one administered at bedtime, and

another 2-5 hours later—in the form of a 500 mg/mL aqueous solution. This would have been obvious in December 1998, because aqueous solutions of sodium gamma-hydroxybutyrate were known ('632 patent), and it methods for using a dual dose treatment at bedtime was known (Scharf).[17] The only difference between the prior art and claim 1 is the 4.5 gram minimum dose claimed, where the prior art taught at least 3 grams, but higher doses are taught by Scrima 1990.

Claim 1 of the '506 Patent	Scharf + '632 patent + Scrima 1990
A method of treating a condition responsive to sodium gamma-hydroxybutyrate, comprising	Scharf teaches a method of treating narcolepsy.
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	Scharf teaches orally administering to a patient afflicted with the condition an aqueous composition comprising a first dose of 3 grams of sodium gamma-hydroxybutyrate within an hour prior to initial sleep onset (i.e., bedtime). Scharf teaches orally administering an aqueous composition comprising a second dose of 3 grams within 2 to 5 hours following initial sleep onset (more specifically, 4 hours). Scrima teaches that "[h]igher doses of GHB, or longer treatment periods than were used in the present experiment may be needed to cause a more pronounced and subjectively noticeable decrease in sleepiness in narcolepsy patients." (Scrima at 488, first full paragraph).
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	Scharf teaches an aqueous composition of sodium gamma-hydroxybutyrate of 50 mg/mL. Example 2 of the '632 patent teaches 6.05 g of "gamma-hydroxy butyric acid, sodium salt," in an aqueous solution of 20 mL, which is a concentration of 302.5 mg/mL.
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.	Scharf teaches a method of treating narcolepsy.

For the '506 patent, the examiner allowed the claims after the applicants amended their claims to require the 500 mg/mL concentration, and provided the following reasons for allowance:

> In the art of record applied under 35 U.S.C. § 103, there simply is no suggestion or teaching or common sense dictate for employing sodium gamma-hydroxybutyrate may be found. Thus, one or ordinary skill in the art would not have found it to have been obvious to employ sodium

[17] Broughton and Scrima also teach twice nightly administrations of sodium gamma-hydroxybutyrate.

> gamma-hydroxybutyrate in the amount claims and thus the present claims reciting such concentration, i.e., claims 14, 19 and 20, are in condition for allowance.

('506 patent application, Oct. 8, 2010, Response). According to the examiner, the basis for the patent was not the method of treating narcolepsy or the amounts for the administration, but rather, the 500 mg/mL concentration.

The claimed "about" 500 mg/mL concentration is obvious, however, over the prior art 302.5 mg/mL concentration in the '632 patent.[18] There is no indication that the specified "about 500 mg/mL" concentration range itself was novel, and the dose administrated to patients is more relevant than the concentration for the purpose of using the claimed pharmaceutical composition. The total daily dose claimed by the '506 patent (9 gram to 20 grams) overlaps with the prior art disclosure of 9 g/night. *See also Mamalek* at 287.[19] Furthermore, because concentrated oral solutions were known—i.e., a concentrated liquid dosage form to be diluted before administration were known—if the target concentration of NaGHB is around 302.5 mg/mL, then in a concentrated solution for later dilution, would naturally be even higher.[20]

The '506 patent provides no specific evidence of secondary considerations of non-obviousness, and the applicants did not rely on unexpected results to overcome an obviousness rejection during prosecution. It is the patentee's obligation to present evidence of secondary considerations, if any, to rebut a *prima facie* case of obviousness. In earlier patents within the same family as the '506 patent, the applicants argued that they unexpectedly found that higher concentration of sodium oxybate was self-sterilizing, but this property is an inherent law of nature. *Mayo Collaborative Serv. v. Prometheus Labs., Inc.*, 132 S.Ct. 1289 (2012) (citing *Diamond v. Diehr*, 450 U. S. 175, 185 (1981); *see also Bilski v. Kappos*, 130 S.Ct. 3218, 3238 (2010); *Diamond v. Chakrabarty*, 447 U. S. 303, 309 (1980).[21] The problem presented by the inventors was finding a method for treating narcolepsy using sodium oxybate. Scharf, Scrima 1990, and Broughton teach such a method. The patentees have not established that any need was

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18 Although the New Jersey District Court in the *Jazz* case decided not to construe the term "about," the patent states: "As used herein, the term 'about' generally means within about 10-20%." ('506 patent, col. 4, lines 8-9) A 10% decrease results in 450 mg/mL and a 20% decrease results in 400 mg/mL.

19 The '506 patent is further invalid for lack of enablement for the full scope of the claimed dosage (9 grams to 20 grams) because daily doses above 9 grams are not shown to be effective in treating the claimed ailments. The Xyrem® label explicitly states: "Doses higher than 9 g per night have not been studied and should not ordinarily be administered." (Xyrem® label at 2.)

20 The "oral solution" is a common dosage form for drugs. "Oral solutions may be formulated for direct oral administration to the patient or they may be dispensed in a more concentrated form that must be diluted prior to administration." USP <1151>.

21 The '506 patent states that concentrations above 150 mg/mL are "suitably resistant to microbial contamination" at pH ranges of 7.5. ('506 patent, col. 12, lines 28-35.) *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); *see also Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention.").

met by, nor commercial success attributable to, the claimed subject matter, rather than the compound of the prior art disclosure of a sodium oxybate in an aqueous solution.

Claim 1 is additionally obvious over the '632 patent and Scrima 1990.

Claim 1 of the '506 Patent	'632 patent + Scrima 1990
A method of treating a condition responsive to sodium gamma-hydroxybutyrate, comprising	Scrima teaches a method of treating narcolepsy.
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	Example 2 of the '632 patent teaches 6.05 g of "gamma-hydroxy butyric acid, sodium salt," in an aqueous solution of 20 mL. Scrima teaches administering to subjects 25 mg/kg of GHB (not NaGHB) at "h.s." and 3 hours later.[22] Depending on the weight of the subject, this may be less than 4.5 grams. Scrima, however, teaches that "[h]igher doses of GHB, or longer treatment periods than were used in the present experiment may be needed to cause a more pronounced and subjectively noticeable decrease in sleepiness in narcolepsy patients." (Scrima at 488, first full paragraph).
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	Example 2 of the '632 patent teaches 6.05 g of "gamma-hydroxy butyric acid, sodium salt," in an aqueous solution of 20 mL, which is a concentration of 302.5 mg/mL.
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.	Scrima teaches a method of treating narcolepsy.

Claim 2 is directed to the method of claim 1 "wherein the condition is narcolepsy." This claim is obvious for the same reasons claim 1 is obvious. As indicated above, Scharf teaches a method of treating narcolepsy. The '506 patent itself acknowledges that a "good safety profile for GHB consumption, when used long term for treatment of narcolepsy, has been reported." ('506 patent, col. 1, lines 53 - col. 2, line 24).

Claim 3 is directed to the method of claim 1 "wherein the condition is cataplexy." "Cataplexy" is not defined in the specification of the '506 patent, but generally refers to a sudden loss of muscle tone and strength, which can be associated with narcolepsy. The use of sodium gamma-hydroxybutyrate to treat cataplexy associated with narcolepsy was known in the art. *See also Mamalek* at 287.

[22] "h.s." means "hora somni," i.e., before sleep, at bedtime.

F. CONCLUSION

For the reasons stated above, claims 1-3 of the '506 patent are obvious over the prior art, and claims 1-3 are not infringed, either literally or under the doctrine of equivalents. Par reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these patents are invalid, unenforceable or not infringed.

VIII. THE '275 PATENT

A. OVERVIEW OF THE '275 PATENT

1. Specification of the '275 Patent

U.S. Patent No. 8,324,275 is directed, *inter alia*, to a method of treating various conditions responsive to gamma-hydroxybutyrate, including narcolepsy, by administering an aqueous composition of the compound on a particular schedule. The '275 patent is titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," and is assigned on its face to Jazz. The patent lists five inventors on its face: Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad, and Dayton Reardan.

According to the '275 patent, the "invention particularly relates to the field of pharmaceutical production of microbiologically resistant and chemically stable preparations or solutions of gamma-hydroxybutyrate (GHB), also known as 4-hydroxybutyrate, and the sodium salt of GHB (sodium oxybate) and other salts such as magnesium, ammonium and calcium. . . ." ('275 patent).

According to the '275 patent, GHB was known to be useful in the treatment of narcolepsy when administered as an oral solution. ('275 patent, col. 1, lines 59 - col. 2, line 16). According to the '275 patent, organic salts of GHB were known, including magnesium and calcium salts: "Organic salts and amides of GHB have been produced to reduce the physiological side effects of GHB (U.S. Pat. No. 5,380,937). Magnesium and calcium salt have been produced to reduce the hygroscopic nature of GHB or powdered forms (U.S. Pat. No. 4,393,236; British Patent No. 922,029)." ('275 patent, col. 2, lines 48-52).

The '275 patent indicates that the main problem with existing solutions of GHB was degradation and contamination.

> However, problems with the storage of GHB solutions still exist. GHB degrades into gamma-butyrolactone (GBL) and possibly other degradants in solution depending upon the pH and other factors. Also, the contamination by microorganisms in GHB solutions rapidly surpass acceptable limits, and preservatives can adversely affect the pH and thus, GHB's stability. As a chronically used product which requires high levels of drug, the volume of a non-concentrated product creates cost and handling issues. Thus, there is an immediate need for effective solutions of GHB that are stable to biological or chemical degradation.

('275 patent, col. 2, lines 52 – 62).

According to the '275 patent, they solved the contamination and stability problems using a pH adjusted solution resistant to microbial growth without compromising stability. ('275 patent, col. 2, line 65 – col. 3, line 20).

2. Prosecution History of the '275 Patent

The '275 patent issued from U.S. Application No. 13/446,892 ("the '892 application"), filed April 13, 2012, claiming priority to U.S. Provisional No. 60/113,745, filed December 23, 1998.

On April 13, 2012, the applicants filed their '892 application as a continuation of abandoned Application No. 12/913,644, which itself is a continuation of the application leading to U.S. Patent No. 7,851,506. The original application contained 2 claims, including the following by way of example:

> 1. A method of 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 10 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 10 4.5 to about 10 grams of sodium gamma-hydroxybutyrate; (iii) orally administering to a patient having narcolepsy the first dose within an hour prior to initial sleep onset; and (iv) orally administering to the patient having narcolepsy the second dose within 2.5 to 4 hours following initial sleep onset.

('275 patent application, Apr. 13, 2012, Claims).

On June 28, 2012, the examiner issued a non-final rejection, rejecting the claims as obvious over the prior art: "Claims 1 and 2 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Broughton et al. ("The Treatment of Narcolepsy-Cataplexy with Nocturnal Gamma- Hydroxybutyrate", Can.J.Neurol. Sci. , 1979, vol. 6, no. 1, pp. 1-6; cited in IDS) in view of Gessa et al., EP 0 344704 (cited in PTO-892)." ('275 patent application, June 28, 2012, Application). The examiner also rejected the claims for obviousness type double patenting. On August 24, 2012, the applicants filed a terminal disclaimer to avoid the obviousness type double patenting.

On August 24, 2012, the applicants amended their claims and responded to the rejections.

> Claims 1 and 2 are rejected under 35 U.S.c. 103(a) as being unpatentable over Broughton et al. ("The Treatment of Narcolepsy-Cataplexy with Nocturnal Gamma-Hydroxybutyrate", Can. l. Neurol. Sci., 1979, vol. 6, no. 1, pages 1-6; cited in IDS) in view of Gessa et al., EPO 344704 (cited in PTO-892). Applicants respectfully traverse the rejection

because Broughton et al. and Gessa et al., alone or in combination, do not teach or suggest the claimed methods, and further, because the prior art provides a teaching away from the claimed methods, as explained below. . . .

The methods of the present claims recite **relatively high concentrations of GHB (about 500 mg/mL), relatively high doses of GHB (minimum of 6.0 g of GHB in two doses (claim 2) to 9.0 g ofGHB in two doses (claim 1))), and less frequent administration ofGHB over the course of one night (two doses only)**. Broughton et al. and Gessa et al., alone or in combination, do not teach or suggest such high doses of GHB, such high concentrations of GHB, or such decreased frequency of administration of GHB for treating cataplexy or daytime sleepiness in a patient diagnosed with narcolepsy, as explained below.

The primary reference, Broughton et al., discloses that multiple low dosing of GHB throughout the night subjectively improves the quality of night sleep and diminishes daytime attacks of sleep and cataplexy in certain narcoleptic patients. In particular, Broughton et al. discloses an early study of the treatment of 16 patients with gamma-hydroxybutyrate (GHB) in an "attempt to 'normalize' the nocturnal sleep patterns of patients with narcolepsy and cataplexy." (Page 2). The patients were given relatively low doses of GHB (1.5 - 2.25 g followed by further multiple doses containing 1.0 - 1.5 g per dose for every reawakening, if at least 2.5 hours had passed since the previous dose) which, after dilution, were given at concentrations of 150 – 225 mg/mL. The GHB was given in multiple divided unit doses, 2 - 3 x/night. Eight of the patients received two doses, for a total dose of 3.75 g. Seven patients received three doses, affording a total dose of 4.5 - 6.25 g. *See* page 2, Co1. 3; Table 1. Apart from one patient, who took only a single bedtime dose, "the subjective quality of night sleep improved in all patients and the number of irresistible daytime attacks of sleep and cataplexy diminished" according to the publication (Abstract).

In contrast to Broughton et al., the present claims recite higher doses and less frequent administration of GHB. In particular, the present claims recite diluting an aqueous solution comprising 500 mg/mL GHB to provide a first and a second dose, each dose containing about 4.5 - 9 g (claim 1) or 3 - 9 (claim 2) g of GHB. One dose is administered prior to initial sleep onset and the second dose is administered within 2.5 - 4 hours following initial sleep onset. Therefore, **the patient receives a minimum of 6.0 g of GHB in two doses (claim 1) to 9.0 g of GHB in two doses (claim 2) over the course of one night**. As recited by claims 3 and 4, each diluted dose contains about 50 mg/mL to about 150 mg/mL, or about 50 mg/mL to about 75 mg/mL GHB, concentration ranges that are substantially lower than those prepared by Broughton et al., that contained 150 - 225 mg/mL (page 2, co1. 3). . . .

> Gessa et al does not cure the defects of Broughton et al. . . .
>
> **While Gessa et al discloses a "typical dose" for a GHB salt can be as high as 0.1 g/Kg or about 6 - 8.5 g, e.g., two doses of 3 - 4.25 g/day, the preferred dose is disclosed to be much lower, e.g., 0.05 g/Kg, as discussed above.** Further, the doses disclosed in Gessa et al. are to "release" an alcoholic from "ethyl alcohol consumption" (claim 1), not to treat an otherwise healthy individual with narcolepsy and/or cataplexy.

('275 patent application, Aug. 24, 2012, Responses (emphasis added)).

On October 3, 2012, the examiner issued a notice of allowance for the claims, stating: "Applicant's arguments, filed August 24, 2012, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn." ('275 patent application, Oct. 3, 2012, Responses).

3. Claims of the '275 Patent

The '275 patent issued with the following claims:

#	Claims of the '275 Patent
1	A method of 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; and (iv) orally administering to the patient having narcolepsy the second dose within 2.5 to 4 hours following initial sleep onset.
2	A method of 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 3 to about grams of sodium gamma-hydroxybutyrate; (ii) dilution an aqueous solution comprising about 500 mg/mL of sodium gamma-hydroxybutyrate with an aqueous medium to provide a second dose of about 3 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; and (iv) orally administering to the patient having narcolepsy the second dose within 2.5 to 4 hours following initial sleep onset.
3	The method of claim 1 or 2 wherein each dose contains about 50-150 mg/mL of sodium gamma-hydroxybutyrate.
4	The method of claim 3 wherein each dose contains about 50-75 mg/mL of sodium gamma-hydroxybutyrate.

B. LEVEL OF SKILL IN THE ART OF THE '275 PATENT

The subject matter of the '275 patent falls within the field of pharmaceutical compositions and methods for treating narcolepsy and cataplexy using sodium oxybate.

Depending on the claim, the person of ordinary skill in this field would be a pharmacist, formulator, chemist, organic chemist, process chemist, physical chemist, or medicinal chemist. Such an individual would have a Masters or Ph.D. degree and several years of experience in the field, the amount of post-graduate experience depending upon the level of formal education. *E.I. DuPont de Nemours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), *aff'd*, 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein and would have the capability to draw inferences from them.

C. CLAIM CONSTRUCTION OF THE '275 PATENT

One of ordinary skill in the art and a court would interpret the claims of the '275 patent according to their plain and ordinary meaning unless otherwise specified herein. On September 14, 2012, the U.S. District Court for the District of New Jersey issued an claim construction order for terms that appear in the '275 patent in the case of *Jazz Pharm. Inc. v. Roxane Labs, Inc.,* No. 10-6108, D.I. 151 (D.N.J. Sept. 14, 2012). The '275 patent was not at issue in the *Jazz* case when the claim construction order issued. The district court's constructions for several relevant terms are briefly discussed below. Par includes these constructions for informational purposes only and reserves its right to challenge these constructions.

In the Jazz case, the parties disputed the meaning of the terms "about" and "dose" in the *Jazz* litigation, but the district court found that no construction was necessary. *Jazz Pharm. Inc. v. Roxane Labs, Inc.,* No. 10-6108, D.I. 151, at *14-16, *22-14 (D.N.J. Sept. 14, 2012).

D. NONINFRINGEMENT OF THE '275 PATENT

Par does not directly infringe the claims of the '275 patent because it does not use the product to treat, *inter alia*, narcolepsy.

Par also does not induce infringement. 35 U.S.C. § 271(b). Claim 1 of the '275 patent at most covers a minimum dosing regimen of 9 grams per night, e.g., 4.5 g at bedtime and 4.5 g taken 2.4-4 hours later (both of which are the lowest claimed doses), whereas Xyrem®'s label indicates a starting dose of 4.5 mg/mL. Claim 1 cannot cover the 4.5, 6, or 7.5 g nightly doses. Similarly, claim 2 of the '275 patent at most covers a minimum dosing regimen of 6 grams. Par does not infringe under § 271(b) because the Par has a good faith belief that the '275 patent is invalid, which negates the requisite intent for induced infringement. *Commil USA, LLC v. Cisco Systems, Inc.*, 720 F.3d 1361, 1364 (Fed. Cir. Jun. 25, 2013) ("we find that Cisco's evidence of a good-faith belief of invalidity may negate the requisite intent for induced infringement.").

E. OBVIOUSNESS OF THE '275 PATENT

1. The Scope and Content of the Prior Art

The earliest effective U.S. filing date for the '275 patent is December 23, 1998, based on the filing date for U.S. Provisional Application 60/113,745. This date is the same as that of the '889, '219, and '506 patents. A description of the prior art can be found in sections V(E)(1) and VI(E)(1), above.

2. Application of the Prior Art

Claim 1 is directed to a method of treating conditions associated with narcolepsy using two doses of 4.5-9 grams of sodium gamma-hydroxybutyrate—one administered at bedtime, and another 2-4 hours later—in the form of a diluted 500 mg/mL aqueous solution. This would have been obvious in December 1998, because diluted aqueous solutions of sodium gamma-hydroxybutyrate were known ('632 patent), and methods for using a dual dose treatment at bedtime were known (Scharf).[23] The only difference between the prior art and claim 1 is the 4.5 gram minimum dose claimed, where the prior art taught at least 3 gram, but higher doses are taught by Scrima 1990.

Claim 1 of the '275 Patent	Scharf + '632 patent + Scrima 1990
A method of treating cataplexy or daytime sleepiness in a patient who has been diagnosed with narcolepsy, comprising:	Scharf teaches a method of treating narcolepsy.
(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;	Scharf teaches orally administering to a patient afflicted with the condition an aqueous composition comprising a first dose of 3 grams of sodium gamma-hydroxybutyrate within an hour prior to initial sleep onset (i.e., bedtime). As mentioned above, Mamalek teaches total daily doses of 9 g/night. *See also* Mamalek at 287
(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;	Scharf teaches orally administering an aqueous composition comprising a second dose of 3 grams within 2 to 5 hours following initial sleep onset (more specifically, 4 hours). Scrima teaches that "[h]igher doses of GHB, or longer treatment periods than were used in the present experiment may be needed to cause a more pronounced and subjectively noticeable decrease in sleepiness in narcolepsy patients." (Scrima at 488, first full paragraph).
(iii) orally administering to a patient having narcolepsy the first dose within an hour prior to initial sleep onset; and	Although Scharf teaches an aqueous composition of sodium gamma-hydroxybutyrate of 50 mg/mL, Example 2 of the '632 patent teaches 6.05 g of "gamma-hydroxy butyric acid, sodium salt," in an aqueous solution of 20 mL, which is a concentration of 302.5 mg/mL.
(iv) orally administering to the patient having narcolepsy the second dose within 2.5 to 4 hours following initial sleep onset.	

The examiner allowed the claims in view of the applicants' arguments distinguishing Broughton and the '632 patent. In short, the applicants argued:

> The methods of the present claims recite relatively high concentrations of GHB (about 500 mg/mL), relatively high doses of GHB (minimum of 6.0 g of GHB in two doses (claim 2) to 9.0 g of GHB in two doses (claim 1))),

[23] Broughton and Scrima also teach twice nightly administrations of sodium gamma-hydroxybutyrate.

> and less frequent administration of GHB over the course of one night (two doses only). Broughton et al. and Gessa et al., alone or in combination, do not teach or suggest such high doses of GHB, such high concentrations of GHB, or such decreased frequency of administration of GHB for treating cataplexy or daytime sleepiness in a patient diagnosed with narcolepsy. . .

('275 patent application, Aug. 24, 2012, Responses).

First, the less frequent administration (i.e., twice at night, once at bedtime and then another after several hours) is taught by Scharf, Mamalek, and Scrima.

Second, the claimed "about 500 mg/mL" concentration is obvious over the prior art 302.5 mg/mL concentration in the '632 patent. There is no indication that the "about 500 mg/mL" concentration itself was novel, and the dose administrated to patients is more relevant than the concentration for the purpose of using the claimed pharmaceutical composition. In fact, the claims require the 500 mg/mL concentration to be diluted, which would decrease the concentration. Claim 1 encompasses diluted doses administered to the patient of 50 mg/mL, which is necessitated by claim differentiation: Claims 3 and 4 are dependent and further require diluted ranges of "each dose contains about 50 mg/mL" to either 150 mg/mL or 75 mg/mL. Scharf teaches the use of 50 mg/mL for administration to patients. The dose in the study described by Scharf was 3 g (3,000 mg) dissolved in 2 ounces of water. One ounce of water is 29.5735 milliliters, for a concentration of 50 mg/mL. Moreover, the total daily dose claimed by the '275 patent (9 gram to 20 grams) overlaps with the prior art disclosure of 9 g/night. *See also* Mamalek at 287.[24]

Furthermore, because concentrated oral solutions were known—i.e., a concentrated liquid dosage form to be diluted before administration were known—, if the target concentration of NaGHB is around 302.5 mg/mL, then in a concentrated solution for later dilution, would naturally be even higher.[25]

The '275 patent provides no specific evidence of secondary considerations of non-obviousness. The applicants did argue during prosecution, that assuming arguendo, that the prior art teaches a prima facie case of obviousness, evidence of teaching away rebuts it. Applicants argued that high doses of sodium oxybate are toxic, which would have motivated one of ordinary skill to avoid 6 g of nightly doses. ('275 patent application, Aug. 24, 2012, Responses). This is misleading. As mentioned above, Mamalek teaches total daily doses of 9 g/night. *See also* Mamalek at 287.[26] The problem presented by the inventors was finding a method for treating

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[24] The claims are also invalid for the lack of enablement over the full scope of the claimed dosages because daily doses above 9 gram are not shown to be effective in treating the claimed ailments. The Xyrem® label explicitly states: "Doses higher than 9 g per night have not been studied and should not ordinarily be administered." (Xyrem® label at 2.)

[25] The "oral solution" is a common dosage form for drugs. "Oral solutions may be formulated for direct oral administration to the patient or they may be dispensed in a more concentrated form that must be diluted prior to administration." USP <1151>.

[26] In earlier patents within the same family as the '275 patent, the applicants argued that they unexpectedly found that higher concentration of sodium oxybate was self-sterilizing, but this property is an inherent law of nature.

narcolepsy using sodium oxybate. Scharf, Scrima, Mamalek, and Broughton teach such a method. The patentees have not established that any need was met by, nor commercial success attributable to, the claimed subject matter, rather than the compound of the prior art disclosure of a sodium oxybate in an aqueous solution.

Claim 1 is additionally obvious over Mamelak 1986, Broughton, and USP <1151>.

Claim 1 of the '275 Patent	Mamelak 1986 + Broughton + USP <1151>
A method of treating cataplexy or daytime sleepiness in a patient who has been diagnosed with narcolepsy, comprising:	Mamelak teaches a method of treating narcolepsy.
(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;	**500 mg/mL initial dose** – Broughton teaches an administered dose of around 225 mg/mL, e.g., 1.0-1.5 gm/10-15 mL. Diluting a concentrated aqueous solution dosage form was known. USP <1151>. Therefore, if the target diluted concentration, is 225 mg/mL, the concentrated concentration would be higher, and it would be obvious to started with concentrations of 500 mg/mL, among other high concentrations.
(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;	**Twice Daily** – Mamelak teaches a twice daily schedule of administering between 2.25-3 gram at night, and in one set of patients, the GHB "ranges from 4.5 to 9 g/night." (Mamelak at 287) At the 9 g/night dose, the patient receives a twice daily dose of 4.5 grams which falls within claim 1. Mamelak further teaches that GHB at lower doses promotes a normal sequence of NREM and REM sleep lasting ~2 to 3 hours, which motivates the person of ordinary skill to administer the two doses within 2 to 3 hours of one another. (Mamelak 1986 at 285).
(iii) orally administering to a patient having narcolepsy the first dose within an hour prior to initial sleep onset; and	
(iv) orally administering to the patient having narcolepsy the second dose within 2.5 to 4 hours following initial sleep onset.	

Claim 2 is similar to claim 1, but slightly broader. Claim 2 is directed to a method of treating cataplexy or daytime sleepiness in a patient who has been diagnosed with narcolepsy, with similar limitations to claim 1, but instead of 4.5 to 9 grams per administration, claim 2

Mayo Collaborative Serv. v. Prometheus Labs., Inc., 132 S.Ct. 1289 (2012) (citing *Diamond v. Diehr*, 450 U. S. 175, 185 (1981); *see also Bilski v. Kappos*, 130 S.Ct. 3218, 3238 (2010); *Diamond v. Chakrabarty*, 447 U. S. 303, 309 (1980). The '275 patent states that concentrations above 150 mg/mL are "suitably resistant to microbial contamination" at pH ranges of 7.5. ('275 patent, col. 12, lines 28-35.) *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); *see also Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention.").

requires 3 to 9 grams per administration. Because claim 2 is broader than claim 1, claim 2 is obvious for the same reasons as claim 1.

Claim 3 is directed to the method of claim 1 or 2, "wherein each dose contains about 50-150 mg/mL of sodium gamma-hydroxybutyrate." Scharf teaches the use of 50 mg/mL for administration to patients. The dose in the study described by Scharf was 3 g (3,000 mg) dissolved in 2 ounces of water. One ounce of water is 29.5735 milliliters, for a concentration of 50 mg/mL. Broughton teaches an administered dose of around 67 - 225 mg/mL, e.g., 1.0-1.5 gm/10-15 mL.

Claim 4 is directed to the method of claim 3 "wherein each dose contains about 50-75 mg/mL of sodium gamma-hydroxybutyrate." As indicated for claim 3, Scharf teaches 50 mg/mL, and Broughton teaches 67 - 225 mg/mL.

F. CONCLUSION

For the reasons stated above, claims 1-4 of the '275 patent are obvious over the prior art. Par reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these patents are invalid, unenforceable or not infringed.

IX. THE '650 PATENT

A. OVERVIEW OF THE '650 PATENT

1. Specification of the '650 Patent

U.S. Patent No. 8,263,650 is directed, *inter alia*, to a method of treating various conditions responsive to gamma-hydroxybutyrate, including narcolepsy, by administering an aqueous composition of the compound on a particular schedule. The '650 patent is titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," and is assigned on its face to Jazz. The patent lists five inventors on its face: Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad, and Dayton Reardan.

According to the '650 patent, the "invention particularly relates to the field of pharmaceutical production of microbiologically resistant and chemically stable preparations or solutions of gamma-hydroxybutyrate (GHB), also known as 4-hydroxybutyrate, and the sodium salt of GHB (sodium oxybate) and other salts such as magnesium, ammonium and calcium. . . ." ('650 patent).

According to the '650 patent, GHB was known to be useful for the treatment of narcolepsy when administered as an oral solution. ('650 patent, col. 1, lines 59 - col. 2, line 18). According to the '650 patent, organic salts of GHB were known, including magnesium and calcium salts: "Organic salts and amides of GHB have been produced to reduce the physiological side effects of GHB (U.S. Pat. No. 5,380,937). Magnesium and calcium salt have been produced to reduce the hygroscopic nature of GHB or powdered forms (U.S. Pat. No. 4,393,236; British Patent No. 922,029)." ('650 patent, col. 2, lines 52-56).

The '650 patent indicates that the main problem with existing solutions of GHB was degradation and contamination.

> However, problems with the storage of GHB solutions still exist. GHB degrades into gamma-butyrolactone (GBL) and possibly other degradants in solution depending upon the pH and other factors. Also, the contamination by microorganisms in GHB solutions rapidly surpass acceptable limits, and preservatives can adversely affect the pH and thus, GHB's stability. As a chronically used product which requires high levels of drug, the volume of a non-concentrated product creates cost and handling issues. Thus, there is an immediate need for effective solutions of GHB that are stable to biological or chemical degradation.

('650 patent, col. 2, lines 56 – 67).

According to the '650 patent, they solved the contamination and stability problems using a pH adjusted solution resistant to microbial growth without compromising stability. ('650 patent, col. 3, lines 3 – 23).

2. Prosecution History of the '650 Patent

The '650 patent issued from U.S. Application No. 13/446,940 ("the '940 application"), filed April 13, 2012, although claiming priority to U.S. Provisional No. 60/113,745, filed December 23, 1998.

On April 13, 2012, the applicants filed their '940 application as a continuation of abandoned Application No. 13/182,324, which itself is a continuation of abandoned Application No. 12/913,644, which itself is a continuation of the application leading to U.S. Patent No. 7,851,506. The original application contained 18 claims, including the following by way of example:

> 1. 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.

('650 patent application, Apr. 13, 2012, Claims).

On June 11, 2012, the examiner issued an office action, rejecting all claims (1-18). ('650 patent application, Jun. 11, 2012, Non-Final Rejection). The claims were rejected for obviousness type double patenting over claims in both U.S. Patent Nos. 6,780,889 and 6,472,431. In response, the applicants filed a terminal disclaimer. *Id.*

On July 16, 2012, the examiner issued a notice of allowance. ('650 patent application, Jul. 16, 2012, Notice of Allowability). On August 16, 2012, the applicant initiated an interview with the examiner regarding the terminal disclaimers.

On September 11, 2012, the '650 patent issued with 18 claims.

3. Claims of the '650 Patent

The '650 patent issued with the following claims:

#	Claims of the '650 Patent
1	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.
2	The pharmaceutical composition of claim 1, wherein the composition has a pH of about 7.5.
3	The pharmaceutical composition of claim 1, wherein the composition has a pH of about 8.0.
4	The pharmaceutical composition of claim 1, wherein the composition has a pH of about 8.5.
5	The pharmaceutical composition of claim 1, wherein the composition additionally comprises a pH adjusting or buffering agent.
6	The pharmaceutical composition of claim 5, wherein the pH adjusting or buffering agent is an acid.
7	The pharmaceutical composition of claim 6, wherein the acid is an inorganic acid.
8	The pharmaceutical composition of claim 6, wherein the acid is an organic acid.
9	The pharmaceutical composition of claim 6, wherein the acid is selected from the group consisting of malic acid, citric acid, acetic acid, boric acid, lactic acid, hydrochloric acid, phosphoric acid, sulfuric acid, and nitric acid.
10	The pharmaceutical composition of claim 6, wherein the acid is malic acid.
11	A method of treating cataplexy or daytime sleepiness in a patient having narcolepsy comprising diluting the pharmaceutical composition of claim 1, and administering to the patient the diluted pharmaceutical composition.
12	The method of claim 11, wherein the pharmaceutical composition is administered orally.
13	The method of claim 12, wherein the pharmaceutical composition is administered orally as two consecutive single doses daily.
14	The method of claim 13, wherein the first dose is administered prior to bedtime and the second dose is administered from about 2.5 to about 4.0 hours after administration of the first dose.
15	A set comprising the pharmaceutical composition of claim 1 in one or more container means.
16	The set of claim 15, wherein the one or more container means are selected from the group consisting of a drinking cup, a dosing cup, a syringe, a pipette, a vial, an ampule, a test tube, a flask, a bottle, and a pouch syringe.
17	The set of claim 15, comprising a third container means capable of retaining a first

#	Claims of the '650 Patent
	container means, a second container means, and one or more delivery vehicles capable of administering the pharmaceutical composition to the patient.
18	The set of claim 17, wherein the first container means comprises the pharmaceutical composition, and the second container means comprises a diluent.

B. LEVEL OF SKILL IN THE ART OF THE '650 PATENT

The subject matter of the '650 patent falls within the field of pharmaceutical compositions, and in particular, aqueous solutions designed to resist microbial growth. Depending on the claim, the person of ordinary skill in this field would be a pharmacist, formulator, chemist, organic chemist, process chemist, physical chemist, or medicinal chemist. Such an individual would have a Masters or Ph.D. degree and several years of experience in the field, the amount of post-graduate experience depending upon the level of formal education. *E.I. DuPont de Nemours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), *aff'd*, 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein and would have the capability to draw inferences from them.

C. CLAIM CONSTRUCTION OF THE '650 PATENT

One of ordinary skill in the art and a court would interpret the claims of the '650 patent according to their plain and ordinary meaning unless otherwise specified herein.

On September 14, 2012, the U.S. District Court for the District of New Jersey issued an claim construction order for terms that appear in the '650 patent in the case of *Jazz Pharmaceuticals Inc. v. Roxane Laboratories Inc.,* No. 10-6108, D.I. 151 (D.N.J. Sept. 14, 2012). Because the '650 patent issued (September 2012) after the Jazz case was filed (2010), it was not specifically considered during claim construction.

The district court's constructions for several relevant terms are briefly discussed in section V(C), above. Par includes these constructions for informational purposes only and reserves its right to challenge these constructions.

D. NONINFRINGEMENT OF THE '650 PATENT

1. Par's Sodium Oxybate Solution Does Not Infringe Claims 1-18 Because It Contains a Preservative

Par's Sodium Oxybate Solution does not literally infringe claim 1 because Par's product is not "free of preservatives." Par's product contains sodium benzoate, which is described as a "preservative" in the '650 patent.

> In certain embodiments, the pharmaceutical composition may contain a preservative. 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**, methylparaben, ...

('219 patent, col. 8, lines 21-44 (emphasis added)).

Par's Sodium Oxybate Solution would not infringe under the doctrine of equivalents. Because the '650 patent specification describes "sodium benzoate" as a preservative, and claim 1 specifically precludes preservatives, Jazz should not be able to expand claim 1 to cover a composition that includes sodium benzoate. When a patentee discloses, but does not specifically claim, a particular embodiment, the doctrine of equivalents cannot be used to expand a claim to cover that non-claimed embodiment. *See Johnson & Johnston Assocs. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002).

Claims 2 – 18 depend from claim 1. Because independent claim 1 is not infringed literally or under the doctrine of equivalents, claims 2 - 18 cannot be infringed literally or under the doctrine of equivalents. *Wahpeton Canvas*, 870 F.2d at 1553.

2. Par's Sodium Oxybate Solution Does Not Infringe Claim 2 Because It Does Not Have a pH of "about 7.5."

Par's Sodium Oxybate Solution does not literally infringe claim 1 because Par's product does not comprise a composition which "has a pH of about 7.5." A person of ordinary skill in the art would interpret "about 7.5" to mean 7.5 +/- 0.1, which does not cover the pH of Par's proposed solution is 8.2 +/- 0.30.

The word "about" means "approximately," which means that the upper 7.5 limit is not confined to 7.5 exactly. Par's Sodium Oxybate Solution would not infringe under the doctrine of equivalents. Because the '650 patent specification describes other pHs, including 8.2, and claim 1 specifically claims "about 7.5," Jazz should not be able to expand claim 1 to cover a composition that includes a pH of 8.2. When a patentee discloses, but does not specifically claim, a particular embodiment, the doctrine of equivalents cannot be used to expand a claim to cover that non-claimed embodiment. *See Johnson & Johnston Assocs. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002).

3. Par's Sodium Oxybate Solution Does Not Infringe Claim 7 Because It Does Not Have an Inorganic Acid

Par's Sodium Oxybate Solution does not literally infringe claims 7 because Par's product contains no inorganic acid. Par's Sodium Oxybate Solution would not infringe under the doctrine of equivalents. Because the '650 patent specification describes other organic acids, including malic acid, Jazz should not be able to expand claim 7 to cover a composition that includes malic acid. *See Johnson & Johnston.*, 285 F.3d at 1054.

E. OBVIOUSNESS OF THE '650 PATENT (CLAIMS 1-18)

1. The Scope and Content of the Prior Art

The earliest effective U.S. filing date for the '650 patent is December 23, 1998, based on the filing date for U.S. Provisional Application 60/113,745. This date is the same as that of the '889, '219, '506, and '275 patents. A description of the prior art can be found in sections V(E)(1) and VI(E)(1) above.

2. Application of the Prior Art (Claim 1)

Sodium gamma-hydroxybutyrate is an old compound. Claim 1 is directed to a particular preservative free aqueous solution of sodium gamma-hydroxybutyrate at a concentration of about 500 mg/mL, where the pH is adjusted to 7.3-8.5. This would have been obvious in December 1998, because aqueous solutions of sodium gamma-hydroxybutyrate were known ('632 patent), and it was known that pharmaceutical solutions are normally at physiological pH ('083 patent). The claimed features, wherein the claimed composition is chemically stable and resistant to microbial growth, are inherent properties of an obvious composition.

Claim 1 of the '650 Patent	'632 patent + '083 patent
A pharmaceutical composition, comprising	The '632 patent teaches a pharmaceutical composition.
an aqueous solution of about 500 mg/mL sodium gamma-hydroxybutyrate,	Example 2 of the '632 patent teaches 6.05 g of "gamma-hydroxy butyric acid, sodium salt," in an aqueous solution of 20 mL, which is a concentration of 302.5 mg/mL. Because concentrated oral solutions were known, if the target concentration of NaGHB was 302.5 mg/mL, then in a concentrated solution for later dilution, would naturally be even higher.
wherein the composition has a pH of about 7.3 to about 8.5,	The '083 patent teaches a pharmaceutical aqueous solution (not of gamma-hydroxy butyric acid) where the pH is adjusted using malic acid., acetic acid, or lactic acid, each of which is metabolisable.[27] ('083 patent, col. 4, lines 23-32). The '083 patent teaches obtaining a solution with a physiological pH, which is 7.365.
wherein the composition is chemically stable and resistant to microbial	Both the chemical stability and resistance to microbial growth of the resulting composition of 302.5 mg/mL with a pH of about 7.3 using malic acid as a pH adjusting agent are inherent properties of the composition.

[27] Malic acid is a general-purpose acidulant, and listed as a GRAS ("Generally Recognized as Safe") substance by the FDA.

growth, and wherein the composition is free of preservatives.	The '632 patent does not require preservatives, and it would have been obvious to create, or try, a preservative free composition.

The claimed 500 mg/mL concentration is obvious over the prior art 302.5 mg/mL concentration in the '632 patent. There is no indication that the specified 500 mg/mL concentration itself was novel, and the dose administrated to patients is more relevant than the concentration for the purpose of using the claimed pharmaceutical composition. Furthermore, because concentrated oral solutions were known, if the target concentration of NaGHB is around 300 mg/mL, then in a concentrated solution for later dilution, would naturally be even higher.[28] The '650 patent states that concentrations above 150 mg/mL are "suitably resistant to microbial contamination" at pH ranges of 7.5. ('650 patent, col. 12, lines 21-24). Furthermore, the '083 patent teaches a pharmaceutical aqueous solution (not of gamma-hydroxy butyric acid) where the pH is adjusted using malic acid, acetic acid, or lactic acid, each of which is metabolisable. ('083 patent, col. 4, lines 23-32).[29] The '083 patent teaches obtaining a pharmaceutical solution with a physiological pH, which is 7.365.

The examiner allowed claim 1 without providing reasons for allowance. In related patents within the same family as the '650 patent, including the '219 patent, the applicants argued that even if the composition was prima facie obvious, the self-sterilization of the composition at the claimed concentrations was "unexpected." ('219 patent application, Feb. 21, 2007, Amendment and Response). The applicants' observation that higher concentrations of sodium oxybate are "resistant to microbial growth" without preservatives cannot create novelty. According to the Supreme Court, laws of nature are not patentable. *Mayo Collaborative Serv. v. Prometheus Labs., Inc.*, 132 S.Ct. 1289 (2012) (citing *Diamond v. Diehr*, 450 U. S. 175, 185 (1981); *see also Bilski v. Kappos*, 130 S.Ct. 3218, 3238 (2010); *Diamond v. Chakrabarty*, 447 U. S. 303, 309 (1980).

The resistance to microbes and chemical stability of the composition of aqueous solution of 500 mg/mL sodium gamma-hydroxybutyrate, at a pH of 7.3-8.5 are inherent properties of the composition, which itself is obvious in view of the prior art. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); *see also Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320 (Fed. Cir. 2004)("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."). By the patentees' own admission, concentrations of GHB above 150 mg/mL are resistant to microbial contamination ('650 patent, col. 12, lines 22-25), and the '632 patent

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28 The "oral solution" is a common dosage form for drugs. "Oral solutions may be formulated for direct oral administration to the patient or they may be dispensed in a more concentrated form that must be diluted prior to administration." USP <1151>.

29 Compositions containing malic acid were known. *See, e.g.*, U.S. Patent 4,183,916 (claim 1).

teaches a solution at 302.5 mg/mL. Based on this fact, there is no motivation to add a preservative to the solution.[30]

Furthermore, the pH and formulation for the sodium oxybate solution was the result of routine formulation work, which is described in the '650 patent itself, see Example 4. When a person of ordinary skill is faced with "a finite number of identified, predictable solutions" to a problem and pursues "the known options within his or her technical grasp," the resulting discovery "is likely the product not of innovation but of ordinary skill and common sense." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 127 S. Ct. 1727, 1742 (2007). "Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress." *Id.* at 1741. *See, e.g., Pfizer v. Apotex*, 408 F.3d 1348 (Fed. Cir. 2007) (selection of the phosphate salt from a small, well-defined set of possible candidates was obvious because it was merely the routine optimization of a single variable using techniques common in the pharmaceutical sciences).

The '650 patent provides no specific evidence of secondary considerations of non-obviousness, and the applicants did not rely on unexpected results during prosecution of the '650 patent. "[O]nce a challenger has presented a *prima facie* case of invalidity, the patentee has the burden of going forward with rebuttal evidence." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359–60 (Fed. Cir. 2007). It is the patentee's obligation to present evidence of secondary considerations, if any, to rebut a *prima facie* case of obviousness. The problem presented by the inventors was finding a way to formulate a solution of sodium oxybate in a way that maintained chemical stability and sterility. Even if the use of preservatives in an oral pharmaceutical solution was obvious, not using preservatives was also obvious. The patentees have not established that any need was met by, nor commercial success attributable to, the claimed subject matter, rather than the compound of the prior art disclosure of a sodium oxybate in an aqueous solution.

Claim 1 is additionally obvious over the combination of '632 patent, '083 patent, and the '331 patent. Whereas the '632 patent discloses oral solutions of NaGHB and the '083 patent teaches the use of malic acid, the '331 patent teaches pharmaceutical compositions containing gamma hydroxybutyrate, including the following "pharmaceutical compositions may be administered in the form of injectable compositions either as liquid solutions of suspensions" ('331 patent, col. 7, lines 17 -18). The '331 patent specifies that "the pH and exact concentration of the various components the pharmaceutical composition are adjusted according to well known parameters." ('331 patent, col. 7, lines 36-38).

3. Application of the Prior Art (Claims 2-18)

Claims 2 – 4 are directed to the composition of claim 1, wherein the pH is specifically claimed: 7.5 (claim 2), 8.0 (claim 3), and 8.5 (claim 4). The '083 patent teaches obtaining a

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[30] There was a motivation in December 1998 not to use preservatives. *See, e.g.*, Kabara, Jon, "Preservative-Free and Self-Preserving Cosmetic and Drug: Principle and Practice," Marcel Dekker, Inc. (1997), is prior art to the '889 patent under 35 U.S.C. § 102(b) based on its 1990 publication. Chapter 11, "Preservative-Free and Self-Preserving Cosmetic and Drug Products: The Future," explains that "preservative-free and self-preserving cosmetic and drug products "are not new."

solution with a physiological pH, which is 7.365. pH of 8 and 8.5 are obvious variations. The '331 patent specifies that "the pH and exact concentration of the various components the pharmaceutical composition are adjusted according to well known parameters." ('331 patent, col. 7, lines 36-38).

Claims 5 – 10 are directed to the composition of claim 1, wherein the pH is adjusted using a particular pH adjusting or buffering agent. Claims 5 – 6 and 8 – 10 encompass organic acids and malic acid in particular. If the use of malic acid in the claimed composition was obvious, claims 5-6 and 8-10 are obvious. The '083 patent teaches a pharmaceutical aqueous solution (not of gamma-hydroxy butyric acid) where the pH is adjusted using malic acid, acetic acid, or lactic acid, each of which is metabolisable. ('083 patent, col. 4, lines 23-32). Claim 7 is directed to the composition wherein the acid is an "inorganic acid," e.g., hydrochloric, nitric, phosphoric, and sulfuric. ('650 patent, col. 7, lines 10-13). Because the claimed acids are readily available, one of ordinary skill in the art would be motivated to try them, even if a formulator may first try other acids.

Claims 11 – 14 are directed to a method of treating cataplexy or daytime sleepiness in a patient having narcolepsy comprising diluting the pharmaceutical composition of claim 1, and administering to the patient the diluted pharmaceutical composition. This would have been obvious in December 1998, because diluted aqueous solutions of sodium gamma-hydroxybutyrate were known ('632 patent), and methods for using a dual dose treatment at bedtime were known (Scharf).[31] Scharf teaches orally administering to a patient afflicted with the condition an aqueous composition comprising a first dose of 3 grams of sodium gamma-hydroxybutyrate within an hour prior to initial sleep onset (i.e., bedtime). Scharf teaches orally administering an aqueous composition comprising a second dose of 3 grams within 2 to 5 hours following initial sleep onset (more specifically, 4 hours).[32] Although Scharf teaches an aqueous composition of sodium gamma-hydroxybutyrate of 50 mg/mL, Example 2 of the '632 patent teaches 6.05 g of "gamma-hydroxy butyric acid, sodium salt," in an aqueous solution of 20 mL, which is a concentration of 302.5 mg/mL.

Claims 15 – 18 are directed to a "set comprising the pharmaceutical composition of claim 1 in one or more container means," wherein contains means encompasses "drinking cups" and "bottles." It would have been obvious in December 1998 to place the compositions of claim 1 in a bottle or drinking cup given that the composition is an aqueous solution. Claims 17 and 18 are directed to set, wherein another container is used to dilute the composition, which would have been obvious.

F. CONCLUSION

For the reasons stated above, claims 1-18 of the '650 patent are obvious over the prior art. Claims 1 – 18 of the '650 are not infringed, either literally or under the doctrine of equivalents.

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31 Broughton and Scrima also teach twice nightly administrations of sodium gamma-hydroxybutyrate.

32 Scrima teaches that "[h]igher doses of GHB, or longer treatment periods than were used in the present experiment may be needed to cause a more pronounced and subjectively noticeable decrease in sleepiness in narcolepsy patients." (Scrima at 488, first full paragraph.)

Par reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these patents are invalid, unenforceable or not infringed.

X. THE '730 PATENT

A. OVERVIEW OF THE '730 PATENT

1. Specification of the '730 Patent

U.S. Patent No. 7,668,730 patent is directed, *inter alia*, to computerized methods of distributing a prescription drug under control of an exclusive central pharmacy, including methods of distributing gamma hydroxy butyrate (GHB). The '730 patent is titled "Sensitive Drug Distribution System and Method," and is assigned on its face to JPI Commercial, LLC, but has subsequently been assigned to Jazz. The patent lists three inventors on its face: Dayton T. Reardan, Patti Engle, and Bob Gagne.

According to the '730 patent, the "invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs." ('730 patent). According to the '730 patent, sensitive drugs requiring control of distribution include GHB. ('730 patent, col. 1, lines 11-29). The '730 patent indicates that there is a need for a distribution system to address abuse. ('730 patent, col. 1, lines 30-33).

The invention purports to provide a drug distribution system and method utilizing 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.

2. Prosecution History of the '730 Patent

The '730 patent issued from U.S. Application 10/322,348("the '348 application") filed December 7, 2002, which claims no benefit to an earlier application. The '348 application was filed with 25 total claims, including 4 independent claims.

During prosecution the the Examiner repeatedly rejected the claims as obvious over U.S. Patent Application No. 2004/0019794 ("Moradi '794"), U.S. Patent Application No. 2004/0176985 ("Lilly '985"), U.S. Patent Application No. 2003/0033168 ("Califano '168"), U.S. Patent No. 5,845,255 ("Mayaud '255"), and U.S. Patent Application No. 2003/0160698 ("Andreasson '698"). (*See, e.g.,* '730 patent application, June 29, 2005, Non-Final Rejection; Dec. 29, 2005, Final Rejection; June 19, 2006, Non-Final Rejection; Octo. 18, 2006, Final Rejection).

On October 15, 2009, the Examiner agreed to reconsider the applied references in light of amendments made in an RCE. ('730 patent application, Oct. 21, 2009, Interview Summary).

On November 02, 2009, the applicants filed an Amendment with an RCE . Claims 32, 33, and 38-42 were amended. Specifically, **the applicants amended the claims such that prescriptions are received only at the central pharmacy; that all prescriptions are processed only by the exclusive pharmacy and using only the exclusive computer database; that the sensitive drug is mailed to patients only if no potential abuse is found**. The applicants provided support from the specification for the claim amendments. The following amendment to claim 32 is representative of the nature of the amendments to the claims:

> 32. (Currently Amended) A computerized method of distributing a sensitive 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 drug, only at the exclusive central pharmacy from [[a]] any and all medical doctors allowed to prescribe the sensitive drug, the prescription requests containing information identifying [[a]] patients, the sensitive 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 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;

confirming with a [[the]]] patient that educational material has been read prior to shipping the sensitive drug;

checking the exclusive computer database for potential abuse of the sensitive drug;

~~only~~ mailing the sensitive drug to the patient only if no potential abuse is found by ~~the checking of the computer database~~ the patient to whom the sensitive drug is prescribed and the doctor prescribing the sensitive drug;

confirming receipt by the patient of the sensitive drug; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns,

On December 31, 2009, the Examiner issued a Notice of Allowance, allowing claims 32-42. By Examiner's Amendment, the term "sensitive drug" where present in the claims was amended to "prescription drug" and the following step, where present in the claims, was amended as shown:

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;

The reasons for allowance included as follows:

The closest prior art of record, Moradi (US 2004/0019794 A 1), 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 prescriber prescribing the prescription drug.

('730 patent application, Dec. 31, 2009, Notice of Allowance).

On February 23, 2010, the '730 patent issued with 11 claims. According to the face page of the '730 patent, the term was extended or adjusted under 35 U.S.C. § 154(b) by 446 days.

On February 23, 2010, applicants filed a Request for Recalculation of Patent Term Adjustment in view of *Wyeth*. On April 20, 2010, the USPTO issued a communication granting the Request for Recalculation and providing a recalculated patent term adjustment of 547 days. On December 7, 2010, the USPTO issue a Certificate of Correction correcting the patent term adjustment noted on the Title Page to 547 days.

3. Claims of the '730 Patent

The '730 patent issued with the following claims:

#	Claims of the '730 Patent
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 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

#	Claims of the '730 Patent
	generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.
2	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 containing information identifying patients, the 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 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 prescription drug; 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; confirming receipt by the patient of the prescription drug; and generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.
3	The method of claim 2 wherein the exclusive central pharmacy controls the exclusive computer database.
4	The method of claim 2 and further comprising selectively blocking shipment of the prescription drug to a patient.
5	The method of claim 2 wherein an abuse pattern is associated with a patient, and shipment is blocked upon such association.
6	The method of claim 2 wherein the prescription drug comprises gamma hydroxy butyrate (GHB).
7	A computerized method of distributing a 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 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;

#	Claims of the '730 Patent
	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; 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 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 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; confirming receipt by the patient of the prescription drug; and generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.
8	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

#	Claims of the '730 Patent
	generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns.
9	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 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.
10	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;

#	Claims of the '730 Patent
	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.
11	A computerized method of distributing a 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 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; 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; 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 prescription drug to the patient; 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; 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 confirming receipt by the patient of the prescription drug.

B. LEVEL OF SKILL IN THE ART OF THE '730 PATENT

The subject matter of the '730 patent falls within the field of designing computer systems. Depending on the claim, the person of ordinary skill in this field would be a programmer, or a systems analyst/programmer. Such an individual would have a Bachelors Degree in Computer Science and several years of experience in the field. *E.I. DuPont de Nemours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), *aff'd*, 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein and would have the capability to draw inferences from them.

C. NONINFRINGEMENT OF THE '730 PATENT

Par does not directly infringe any claim of the '730 patent under 35 U.S.C. § 271(a) because Par does not perform the claimed method. Notably, independent claims 1, 2, and 7-11 all describe "a computerized method of distributing a prescription drug" which requires that an "an exclusive central pharmacy" receive "all prescription requests, for any and all patients being prescribed the prescription drug". Independent claims 8-10 further identify the drug as gamma hydroxyl butyrate. Par will not infringe these claims if granted approval for its generic product, because it will not control "an exclusive central pharmacy" that receives all of the prescriptions for the drug gamma hydroxyl butyrate or any other prescription drug.

Par further does not infringe claims 6, and 8-10, as they require the drug to be "gamma hydroxyl butyrate," whereas Par's proposed product contains sodium oxybate (sodium gamma-hydroxybutyrate).

Par also does not contributorily infringe under 35 U.S.C. § 271(c) because the claimed process has noninfringing uses. Furthermore, Par does not infringe claims 1-11 of the '730 patent under § 271(b) because the Par has a good faith belief that the '730 patent is invalid, which negates the requisite intent for induced infringement. *Commil USA, LLC v. Cisco Systems, Inc.*, 720 F.3d 1361, 1364 (Fed. Cir. Jun. 25, 2013) ("we find that Cisco's evidence of a good-faith belief of invalidity may negate the requisite intent for induced infringement.")

D. CLAIM CONSTRUCTION OF THE '730 PATENT

One of ordinary skill in the art and a court would interpret the claims of the '730 patent according to their plain and ordinary meaning unless otherwise specified herein. On September 14, 2012, the U.S. District Court for the District of New Jersey issued a claim construction order for terms in the '730 patent in the case of *Jazz Pharmaceuticals Inc. v. Roxane Laboratories Inc.*, No. 10-6108, D.I. 151 (D.N.J. Sept. 14, 2012). The district court's constructions for several relevant terms are briefly discussed below. Par includes these constructions for informational purposes only and reserves its right to challenge these constructions.

a. "prescription drug"

The court construed this as "an FDA approved dosage form that may be dispensed only upon a prescription."

b. "exclusive"

The court construed "exclusive" as "single or sole." The court found that the term "exclusive" was narrowed during prosecution in "an effort to distinguish the prior art" of Lilly et. al.

E. ANTICIPATION AND OBVIOUSNESS OF THE '730 PATENT

1. The Scope and Content of the Prior Art

The earliest possible effective U.S. filing date for the '730 patent is December 17, 2002, based on the filing date of U.S. Application 10/322,348.

a. FDA Safety Review

The FDA Safety Review reviewed Orphan Medical, Inc.'s, NDA for Xyrem®, which is prior art under 35 U.S.C. § 102(b) based on its May 5, 2001 date. It is a printed publication because it was posted on the FDA website, any person could have copied the materials, and the FDA website has a search tool that would have located it. *See Voter Verified, Inc. v. Premier Election Solutions, Inc.*, 698 F.3d 1374, 104 U.S.P.Q.2d 1553 (Fed. Cir. 2012) (holding that webpage is a printed publication if website is well known to the interested community; submissions are treated as public disclosures; users can freely copy; and search tool would have retrieved the article). The FDA Safety Review is also be prior art under § 102(b) as a public use. Public use of an invention includes "use by a person other than the inventor who is under no limitation, restriction or obligation of secrecy to the inventor." *In re* Smith, 714 F.2d 1127, 1134 (Fed. Cir. 1983). The FDA Safety Review was disclosed to the FDA, which publically displayed the reference on its website before the critical date. Thus, the reference qualifies as being in public use under § 102(b).

The FDA Safety Review was not considered by the examiner during prosecution of the '730 patent. The FDA Safety Review includes a summary of the "Risk Management Program" proposed by Orphan Medical with comments from the FDA. The FDA Safety Review describes a "closed-look distribution system," wherein "Xyrem® will NOT be placed in retail pharmacy outlets," and instead, the document describes a "primary and exclusive distributor of Xyrem®." (*Id.* at 108).

b. FDA Briefing Booklet, June 6, 2001

Orphan Medical submitted to the FDA a Briefing Booklet for the June 6, 2001, presentation to the Peripheral and Central Nervous System Drugs Advisory Committee ("Briefing Booklet"). The Briefing Booklet is prior art under 35 U.S.C. § 102(b) based on its June 6, 2001, submission date. It is a printed publication because it was posted on the FDA website, any person could have copied the materials, and the FDA website has a search tool that would have located it. *See Voter Verified, Inc.*, 698 F.3d 1374. The FDA Safety is also prior art under § 102(b) as a public use. The Briefing Booklet was not considered by the examiner during prosecution of the '730 patent.

The Briefing Booklet teaches systems for managing risks for medical products, including a closed distribution system that confirms the shipment and receipt of medicine. (Briefing Booklet at 293). It also discloses a single, central pharmacy to handle distribution of Xyrem® and education materials, and also keep consolidated records for physicians and patients, and the other roles of the central pharmacist.

> 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.

(Briefing Booklet at 306).

c. Xyrem® Prescription and Distribution Process Video, May 30, 2001

Orphan Medical submitted to the FDA a Xyrem Prescription and Distribution Process on May 30, 2001 ("Video"). The Video was submitted for the FDA's Peripheral and Central Nervous System Drugs Advisory Committee meeting on June 6, 2001. The Video is prior art under 35 U.S.C. § 102(b) based on its June 6, 2001, submission date. It is a printed publication because it was posted on the FDA website, any person could have copied the materials, and the FDA website has a search tool that would have located it. *See Voter Verified, Inc.*, 698 F.3d 1374. The Video is also prior art under § 102(b) as a public use. The Video was not considered by the examiner during prosecution of the '730 patent.

This Video describes Orphan Medical's planned distribution of Xyrem® through a central pharmacy.

> 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.

(Video at ¶ 13 (bold emphasis added)).

d. U.S. Publication 2002/0177232 ("Melker")

U.S. Publication 2002/0177232 ("Melker") is prior art to the '730 patent under 35 U.S.C. § 102(e) based on its U.S. Provisional 60/292,962 (filed May 23, 2001), and is also prior art under § 102(a) based on its November 28, 2002, publication. Melker was considered by the examiner during prosecution of the '730 patent.

e. U.S. Publication 2004/0019794 ("Moradi '794")

U.S. Publication 2004/0019794 ("Moradi") is prior art to the '730 patent under 35 U.S.C. § 102(e) based on the July 29, 2002, filing date of U.S. Application 10/207,402. Moradi was considered by the examiner during prosecution of the '730 patent. Moradi is titled "Method and System for Delivering Prescription Medicine," and is directed to a system for securely providing prescription medication to patients.

f. U.S. Publication 2004/0176985 ("Lilly")

U.S. Publication 2004/0176985 ("Lilly") is prior art to the '730 patent under 35 U.S.C. § 102(e) based on the filing date of its U.S. Provisional 60/332,801 (filed Nov. 14, 2001). Lilly was considered by the examiner during prosecution of the '730 patent.

g. U.S. Publication 2003/0033168 ("Califano")

U.S. Publication 2003/0033168 ("Califano") is prior art to the '730 patent under 35 U.S.C. § 102(e), based on the filing date of U.S. Provisional 60/283,809 (filed April 13, 2001). Califano was considered by the examiner during prosecution of the '730 patent.

h. U.S. Publication 2003/0074225 ("Borsand")

U.S. Publication 2003/0074225 ("Borsand") is prior art to '730 patent under 35 U.S.C. § 102(e), based on filing date of U.S. Application 09/976,650 (filed Oct. 12, 2001). Borsand was neither identified nor considered by the examiner during prosecution of the '730 patent. Borsand discloses pharmaceutical-related information stored in a single database.

i. U.S. Patent No. 6,315,720 ("Williams")

U.S. Patent No. App 6,315,720 ("Williams") is prior art to the '730 patent under 35 U.S.C. § 102(b) based on its November 13, 2001, issue date. Williams was disclosed by an IDS but not referenced by the examiner during prosecution of the '730 patent. Williams discloses a computer readable storage medium in which the prescriber, pharmacy, and patient may be registered.

j. "An Interview with Orphan Medical about Xyrem"

"An Interview with Orphan Medical about Xyrem," Feb. 12, 2001, http://www.talkaboutsleep.com/sleep-disorders/archives/Narcolepsy_xyrem_interview.htm, is prior art to the '730 patent under 35 U.S.C. § 102(b), based on its February 12, 2001 publication. The article was considered by the patent examiner.

This article included input from Orphan Medical CEO John Bullion, Chief Operating Officer William Houghton M.D., and Vice President of Marketing Patti Engel. The article discloses *inter alia*:

> To order Xyrem, a physician will write a prescription and fax that to the **central pharmacy.** That pharmacy will process the prescription request, call the physician to

verify the prescription, call the patient to assist them in gaining coverage from their insurance company, and then set up a delivery time directly to the patient so that they may receive their medicine.

This system was designed by Orphan Medical with assistance and input from State Scheduling authorities, experts in specialty distribution, drug diversion investigators, field law enforcement, narcolepsy patient groups, and pharmacists experienced in dealing with Scheduled medicines.

k. "Specialty Pharmacy," Jun. 5, 2000, Drug Topics, v. 144, p. 40 ("Ukens")

Ukens is prior art to the '730 patent under 35 U.S.C. § 102(b), based on its June 5, 2000, publication. This article was considered by the patent examiner. The article discloses, *inter alia*, that one advantage of a central pharmacy is limiting the distribution of dangerous drugs.

2. Anticipation and/or Obviousness in Light of the Briefing Booklet and FDA Safety Review (Claim 1)

Claim 1 of the '730 patent is anticipated and/or obvious over the Briefing Booklet.

Claim 1 is directed to a computerized method of distributing prescription drugs, which essentially involves forcing patients to obtain the drug from a single central pharmacy which maintains an exclusive computer database of information allowing the pharmacy to perform checks of potential abuse before mailing the drug to the patient. There is nothing novel about the alleged invention. Both the Briefing Booklet and the FDA Safety Review documents teach the use of an exclusive central pharmacy which collects information about documents and patients to check for potential abuse. See chart below for each disclosed element and further analysis thereof.

Claim 1 of the '730 Patent	Briefing Booklet	FDA Safety Review
A computerized method of distributing a prescription drug under **exclusive control** of an **exclusive central pharmacy**, the method comprising:	In Orphan Medical's Briefing Booklet, it teaches use of a database using an exclusive specialty pharmacy. The reference to "real-time data" implies a computer processor managing the database.	The FDA Safety Review teaches a method of distributing a prescription drug (Xyrem®) under exclusive control of an exclusive central pharmacy (or distributor). (FDA Safety Review at 108). Orphan Medical proposed Nova Factor to be the central pharmacy.
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;	"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	It describes a "closed-loop distribution system," wherein "Xyrem® will NOT be placed in retail pharmacy outlets," and instead, the document describes a **"primary and exclusive distributor of Xyrem®."** *Id.* at 108. The FDA Safety Review teaches that "[u]pon receipt of a prescription," the exclusive distributor "will

	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." (Briefing Booklet at 306). "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." (Briefing Booklet at 311).	contact the prescribing physician and identify his/her name, license and DEA registration."
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;	The Briefing Booklet teaches data collection into the central database. "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." (Briefing Booklet at 310).	The FDA Safety Review teaches that a single, sole, and secure database. "Every patient and prescribing physician will be registered with [the exclusive distributor] in **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." *Id.* at 110.
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;	The Briefing Booklet describes using the database to check doctors. "Once a physician decides that Xyrem is appropriate for a given	The FDA Safety Review teaches that "[u]pon receipt of a prescription," the exclusive distributor "verify that the physician is eligible to prescribe Xyrem®." *Id.* at 109.

	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." (Briefing Booklet at 310).	"[T]he National Practitioner Databank which contains current information about the authority of individual physicians to prescribe controlled substances. This stage of verification 'vvill [sic?] include confirming that the physician has an active DEA number and will check on whether any actions are pending against the physician."
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;	The Briefing Booklet describes checking patients and providing educational material. "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." (Briefing Booklet at 310).	The FDA Safety Review teaches an approval process for the patient, including requiring patients to confirm reading educational material prior to shipment. The Orphan Medical proposed an "optional Patient Consent" whereby patients "acknowledge in writing that they understand the safety, abuse, diversion and other issues that relate to the use of Xyrem®, and their responsibility to use the medication as prescribed by that patient; this form is intended to be kept as part of the patient's medical record." (*Id.* at 109). Although the proposal was for optional consent, the Office of Post-Marketing Drug Risk Assessment proposed that "the proposed consent form should be mandatory rather than optional so as to ensure that each patient fully understands the educational material provided," and "the patient registry information and benefit forms should be received by Nova Factor prior to the initial dispensing of the drug." (*Id.* at 115).[33] In the same document, Dr. R. Temple, Office Director proposed "Obtaining the patient's signed confirmation that he/she fully understands how GHB is to be used prior to the first prescription being

[33] The Office also proposed "confirmation that physicians have read and grasped the educational material provided by the sponsor could be obtained by requiring each physician to complete a questionnaire prior to dispensing of the drug to the patient."

		mailed." (*Id.* at 115).
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	Once the shipment designee and time of delivery is determined, the Xyrem prescription and the Patient Success ProgramSM 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. (Briefing Booklet at 310).	The FDA Safety Review teaches that after a patient is approved, the drug is shipped (or mailed) to the patient. (*Id.* at 109 ("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").
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	"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." (Briefing Booklet at 304).	The Office of Post-Marketing Drug Risk Assessment proposed that "In addition to the standard post-marketing adverse event **reporting, postmarketing safety assessments should also focus on drug abuse and dependence, diversion** and accidental overdosage (e.g., by small children)." (*Id.* at 115).

The examiner allowed claim 1 because the prior art considered by the examiner did not teach an exclusive pharmacy using an exclusive computer database.

> 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 prescriber prescribing the prescription drug.

('730 patent application, Dec. 31, 2009, Notice of Allowance). The examiner, however, never considered either the Briefing Booklet or the FDA Safety Review, and instead, the examiner found that "the closest prior art of record" was Moradi, Lilly et al., Califano et al., and Ukens ("Specialty Pharmacy"). Unlike those references, both the Briefing Booklet and the FDA Safety Review teach a central pharmacy and an exclusive database.

It is the patentee's obligation to present evidence of secondary considerations, if any, to rebut a *prima facie* case of obviousness. The '730 patent provides no specific evidence of secondary considerations of non-obviousness. Any evidence of secondary considerations is insufficient to overcome the strong case of *prima facie* obviousness of the claimed subject matter.

3. Obviousness in Light of Borsand (Claim 1)

Claim 1 of the '730 patent is obvious over Borsand. See chart below for each disclosed element and further analysis thereof.

Claim 1 of the '730 Patent	Borsand
A computerized method of distributing a prescription drug under **exclusive control** of an **exclusive central pharmacy**, the method comprising:	Borsand teaches a method for treating a patient with a drug that has the potential for abuse, i.e., it discloses that its system reduces fraud, redundancy, pharmaceutical abuse, pharmaceutical misuse, and errors, with respect to prescription drugs. (Borsand ¶¶ 33; 38).
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;	Borsand teaches an exclusive central computer system, which contains patient and doctor information. Borsand discloses a prescription subsystem where "prescriptions are only issued by a certain subset of health care providers, such as physicians ...." Processing a prescription requires inputting "patient record which includes patient information relevant to pharmaceutical selection." Each doctor must use a unique "UserID" and a patient is assigned a unique "PatientID." (Borsand ¶¶ 57-58; Figure 4b). Borsand addresses prior art deficiencies where "[i]t would be desirable for pharmaceutical information to be stored only once and in a **centralized location** accessible by the appropriate parties." (Borsand ¶ 3).
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;	Borsand teaches an exclusive computer database associated with an exclusive computer system. For example, Borsand discloses a system that allows for "pharmaceutical information to be stored only once and in a centralized location accessible by the appropriate parties." (Borsand ¶ 3). Borsand teaches that all relevant data is housed in a computer that "can be a single centralized computer or server, a single network ...." (Borsand ¶ 31). According to Borsand, in the preferred embodiment, "all pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate regulations, policies, and guidelines." (Borsand ¶ 43). Borsand also teaches that the relevant data must be entered in the system by the provider, *see, e.g.,* Borsand ¶¶ 58; 108, or the pharmacist. *See* (Borsand ¶ 86 ("If the pharmacist fills a pharmaceutical prescription, that information needs to be memorialized at 40.02 or its related pages.")).

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;	Borsand teaches an exclusive central computer system, which contains patient and doctor information. Borsand discloses a prescription subsystem where "prescriptions are only issued by a certain subset of health care providers, such as physicians ...." Processing a prescription requires inputting "patient record which includes patient information relevant to pharmaceutical selection." Each doctor must use a unique "UserID" and a patient is assigned a unique "Patient*ID*." (Borsand ¶¶ 57-58; Figure 4b). Borsand addresses prior art deficiencies where "[i]t would be desirable for pharmaceutical information to be stored only once and in a **centralized location** accessible by the appropriate parties." (Borsand ¶ 3). Borsand teaches an exclusive computer database associated with an exclusive computer system. For example, Borsand discloses a system that allows for "pharmaceutical information to be stored only once and in a centralized location accessible by the appropriate parties." (Borsand ¶ 3). Borsand teaches that all relevant data is housed in a computer that "can be a single centralized computer or server, a single network ...." (Borsand ¶ 31). According to Borsand, in the preferred embodiment, "all pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate regulations, policies, and guidelines." (Borsand ¶ 43). Borsand also teaches that the relevant data must be entered in the system by the provider, *see, e.g.,* Borsand ¶¶ 58; 108, or the pharmacist. *See* (Borsand ¶ 86 ("If the pharmacist fills a pharmaceutical prescription, that information needs to be memorialized at 40.02 or its related pages.")).
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;	The system disclosed by Borsand provides "functionality for tracking pharmaceutical, prescription and related information," where "tracking can be in a proactive and real-time manner, or in the form of reports and analysis ...." (Borsand ¶ 34). Any abuse or violation can be detected by the system which "can be configured to not allow the attempted conduct, or to allow the conduct, but generate a report relating to the undesired activity." (*Id.*).
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	Borsand teaches delivering the prescription drug to the patient, which is the purpose of the system and the drug. Borsand discloses that the pharmaceutical subsystem (part of the overall exclusive central computer system) re-evaluates the prescription before the prescription is filled or sent to a payor, where "medical aspects of a prescription can also be reviewed, so that the appropriateness of the selected pharmaceutical can be confirmed as it relates to ... other patient attributes that could affect the desirability of filling a particular prescription." (Borsand ¶ 87). Borsand discloses in multiple places that desirability of filling prescriptions may be tied to misuse of pharmaceuticals; for example, patient attributes includes patient's refill behavior. (*Id.* at ¶ 53).
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	Borsand discloses that in filling a prescription for a drug, an event can trigger a modification or cancellation of the prescription, where such an event includes "evidence of fraud, misuse, or redundancy on the part of a provider, pharmacist, or patient." (Borsand ¶ 120).

4. Application of the Prior Art (Claims 2-11)

Claim 2 of the '730 patent is similar to claim 1, although slightly broader because it does not require "confirming with a patient that educational material has been read prior to shipping

the prescription drug."[34] Claim 2 is obvious for the same reasons claim 1 is obvious. Additionally, claim 2 is anticipated by The FDA Safety Review and Briefing Booklet as described above.

Claim 3 is directed to the method of claim 2 "wherein the exclusive central pharmacy controls the exclusive computer database." The FDA Safety Review teaches a method wherein the central pharmacy controls the database.

> Every patient and prescribing physician will be registered with [the exclusive distributor] in **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.

(*Id.* at 110). In any event, having the exclusive central pharmacy control the exclusive computer database would have been obvious to a person of ordinary skill in the art in December 2002.

Claims 4 and 5 are directed to the method of claim 2 wherein shipment to the patient is blocked under certain circumstances. The purpose of the prior art method for using a central pharmacy was to block shipment of the drugs to patients with a potential for abuse, and the added limitations of claims 4 and 5 would have been obvious to a person of ordinary skill in the art in December 2002.

Claim 6 is directed to the method of claim 2 wherein "the prescription drug comprises gamma hydroxy butyrate (GHB)." Both the Briefing Booklet and the FDA Safety Review are directed to methods and systems for Risk Management of Xyrem®, which contains gamma hydroxyl butyrate (GHB).

Claim 7 is independent, but is similar to claims 1 and 2. The major difference between claim 7 and claims 1 and 2 is that instead of referring to "medical doctors," claim 7 refers to "authorized prescribes." Claim 7 also requires the exclusive database to be under the "exclusive control of the central pharmacy."

Claims 8-10 are similar to claims 1, 2, and 7, but is directed to a method of distributing gamma hydroxybutyrate (GHB), which essentially involves forcing patients to obtain the drug from a single central pharmacy which maintains an exclusive computer database of information allowing the pharmacy to perform checks of potential abuse before mailing the drug to the patient. Both the Briefing Booklet and the FDA Safety Review are directed to methods and systems for Risk Management of Xyrem®, which contains gamma hydroxyl butyrate (GHB). Claim 10 additionally includes steps for "manufacturing GHB" and then "providing manufactured GHB only to the exclusive central pharmacy." The Briefing Booklet states: "Bulk drug for Xyrem is manufactured at a single site and it is formulated into finished product at a

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[34] The only other difference is that whereas claim 1 recites "requiring entering of the information into the exclusive computer database," claim 2 recites "entering the information into an exclusive computer database."

separate, single site. From there, finished Xyrem is shipped to a central pharmacy." (Briefing Booklet at 309).

Claim 11 similar to claims 1, 2, and 7, and is even broader in the sense that it does not require the final step of "generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns." For the same reasons claims 1, 2, and 7 are obvious, claim 11 is obvious.

F. INVALIDITY UNDER 35 U.S.C. § 101

The claims of the '730 patent are invalid under 35 U.S.C. § 101 because the claimed subject matter is not patentable. The claims of the '730 patent do not satisfy the machine-or-transformation test, and are directed to algorithms and abstract ideas *Bilski v. Kappos*, 130 S.Ct. 3218, 3229-30 (2010); *In re Bilski*, 545 F.3d 943, 962-63 (Fed. Cir. 2008).

Patentability under 35 U.S.C. § 101 is a threshold issue. *See In re Bilski*, 545 F.3d 943, 950-51 (Fed. Cir 2008) (en banc) ("Whether a claim is drawn to patent-eligible subject matter under § 101 is an issue of law."), *aff'd*, 130 S. Ct. 3218 (2010). In order to be actionable, a patent's claims must be drawn to patent-eligible subject matter under § 101. *Id.* at 950. Any claim failing the requirements of § 101 "must be rejected even if it meets all of the other legal requirements of patentability." *Id.* Determining whether a patent claim meets the § 101 requirement involves two steps. First, courts often look at whether the patent claims pass the machine-or-transformation test as an "important clue" to determining whether the patent claims patent-eligible subject matter. *Bilski*, 130 S. Ct. at 3227. Second, courts will determine whether the claim seeks to cover one of the three exceptions to patentable subject matter — laws of nature, physical phenomena, or abstract ideas. *Id.* at 3225; s*ee also Gottschalk v. Benson*, 409 U.S. 63, 67 (1972).

Under the machine-or-transformation test, a process claim is not patentable unless either it: (1) is tied to a particular machine or apparatus; or (2) transforms a particular article into a different state or thing. *Bilski*, 130 S. Ct. at 3225 (citing *Bilski*, 545 F.3d at 954). Not every patent that recites a machine or transformation of an article passes the machine-or-transformation test. In order to pass the test, the claimed machine or transformation must impose ***meaningful*** limits on the claim's scope and be integral to the process. *Dealertrack Inc. v. Huber*, 674 F.3d 1315, 1333 (Fed. Cir. 2012) (citing *SiRF Tech., Inc. v. Int'l Trade Comm'n,* 601 F.3d 1319, 1333 (Fed.Cir. 2010)); *CyberFone Systems, LLC v. Cellco Partnership,* 2012 WL 3528115, at *6 (D. Del. Aug. 16, 2012). If the patent claims only require a computer to be employed for its "most basic function," or is a "general purpose computer programmed in an unspecified manner," that is insufficient to pass the machine prong of this test. *Id.* **6-7 (citing *Bancorp Services, L.L.C. v. Sun Life Assurance Co. of Canada (U.S.)*, 687 F.3d 1266, 1273, 1278 (Fed. Cir. 2012)). On the transformation prong, claims that merely require collecting and organizing data are insufficient to satisfy this prong. *Id.* at *6 (citing *CyberSource*, *CyberSource Corp. v. Retail Decisions, Inc.*, 654 F.3d 1366, 1367 (Fed. Cir. 2011)); *Bancorp*, 687 F.3d at 1273).

In the '730 patent, the process is not tied to a particular machine or apparatus. Although there is a reference to a "computerized method" in the claim preamble, a "computer processor" that receives requests or checks credentials, a "computer database" used to track data relevant to

orders ('730 claims 1-11), there is nothing in the specification to indicate that a computer is integral to implementing the process. Further, while some of the steps require use 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, 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).

The '730 patent claims do not transform an article into a different state or thing. The '730 patent merely claims a method of distributing sensitive drugs that does not transform or make the drugs any less sensitive. Although some claims require 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. Although 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." *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, col. 1, lines 6- 7).

In addition to applying the machine-or-transformation test, courts must also look at whether the patent claims as a whole seek to claim an unpatentable, abstract idea. *See, e.g., Bilski*, 130 S. Ct. at 3230-31; *see also Accenture Global Servs., GMBH v. Guidewire Software, Inc.*, 800 F.Supp.2d 613, 621 (D. Del. 2011). The presence of a "basic concept" in a patent claim can be a clue that the claim is drawn to an abstract idea. *See, e.g., Bilski*, 130 S. Ct. at 3231 (holding that the "basic concept of hedging, or protecting against risk" is an "unpatentable abstract idea."); *Dealertrack*, 674 F.3d at 1333 (holding that the "basic concept" of "processing information through a clearinghouse" is unpatentable).

The Supreme Court has explained that a patent must "also contain other elements or a combination of elements, sometimes referred to as an '***inventive concept***,' sufficient to ensure that the patent in practice amounts to ***significantly more*** than a patent upon the [abstract idea] itself." *Mayo*, 132 S. Ct. at 1294 (citing *Parker v. Flook*, 437 U.S. 584, 594 (1978)); *Bilski*, 130 S. Ct. at 3230) (emphases added); *see also OIP Techs., Inc. v. Amazon.com, Inc.*, No. C-12-1233 EMC, 2012 WL 3985118, at *16 (same) (N.D. Cal. Sept. 11, 2012). The steps in the claimed processes, apart from the abstract ideas themselves, must do more than simply involve "well-understood, routine, conventional activity previously engaged in by [people] in the field." *Mayo*, 132 S. Ct. at 1294. And it is not enough to add to the claim a "field of use or ... token post solution components." *Bilski*, 130 S. Ct. at 3231 (citation omitted).

The Federal Circuit has determined that patent claims are abstract when the "steps can be performed in the human mind, or by a human using a pen and paper." *CyberSource*, 654 F.3d at 1372. In the '730 patent, the process is similar to a clearing house in that the method merely requires collecting and organizing data of doctors who are able to prescribe, and the patients who are able to receive, the medication, and organizing the data describing shipments of the medication, and associated marketing material. This process could equally be performed by pencil, paper, and a traditional filing cabinet system.

The steps of the claims in the '730 patent represent common ways that people have used to restrict allocation of materials for centuries, where a central controlling entity confirms with a validated third-party authority whether a substance should be delivered to an individual. Without meaningful limits, the claims effectively preempt the fundamental concept itself and foreclose a wide range of inventions that the patentee never conceived. For example, in *Dealertrack*, the Federal Circuit determined that the patentee's claimed process in its simplest form includes three steps: receiving data from one source (step A), selectively forwarding the data (step B, performed according to step D), and forwarding reply data to the first source (step C). *Dealertrack,* 674 F.3d at 1333. Because this claim "explain[s] the basic concept of processing information through a clearing-house . . . [t]he steps that constitute the method here do not impose meaningful limits on the claim's scope." *Id.* (citing *Bilski*, 130 S. Ct. at 3231; *Bilski*, 545 F.3d at 961-62) (quotations omitted). The Federal Circuit was "compelled to conclude that the claims are invalid as being directed to an abstract idea ***preemptive of a fundamental concept or idea*** that would foreclose innovation in this area." *Id.* at 1333 (emphasis added); *see also Mayo*, 132 S. Ct. at 1294 (the patent should not "risk disproportionately tying up the use of" the abstract idea in future discoveries). Similarly, here, the steps of the claims in the '730 are directed to a fundamental concept itself, thus are directed to an abstract idea.

In sum, the claims of the patent-in-suit fail to meet the requirements of § 101 because they: (1) fail the machine-or-transformation test and (2) are directed to the abstract idea of a centralized authorization center for prescriptions drugs , which is a fundamental principle that would be improperly preempted by the patent-in-suit. Here, the computer must be integral to the claimed invention, facilitating the process in a way that a person making calculations or computations could not." *Bancorp*, 687 F.3d at 1278. This method could be performed by someone using pencil, paper, and a standard records-keeping system.

For these reasons, the claims of the '730 patent are invalid under 35 U.S.C. § 101.

G. INVALIDITY UNDER 35 U.S.C. § 112

The claims of the '730 patent are also invalid as indefinite under 35 U.S.C. § 112. 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.").

The claims of the '730 patent 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 USPTO 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 patent application, Sept. 30, 2004, Petition to Make Special). 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. Patent claims that require such human mental participation are indefinite and not proper patent-eligible subject matter.

H. CONCLUSION

For the reasons stated above, claims 1-11 of the '730 patent are anticipated and/or obvious over the prior art, and claims 1-11 are invalid under 35 U.S.C. §§ 101, 112. Further, Par will not infringe claims 1-11. Par reserves the right to develop additional grounds, reasons, and authorities that any or all of the claims of these patents are invalid, unenforceable or not infringed.

XI. THE '106 PATENT

A. OVERVIEW OF THE '106 PATENT

1. Specification of the '106 Patent

U.S. Patent No. 7,765,106 ("the '106 patent") issued from U.S. Application 10/979,655, filed November 2, 2004, which is a divisional to U.S. Application 10/322,348 (filed December 17, 2002), which itself issued as U.S. Patent No. 7,668,730. The '106 patent lists three inventors: Dayton Reardon, Patti Engel, and Bob Gagne. It was originally assigned to JPI Commercial, LLC, but was subsequently assigned to Jazz. The '106 patent is titled "Sensitive Drug Distribution System and Method."

The '106 patent is directed, *inter alia*, to therapeutic methods of treating a patient with a prescription drug that is effective for therapeutic purposes but has the potential to be abused, the method including control of distribution by a central computer system and the drug including sodium oxybate/gamma hydroxyl butyrate (GHB). According to the '106 patent, the "invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs." ('106 patent, col. 1, lines 18-35). The '106 patent indicates that there is a need for a distribution system to address abuse. ('106 patent, col. 1, lines 36-39).

The invention purports to provide a drug distribution system and method utilizing 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 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. ('106 patent, col. 1, line 44 to col. 2, line 21.)

2. Prosecution History of the '106 Patent

On November 2, 2004, the applicants filed U.S. Application No. 10/979,665 ("the '665 application") with 36 total claims, including 7 independent claims. The '665 application is a divisional of U.S. Application No. 10/322,348, which issued as U.S. Patent No. 7,668,730 ("the '730 patent"). Applicants also filed a non-entered Preliminary Amendment cancelling claims 1-25 without listing any claims.

On June 22, 2006, applicants filed an IDS and a Preliminary Amendment cancelling originally filed claims 1-25 and listing originally filed claims 26-36.

On June 25, 2009, the USPTO issued a Restriction/Election Requirement identifying Group I (claims 26-32 drawn to controlling distribution of a sensitive drug) and Group II (claims 33-36 drawn to treating a patient). On July 14, 2009, applicants filed a Response to Restriction Requirement, electing Group II without traverse, and a Supplemental IDS.

On November 17, 2009, the USPTO issued a non-final rejection. Claims 33-36 were rejected as directed to non-statutory subject matter.

> The recited steps of independent claim 33 of merely controlling distribution of a sensitive drug via an exclusive central pharmacy, filling a prescription, shipping the sensitive drug, and treating the patient with the drug are not tied to another statutory class (such as a particular apparatus) and do not transform underlying subject matter (such as an article or materials) to a different state or thing. Similar analysis applies for independent claim 35. Therefore, claims 33-36 are deemed to be directed to nonstatutory subject matter.

Claims 33-36 were also rejected for nonstatutory obviousness-type double patenting over claims 26, 27, 29 and 30 of co-pending U.S. Application No. 11/097,985 ("the '985 application"), which the '107 patent.

On March 11, 2010, applicants filed an Amendment and Response, cancelling claims 26-32, extensively amending claims 33-36, and adding new claims 37-40. The following amendment to claim 33 is representative of the claim amendments.

> A therapeutic method for treating a patient ~~in need of treatment~~ with a prescription ~~sensitive~~ 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 ~~sensitive~~ prescription drug using the exclusive central computer system ~~via an exclusive central pharmacy that maintains a central database~~ that tracks all prescriptions of said prescription ~~sensitive~~ drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug ~~situations~~ by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription ~~sensitive~~ drug from periodic reports generated by the exclusive central computer system and the ~~central~~ exclusive computer database based on prescription ~~request~~ data from a medical doctor, wherein said prescription ~~request~~ 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 ~~by said exclusive central pharmacy~~, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system

~~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 ~~sensitive~~ 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 ~~similar~~ 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 ~~the~~ 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 ~~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, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions; authorizing the filling, using ~~by~~ the exclusive central computer system ~~central pharmacy~~, of a prescription for the prescription ~~sensitive~~ 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 ~~shipping~~ the prescription ~~sensitive~~ drug by the central pharmacy to the patient in order to ~~begin~~ treat~~ment~~ the patient with the prescription drug ~~therewith; and treating the patient with the drug~~.

New independent claims 37 and 39 include the same steps, but with differences in scope because of differences in certain of the details. Applicants also filed a Terminal Disclaimer disclaiming any term extending beyond that of a patent issuing from the '985 application.

On April 30, 2010, the USPTO issued a Notice of Allowance, preliminarily determining PTA to be 1251 days and providing the following reasons for allowance.

> Claims 33, 35, 37, and 39, now renumbered as claims 1, 3, 5, and 7, respectively, are directed to a therapeutic method for treating a patient.
>
> The closest prior art of record, Moradi et al. (US 2004/0019794 A 1), Lilly et al. (US 2004/0176985 A 1), Ukens ("Specialty Pharmacy") and

Melker et al. (US 2002/0177232 A 1) teach controlling the distribution of a drug, receiving prescription data from a medical doctor, selecting multiple controls for distribution, filling a prescription for the drug, delivering the drug, determining patterns of potential abuse of the drug, and restricting distribution of a specialty medication to only one pharmacy.

However, the closest prior art of record does not teach or fairly suggest receiving, only into an exclusive central computer system/exclusive computer database, *all* prescriptions for any and all patients being prescribed the prescription drug, 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, and authorizing the filling, using the exclusive central computer system/exclusive computer database, of a prescription for the prescription drug that has been subjected to multiple controls.

Dependent claims 34, 36, 38, and 40 (now renumbered as claims 2, 4, 6, and 8) incorporate the allowable subject matter of their respective independent claims, through dependency, and are also allowable for the same reasons.

On July 27, 2010, the '106 patent issued with 8 claims. According to the face page of the '106 patent, the term was extended or adjusted under 35 U.S.C. § 154(b) by 1645 days, subject to the approved disclaimer over the '985 application.

On November 19, 2010, applicants filed a Petition to correct on the Terminal Disclaimer the name of the assignee from JPI Commercial, LLC to Jazz Pharmaceuticals, Inc. On December 7, 2010, the USPTO dismissed the Petition, thus leaving the original Terminal Disclaimer on the record, deeming that entry into the record of the replacement Terminal Disclaimer filed November 19, 2010 and the Petition is sufficient to complete the record.

3. Claims of the '106 Patent

The '106 patent issued with the following claims:

#	Claims of the '106 Patent
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

#	Claims of the '106 Patent
	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.

#	Claims of the '106 Patent
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

#	Claims of the '106 Patent
	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

#	Claims of the '106 Patent
	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

#	Claims of the '106 Patent
	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;

#	Claims of the '106 Patent
	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.

B. LEVEL OF SKILL IN THE ART OF THE '106 PATENT

The subject matter of the '106 patent falls within the field of designing computer systems. Depending on the claim, the person of ordinary skill in this field would be a programmer, or a systems analyst/programmer. Such an individual would have a Bachelor's Degree in Computer Science and several years of experience in the field. *E.I. DuPont de Nemours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), *aff'd* 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein and would have the capability to draw inferences from them.

C. CLAIM CONSTRUCTION OF THE '106 PATENT

One of ordinary skill in the art and a court would interpret the claims of the '106 patent according to their plain and ordinary meaning unless otherwise specified herein.

On September 14, 2012, the U.S. District Court for the District of New Jersey issued a claim construction order for terms in the '730 patent family, which includes distribution patents, '106, '107, and '059, in the case of *Jazz Pharmaceuticals Inc. v. Roxane Laboratories Inc.,* No. 10-6108, D.I. 151 (D.N.J. Sept. 14, 2012). The district court's constructions for several relevant terms are briefly discussed below as well as in section X(D), above. Par includes these constructions for informational purposes only and reserves its right to challenge these constructions.

a. "controls selected from the group consisting of"

The court construed this clause as an open-ended list of optional controls.

D. NONINFRINGEMENT OF THE '106 PATENT

Par does not directly infringe any claim of the '106 patent under 35 U.S.C. § 271(a) because Par does not perform the claimed method. Notably, independent claims 1, 3, 5, and 7, all describe a therapeutic method for treating a patient which requires that an "an exclusive central computer system" receive "all prescriptions for any and all patients being prescribed the prescription drug." Independent claim 3 specifies that the prescribed drug is sodium oxybate. Par will not infringe these claims if granted approval for its generic product, because it will not control "an exclusive central pharmacy" that receives all of the prescriptions for sodium oxybate or any other prescription drug.

Par does not directly infringe any claim of the '106 patent under 35 U.S.C. § 271(a) because Par does not perform the claimed method. Par also does not contributorily infringe

under 35 U.S.C. § 271(c) because the claimed process has noninfringing uses. Furthermore, Par does not infringe claims 1-8 of the '106 patent under § 271(b) because the Par has a good faith belief that the '106 patent is invalid, which negates the requisite intent for induced infringement. *Commil USA, LLC v. Cisco Systems, Inc.*, 720 F.3d 1361, 1364 (Fed. Cir. Jun. 25, 2013) ("we find that Cisco's evidence of a good-faith belief of invalidity may negate the requisite intent for induced infringement.")

E. OBVIOUSNESS OF THE '106 PATENT

1. The Scope and Content of the Prior Art

The earliest possible effective U.S. filing date for the '106 patent is December 17, 2002, based on the filing date of U.S. Application 10/322,348 for the parent, '730 patent. A description of the prior is located in section (X)(E)(1), above.

2. Obviousness in Light of Borsand (Claim 1)

Claim 1 of the '106 patent is obvious over Borsand, which describes each of the elements of claim 1. Claim 1 is directed to a method for treating patients with a prescription drug that has the potential to be abused, misused, or diverted. The claim essentially requires patients to obtain the prescription drug from a single, central pharmacy that maintains an exclusive computer database of information, thus allowing the pharmacy to perform checks of potential abuse before delivering the drug to the patient. The method of claim 1 controls distribution by subjecting the single, central pharmacy to a multitude of controls before the drug is delivered.

The chart below outlines and describes each element disclosed by Borsand.

Claim 1 of the '106 Patent	Borsand
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:	Borsand teaches a method for treating a patient with a drug that has the potential for abuse, i.e., it discloses that its system reduces fraud, redundancy, pharmaceutical abuse, pharmaceutical misuse, and errors, with respect to prescription drugs. (Borsand ¶¶ 33; 38).
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	Borsand teaches an exclusive central computer system, which contains patient and doctor information. Borsand discloses a prescription subsystem where "prescriptions are only issued by a certain subset of health care providers, such as physicians ...." Processing a prescription requires inputting "patient record which includes patient information relevant to pharmaceutical selection." Each doctor must use a unique "UserID" and a patient is assigned a unique "PatientID." (Borsand ¶¶ 57-58; Figure 4b). Borsand addresses prior art deficiencies where "[i]t would be desirable for pharmaceutical information to be stored only once and in a **centralized location** accessible by the appropriate parties." (Borsand ¶ 3).
requiring entering of the information into an	Borsand teaches an exclusive computer database

Claim 1 of the '106 Patent	Borsand
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;	associated with an exclusive computer system. For example, Borsand discloses a system that allows for "pharmaceutical information to be stored only once and in a centralized location accessible by the appropriate parties." (Borsand ¶ 3). Borsand teaches that all relevant data is housed in a computer that "can be a single centralized computer or server, a single network ...." (Borsand ¶ 31). According to Borsand, in the preferred embodiment, "all pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate regulations, policies, and guidelines." (Borsand ¶ 43). Borsand also teaches that the relevant data must be entered in the system by the provider, *see, e.g.,* Borsand ¶¶ 58; 108, or the pharmacist. *See* (Borsand ¶ 86 ("If the pharmacist fills a pharmaceutical prescription, that information needs to be memorialized at 40.02 or its related pages.")).
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;	The system disclosed by Borsand provides "functionality for tracking pharmaceutical, prescription and related information," where "tracking can be in a proactive and real-time manner, or in the form of reports and analysis ...." (Borsand ¶ 34). Any abuse or violation can be detected by the system which "can be configured to not allow the attempted conduct, or to allow the conduct, but generate a report relating to the undesired activity." (*Id.*)
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	Borsand discloses selecting at least some of the controls for distribution using Borsand's exclusive central computer system: Borsand's prescription subsystem, part of Borsand's overall system, requires a provider to communicate prescriptions thereto in order "to generate prescriptions for a patient" (Borsand ¶ 50); input "patient record which includes patient information relevant to pharmaceutical information" (*Id.* at ¶ 57); input a UserID which is unique to the provider, which necessarily includes physician identifying data (*Id.*); monitor whether prescription has been refilled (*Id.* at ¶ 56); and provide for automatic pre-certification of prescriptions to reduce "the likelihood of fraudulent or abusive behavior" (*Id.*); among others. Further, the system disclosed in Borsand includes

Claim 1 of the '106 Patent	Borsand
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;	a reimbursement system that communicates with the patient's insurance company (payor) and also prevents "[m]isuse of pharmaceuticals by redundant prescriptions, overuse ... and other forms of misuse can be reduced through use of the system. Fraud and error can also be reduced...." (*Id.* at ¶ 75).
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;	Borsand discloses that the pharmaceutical subsystem (part of the overall exclusive central computer system) re-evaluates the prescription before the prescription is filled or sent to a payor, where "medical aspects of a prescription can also be reviewed, so that the appropriateness of the selected pharmaceutical can be confirmed as it relates to ... other patient attributes that could affect the desirability of filling a particular prescription." (Borsand ¶ 87). Borland discloses in multiple places that desirability of filling prescriptions may be tied to misuse of pharmaceuticals; for example, patient attributes includes patient's refill behavior. (*Id.* at ¶ 53).
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	Borsand discloses that in filling a prescription for a drug, an event can trigger a modification or cancellation of the prescription, where such an event includes "evidence of fraud, misuse, or redundancy on the part of a provider, pharmacist, or patient." (Borsand ¶ 120).
delivering the prescription drug to the patient in order to treat the patient with the prescription drug.	Borsand teaches delivering the prescription drug to the patient, which is the purpose of the system and the drug.

The examiner allowed claim 1 because the prior art considered by the examiner did not teach that all prescriptions will be received by an exclusive computer system/database.

> However, the closest prior art of record does not teach or fairly suggest receiving, **only into an exclusive central computer system/exclusive computer database, *all* prescriptions** for any and all patients being prescribed the prescription drug, 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, and authorizing the filling, using the exclusive central computer system/exclusive computer database, of a prescription for the prescription drug that has been subjected to multiple controls.

(Notice of Allowance, Apr. 30, 2010). The examiner, however, never considered Borsand. Instead, the examiner found that "the closest prior art of record" was Moradi , Lilly et al., Melker et al., and Ukens ("Specialty Pharmacy"). Notably, the examiner found that all the elements of claim 1 are disclosed in combination in the prior art of record rendering the alleged invention obvious, except an exclusive central computer system/database that receives all prescriptions from all patients, controls the distribution of the prescriptions, and authorizes distribution of the prescriptions. Furthermore, Borsand, alone, also teaches an exclusive computer system/database that performs the functions recited in claim 1.

It is the patentee's obligation to present evidence of secondary considerations, if any, to rebut a *prima facie* case of obviousness. The '106 patent provides no specific evidence of secondary considerations of non-obviousness. Any evidence of secondary considerations is insufficient to overcome the strong case of *prima facie* obviousness of the claimed subject matter.

3. Anticipation and/or Obviousness in Light of the Briefing Booklet (Claim 1)

Claim 1 of the '106 patent is anticipated and/or obvious over the Briefing Booklet. See chart below for each disclosed element and analysis thereof.

Claim 1 of the '106 Patent	Briefing Booklet
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 Briefing Booklet generally teaches the therapeutic benefits of Xyrem in reducing incidents of cataplexy and improves symptoms of daytime sleepiness. *See generally Briefing Booklet (*e.g., "upon learning about narcolepsy and the clinical results of Xyrem, these parties agreed that the therapeutic need for Xyrem was compelling."). (Briefing Booklet at 7). Further, the Briefing Booklet teaches the potential for abuse, misuse, or diversion of Xyrem (e.g., "They [law enforcement] 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...." (Briefing Booklet at 7).
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	In Orphan Medical's Briefing Booklet, it teaches use of a database using an exclusive specialty pharmacy. The reference to "real-time data" implies a computer processor managing the database. In Orphan Medical's Briefing

Claim 1 of the '106 Patent	Briefing Booklet
information identifying the patient, the prescription drug, and various credentials of the medical doctor who is prescribing the prescription drug	Booklet, it teaches use of a database using an exclusive specialty pharmacy. The reference to "real-time data" implies a computer processor managing the database. "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." (Briefing Booklet at 15). "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." (Briefing Booklet at 20).
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;	The Briefing Booklet teaches data collection into the central database. The reference to "data collection" necessary includes entering the information into the central database "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." (Briefing Booklet at 19).

Claim 1 of the '106 Patent	Briefing Booklet
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;	The Briefing Booklet teaches under the section entitled "Prescribing Options Selected" that the closed-loop distribution system controls distribution by controlling who prescribes Xyrem and controlling how it is prescribed. This, according to the Briefing Booklet, is achieved, in part, "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 of 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." (Briefing Booklet at 15). Further, the Briefing Booklet discloses that "the central pharmacy will identify patients who are attempting to duplicate prescriptions. All data collected will be available to state and federal authorities." (Briefing Booklet at 16).
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	The Briefing Booklet discloses multiple controls that are available in Orphan Medical's distribution system: the closed-loop distribution system "provides for the shipment and receipt of medicine" (Briefing Booklet at 13); verification of the physician's eligibility by checking AMA, DEA, or State Medical Board on-line databases (*Id.* at 19); verifying the prescription by contacting the physician's office to confirm patient information (*Id.*); collecting patient's specific information by the specialty pharmacy to assist "in the building of a patient registry which also aids in diversion prevention" (*Id.*); contacting the insurance company to obtain insurance reimbursement (*Id.*); providing the physician with printed educational materials via the "Physician Success Program" (*Id.*); providing the patient with printed educational materials via the "Patient Success Program" (*Id.* at 20); requiring the pharmacist at the specialty pharmacy to contact the patient to "confirm receipt of the Xyrem prescription and Patient Success Program" (*Id.*); shipping the prescription and the Patient Success Program via Federal Express (*Id.*); contacting the patient

Claim 1 of the '106 Patent	Briefing Booklet
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;	prior to shipping to "arrange a time for a next-day delivery when the patient or his designee is to be present," where the designee cannot be a minor (*Id.* at 19-20); contacting the "appropriate state/federal authorities" if a shipment is lost and attempting only one more "same-day redelivery attempt," after which the prescription "will be returned to the specialty pharmacy." (*Id.* at 20). The Briefing Booklet also discloses that "bulk drug for Xyrem will be 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." (*Id.* at 18). Further, the distribution system imposes inventory controls where "[r]eceiving, 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." (*Id.*). The Briefing Booklet also teaches that through the central pharmacy "all data collected will be available to state and federal authorities, on whatever timeframe they determine to be appropriate." (*Id.* at 16).
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 Briefing Booklet designates the central pharmacy as responsible for distribution of Xyrem subjected to the multiple controls discussed supra. For example, the Briefing Booklet discloses, "[t]he Xyrem risk management system ensures that the centralized pharmacy will identify patients who are attempting to duplicate prescriptions." (Briefing Booklet at 16). The Briefing Booklet also discloses that upon receipt of a prescription from the physician, the central pharmacy will "verify physician's eligibility by checking the AMA, DEA, or State Medical Board on-line databases" to ensure that "the prescription was written by a "real" physician with current privileges to prescribe controlled medications." (*Id.* at 19).
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	The Briefing Booklet discloses that Orphan Medical's distribution system allows for noting abuse, misuse, or diversion of the prescription drug: "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." (Briefing Booklet at 20).
delivering the prescription drug to the patient in order to treat the patient with the prescription drug.	The Briefing Booklet discloses that Xyrem is delivered, at least, via Fedex to the patient for treatment of narcolepsy. (Briefing Booklet at 7; 20).

4. Anticipation and/or Obviousness in Light of the FDA Safety Review (Claim 1)

Claim 1 of the '106 patent is anticipated and/or obvious in light of the FDA Safety Review. See the chart below for each disclosed element and analysis thereof.

Claim 1 of the '106 Patent	FDA Safety Review
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 FDA Safety review discloses that Xyrem is effective for treating narcolepsy, but also "medically prescribed Xyrem may be diverted for illegal use." (FDA Safety Review at 7; 108).
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	The FDA Safety Review teaches a method of distributing a prescription drug (Xyrem®) under exclusive control of an exclusive central pharmacy (or distributor). (FDA Safety Review at 108). Orphan Medical proposed Nova Factor to be the central pharmacy. Further, the FDA Safety Review describes a "closed-loop distribution system," wherein "Xyrem® will NOT be placed in retail pharmacy outlets," and instead, the document describes a "primary and exclusive distributor of Xyrem®." (*Id.* at 108).
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;	The FDA Safety Review teaches that a single, sole, and secure database will store the relevant information. "Every patient and prescribing physician will be registered with [the exclusive distributor] in 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." (*Id.* at 110).
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,	FDA safety review teaches that the exclusive central pharmacy (or distributor) will control distribution by being the primary and exclusive distributor, maintaining inventory and distribution records, and maintaining patient registry. Further, the secure database as described above will include information identifying the patient, drug prescribed, and credentials of the doctor. (FDA Safety Review at 108-10).

Claim 1 of the '106 Patent	FDA Safety Review
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;	The FDA Safety review discloses multiple controls that will be exercised by the central pharmacy: identifying "physician name, address, telephone and facsimile, DEA and state license numbers" (FDA Safety Review at 110); verifying that "the physician is eligible to prescribe Xyrem [by checking] the National Practitioner Databank ... including confirming that the physician has an active DEA number and check on whether any actions are pending against the physician" (*Id.* at 109); shipping "comprehensive printed materials" to all first time physicians" (*Id.*); contacting "patient's insurance company" (*Id.*); shipping "comprehensive printed materials" to the patient that includes educational information, such as "proper handling of the drug and an outline of precautions to be taken against diversion" (*Id.*); verifying "patient's home address and [arrange] shipment (*Id.*); shipping Xyrem via a courier service (*Id.*); confirming receipt of the drug by "a phone call by the pharmacy to the patient, no more than 24 hours after the shipment is delivered" (*Id.*); returning the shipment if "patient is unavailable to accept a shipment of Xyrem and execute required receipt" (*Id.*); launching an investigation if a shipment is lost" (*Id.* at 20); shipping to another pharmacy "if required by the patient's insurance company" (*Id.*); flagging "repeat instances of lost, stolen, destroyed, or spilled prescriptions/supplies" (*Id.*); questioning when "a prescription refill is requested by the patient prior to the anticipated due date" (*Id.*); limiting shipment to "only one month's shipment at a time and never more than 3 months' supply per shipment." (*Id.*). Additionally, the FDA safety review discloses that the secure database discussed supra will be "made available for review by the DEA as well as other federal and state agencies upon request" (*Id.*) and the "bulk drug will be manufactured at a single site" (*Id.* at 108).
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 FDA Safety Review under the single, exclusive distributor's operation requirements discloses all the controls described supra. Thus, it follows that a prescription cannot be authorized if not subjected to such controls. Further, the FDA Safety Review discloses Xyrem is shipped only "[o]nce approval has been established." (FDA Safety Review at 109).
noting, based on one or more of the analysis of	The FDA Safety Review notes in several places

Claim 1 of the '106 Patent	FDA Safety Review
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	potential for abuse, misuse, or diversion: prescriptions refills before anticipation date will be questioned (FDA Safety Review at 110); lost, stolen, destroyed, or spilled prescription/supply will be documented, flagged, and monitored (*Id.*); noting prescribing frequency (*Id.*); among others.
delivering the prescription drug to the patient in order to treat the patient with the prescription drug.	The FDA Safety Review discloses that Xyrem is delivered, at least, via courier services to the patient for treatment of narcolepsy. (FDA Safety Review at 7; 109-10).

5. Obviousness in Light of the Video (Claim 1)

Claim 1 of the '106 patent is obvious in light of the Video. See the chart below for each disclosed element and analysis thereof.

Claim 1 of the '106 Patent	Video
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 video teaches that Xyrem reduces incidence of cataplexy and improves symptoms of daytime sleepiness. Further, as a controlled substance, only patients are prescribed Xyrem and the distribution plan minimizes abuse, misuse, diversion. (Video ¶¶ 3-5).
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	The video discloses a single, centrally-located specialty pharmacy that controls distribution, documentation, and security through a closed-loop distribution system. The prescriptions are sent to the central pharmacy, which verifies that the "physician is an Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data ... to check if there are any pending or previous actions against the physician." (Video ¶¶ 14; 21). The single, specialty pharmacy stores data about prescriptions by patients; thus, it follows that the prescription sent by the physician includes patient identifying information. (*See, e.g.*, Video ¶ 24).
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;	The video teaches that all "data about inventory, physicians, reimbursements, patients, and delivery" is stored in one efficient and quickly-accessible location [single, specialty pharmacy]." (Video ¶ 24). Further, the video teaches that the "closed-loop distribution system … will 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." (Video ¶ 14).
controlling the distribution of said prescription	The video teaches that the "closed-loop

Claim 1 of the '106 Patent	Video
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;	distribution system … will 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." (Video ¶ 14).
and selecting multiple controls for distribution using said exclusive central computer system, the controls selected from the group consisting of	The video teaches that multiple controls are selected by the single, central pharmacy to prevent abuse, misuse, or diversion.
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;	The video discloses that the physician sends the prescription directly to the specialty pharmacy; the specialty pharmacy then verifies if the prescribing physician is an "Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data from the physician's State Board of Health to determine if there are any pending or previous actions against the physician." (Video ¶ 21).
providing comprehensive printed materials to the physician;	The video also teaches that physicians selected to prescribe Xyrem will "receive an educational module, in the mail, called the Physician Success Program." (Video ¶ 10).
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;	The video teaches that 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." (Video ¶26). The verification and documentation controls include contacting the patient directly to "make specific arrangements for the patient to the patient's authorized designee [designee would likely have to be over 18 years of age] to personally receive the package containing Xyrem." (Video ¶¶ 28; 32). The patient will be provided an educational package, Patient Success Program, along with Xyrem that will be "shipped overnight by Federal express utilizing a tracking system designed specifically for the specialty pharmacy." (Video ¶¶ 30-32). Receipt of Xyrem and educational materials is verified by a telephone call placed to the patient where "the

Claim 1 of the '106 Patent	Video
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;	specialty pharmacy will confirm receipt of the Xyrem prescription and the Patient Success program." (Video ¶¶ 34-35). If the patient or designee is unavailable to "receive or sign for the Xyrem, the package will be returned to the specialty pharmacy." (Video ¶ 33). If the package is lost, "the specialty pharmacy will initiate an immediate investigation." (Video ¶ 33). The inventory of Xyrem will be accessible only to qualified pharmacists and technicians and, "[b]oth Orphan and the pharmacy acknowledge and document every time any inventory is moved." (Video ¶¶ 16-17). Patients who inappropriately request refills are "flagged and their physician contacted. The physician verification process is repeated before every refill is sent." (Video ¶ 38).
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 video discloses that the above mentioned controls are "how the specialty pharmacy provides verification and documentation of both the prescription and the prescribing physician before preceeding [sic] to fill any requests for Xyrem." (Video ¶ 18). Further, the video states that "[s]trict adherence to security and verification protocols will minimize diversion of the medication to unauthorized individuals." (Video ¶ 41).
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	The video discloses that the central pharmacy staff 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." (Video ¶ 14). The video also discloses that the specialty pharmacy will keep track of anomalous patient requests to fill their prescriptions. (*Id.* at 38).
delivering the prescription drug to the patient in order to treat the patient with the prescription drug.	The video teaches that Xyrem is delivered to the patient in order to treat the patient for narcolepsy. (Video ¶ 2; 30).

6. Application of the Prior Art (Claims 2 – 8)

Claim 2 of the '106 patent is directed to 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." References that were not considered by the examiner disclose at least one of the controls recited in dependent claim 2. For example, the Briefing

Booklet, Video, and FDA Safety Review disclose all the controls recited in claim 2, thus the claim, at least, obvious. (*See, e.g.,* Briefing Booklet at 19-20; Video at ¶¶ 14, 21, 24, 34-35 ; Safety Review at 110). Similarly, Borsand discloses at least one of the recited controls, e.g., obtaining patient information. (*See, e.g.,* Borsand at ¶ 57).

Claim 3 is an independent claim that differs from claim 1 only by limiting the prescription drug to "sodium oxybate" for treating narcoleptic patients. The Briefing Booklet, Video, and FDA Safety Review disclose that the prescription drug is sodium oxybate. (*See, e.g.,* Briefing Booklet at 7; Video at ¶¶ 3-5; FDA Safety Review at 7). Claim 4 is directed to the method of claim 3 and includes the same controls as dependent claim 2. Thus, for the same reasons claim 2 is either anticipated or rendered obvious, claim 4 is also either anticipated or rendered obvious by the same references.

Claim 5 is an independent claim, but is similar to claim 1. The differences between claim 5 and claim 1 is that claim 5 recites "receiving, only into an exclusive computer database in a computer system" instead of "receiving, only into an exclusive central computer system" and recites "medical doctors" instead of "doctors." However, these differences do not add any limitation that overcomes any of the references discussed above because each reference discloses an exclusive computer database. Further, each reference discloses that only medical doctors will be prescribing the prescription drug. (*See, e.g.,* Briefing Book at 19; FDA Safety Review at 110). Claim 6 is directed to the method of claim 5 and includes the same controls as dependent claim 2. Thus, for the same reasons claim 2 is either anticipated or rendered obvious, claim 6 is also either anticipated or rendered obvious by the same references.

Claim 7 is an independent claim, but is similar to claims 1 and 5. The only difference between claim 7 and claims 1 and 5 is that claim 7 recites "writing" instead of "prescribing" a prescription. Claim 8 is directed to the method of claim 7 and includes the same controls as dependent claim 2. Thus, for the same reasons claim 2 is either anticipated or rendered obvious, claim 8 is also either anticipated or rendered obvious by the same references.

F. INELIGIBLE SUBJECT MATTER UNDER 35 U.S.C. § 101

The claims of the '106 patent are invalid under 35 U.S.C. § 101 because the claimed subject matter is not patentable. The claims of the '106 patent do not satisfy the machine-or-transformation test, and are directed to algorithms and abstract ideas *Bilski v. Kappos*, 130 S.Ct. 3218, 3229-30 (2010); *In re Bilski*, 545 F.3d 943, 962-63 (Fed. Cir. 2008).

In the '106 patent, the claimed process is not tied to a particular machine or apparatus. Although the claims include terms like "computer system" and "computer database," there is nothing in the specification indicating that a computer is integral to implementing the process. Further, while some of the steps require use of a "computer system," 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, col. 3, lines 10-14).[35]

The '106 patent claims do not transform an article into a different state or thing: They merely claim a method of distributing sensitive drugs that does not transform or make the drugs any less sensitive. Although some claims require 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. Although 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." *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, col. 1, lines 6- 7).

The Federal Circuit has determined that patent claims are abstract when the "steps can be performed in the human mind, or by a human using a pen and paper." *CyberSource*, 654 F.3d at 1372. In the '106 patent, the process is similar to a clearing house in that the method merely requires collecting and organizing data of doctors who are able to prescribe, and the patients who are able to receive, the medication, and organizing the data describing shipments of the medication, and associated marketing material. This process could equally be performed by pencil, paper, and a traditional filing cabinet system.

The steps of the claims in the '106 patent represent common ways that people have used to restrict allocation of materials, where a central controlling entity confirms with a validated third-party authority whether a substance should be delivered to an individual. Without meaningful limits, the claims effectively preempt the fundamental concept itself and foreclose a wide range of inventions that the patentee never conceived. For example, in *Dealertrack*, the Federal Circuit determined that the patentee's claimed process in its simplest form includes three steps: receiving data from one source (step A), selectively forwarding the data (step B, performed according to step D), and forwarding reply data to the first source (step C). *Dealertrack,* 674 F.3d at 1333. Because this claim "explain[s] the basic concept of processing information through a clearing-house . . . [t]he steps that constitute the method here do not impose meaningful limits on the claim's scope." *Id.* (citing *Bilski*, 130 S. Ct. at 3231; *Bilski*, 545 F.3d at 961-62) (quotations omitted). The Federal Circuit was "compelled to conclude that the claims are invalid as being directed to an abstract idea ***preemptive of a fundamental concept or idea*** that would foreclose innovation in this area." *Id.* at 1333 (emphasis added); *see also Mayo*, 132 S. Ct. at 1294 (the patent should not "risk disproportionately tying up the use of" the abstract idea in future discoveries). Similarly, here, the steps of the claims in the '106 are directed to a fundamental concept itself, thus are directed to an abstract idea.

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35 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).

In sum, the claims of the patent-in-suit fail to meet the requirements of § 101 because they: (1) fail the machine-or-transformation test and (2) are directed to the abstract idea of a centralized authorization center for prescriptions drugs, which is a fundamental principle that would be improperly preempted by the patent-in-suit. Here, the computer must be integral to the claimed invention, facilitating the process in a way that a person making calculations or computations could not." *Bancorp*, 687 F.3d at 1278. This method could be performed by someone using pencil, paper, and a standard records-keeping system. For these reasons, the claims of the '106 patent are invalid under 35 U.S.C. § 101.

G. CONCLUSION

For the reasons stated above, claims 1-8 of the '106 patent are anticipated and/or obvious over the prior art and claims 1-8 are invalid 35 U.S.C. § 101. Further, Par will not infringe claims 1-8. Par reserves the right to develop additional grounds, reasons, and authorities that any or all of the claims of these patents are invalid, unenforceable or not infringed.

XII. THE '107 PATENT

A. OVERVIEW OF THE '107 PATENT

1. Specification of the '107 Patent

U.S. Patent No. 7,765,107 ("the '107 patent") issued on July 27, 2010, from U.S. Application 11/097,985, filed April 1, 2005, and is a divisional of U.S. Application 10/322,348 (filed December 17, 2002), which itself issued as the '730 patent. The '107 patent lists three inventors: Dayton Reardon, Patti Engel, and Bob Gagne. It was originally assigned to JPI Commercial, LLC, but was subsequently assigned to Jazz.

The '107 patent is titled "Sensitive Drug Distribution System and Method," and is directed, *inter alia*, to computerized methods of distributing a prescription drug under control of an exclusive central pharmacy, including methods of distributing gamma hydroxy butyrate (GHB). According to the '107 patent, the "invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs." According to the '107 patent, sensitive drugs requiring control of distribution include GHB. ('107 patent, col. 1, lines 18-35). The '107 patent indicates that there is a need for a distribution system to address abuse. ('107 patent, col. 1, lines 36-39).

The invention purports to provide a drug distribution system and method utilizing 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 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. ('107 patent, col. 1, line 44 to col. 2, line 21).

2. Prosecution History of the '107 Patent

On April 01, 2005, the applicants filed U.S. Application No. 11/097,985 ("the '985 application") with 25 total claims, including 4 independent claims. The '985 application is a continuation of U.S. Application No. 10/322,348, which issued as the '730 patent. Applicants filed a Preliminary Amendment, cancelling claims 1-25 and adding new claims 26-31, including 2 independent claims. Applicants also filed a Petition to Make Special under 37 C.F.R. § 1.102(d), including a Pre-Examination Statement.

During prosecution the the Examiner rejected the claims under 35 U.S.C. § 103(a) as obvious over U.S. Patent Application No. 2004/0019794 ("Moradi '794"), U.S. Patent Application No. 2004/0176985 ("Lilly '985"), Ukens ("Specialty Pharmacy"), U.S. Patent Application No. 2003/0033168 ("Califano '168"), U.S. Patent No. 6,564,121 ("Wallace et al."), and U.S. Patent Application No. 2003/0160698 ("Andreasson '698"). (*See, e.g.,* '107 patent application, Sept. 14, 2009, Non-Final Rejection). The Examiner further rejected claims 26-31 as directed to non-statutory subject matter; specifically, independent claims 26 and 29 were deemed to recite only mental steps. (*Id.*). Additionally, claims 26-31 were provisionally rejected for non-statutory double patenting over claims from the co-pending U.S. Application Nos. 11/097,651 and 10/979,665, and as indefinite for recitation of a variety of terms. (*Id.*)

On November 3, 2009, applicants filed an amendment and response. The applicants also agreed to file terminal disclaimers in response to the double patenting rejections. The claims were amended throughout to include reference to "computerized" and "computer processor" in response to the non-statutory subject matter rejection. ('107 patent application, Nov. 3, 2009, Amendment and Response). For example, applicants amended independent claim 26, to include

as follows in response to the obviousness rejections.

> A computerized method to control abuse of a sensitive drug comprising:
>
> ~~by~~ controlling with a computer processor the distribution of said sensitive drug ~~thereof~~ via an exclusive central pharmacy that maintains a central database that tracks all prescriptions of said sensitive drug and analyzes for potential abuse situations~~, the method comprising:~~;
>
> receiving in the computer processor all prescription requests, for any and all patients being prescribed the sensitive drug, only at the exclusive central pharmacy, from any and all medical doctors allowed to prescribe the sensitive drug;
>
> processing with the computer processor all prescriptions for the sensitive drug only by the exclusive central pharmacy using only the central database;
>
> determining with the computer processor current and anticipated patterns of potential prescription abuse of said sensitive drug from periodic reports generated only by the central database based on prescription request data from a particular medical doctor and 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 doctor; and
>
> selecting with the computer processor multiple controls for distribution by said exclusive central pharmacy, the controls comprising ~~selected from the group consisting of~~ communicating prescriptions from a physician to the central pharmacy ….

(*Id.*).

On March 10, 2010, the USPTO issued a Notice of Allowance, allowing claims 26-31, preliminarily determining PTA to be 1109 days, and providing the following reasons for allowance. An Examiner's Amendment amended "sensitive drug" to "prescription drug" in claims 26 and 27.

> Claim 26, now renumbered as claim 1, is directed to a computerized method to control abuse of a prescription drug.
>
> The closest prior art of record, Moradi (US 2004/0019794 A 1), Lilly et al. (US 2004/0176985 A1), and Ukens ("Specialty Pharmacy") teach receiving prescription request data from a medical doctor, selecting multiple controls for distribution by a central pharmacy, determining current and anticipated patterns of potential abuse, and restricting distribution of a medication to only one pharmacy.

> However, the closest prior art of record does not teach or fairly suggest 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 and processing with the computer processor all prescriptions for the prescription drug only by the exclusive central pharmacy using only the central database.
>
> Dependent claims 27 and 28 (now renumbered as claims 2 and 3) incorporate the allowable subject matter of claim 26, through dependency, and are also allowable for the same reasons.
>
> Claim 29, now renumbered as claim 4, is directed to a computerized method to control abuse of gamma hydroxy butyrate (GHB).
>
> The closest prior art of record, Moradi (US 2004/0019794 A1), Lilly et al. (US 2004/0176985 A1), Ukens ("Specialty Pharmacy"), and Melker et al. (US 2002/0177232 A1) teach receiving prescription request data from a medical doctor, selecting multiple controls for distribution by a central pharmacy, determining current and anticipated patterns of potential abuse, restricting distribution of a medication to only one pharmacy, and that GHB is an illicit substance.
>
> However, the closest prior art of record does not teach or fairly suggest 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 and processing in the computer processor all prescriptions for GHB only by the exclusive central pharmacy using only the central database.
>
> Dependent claims 30 and 31 (now renumbered as claims 5 and 6) incorporate the allowable subject matter of claim 29, through dependency, and are also allowable for the same reasons.

('107 patent application, March 10, 2010, Notice of Allowance).

On July 27, 2010, the '107 patent issued with 6 claims. According to the face page of the '107 patent, the term was extended or adjusted under 35 U.S.C. § 154(b) by 1369 days, subject to the approved disclaimers.

3. Claims of the '107 Patent

The '107 patent issued with the following claims:

#	Claims of the '107 Patent
1	A computerized method to control abuse of a prescription drug

#	Claims of the '107 Patent
	comprising: 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; 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; processing with the computer processor all prescriptions for the prescription drug only by the exclusive central pharmacy using only the central database; determining with the computer processor current and anticipated patterns of potential prescription abuse of said prescription 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 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 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.
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

#	Claims of the '107 Patent
	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; 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.
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.
4	A computerized method to control abuse of gamma hydroxy butyrate (GHB) comprising: 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; 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; processing in the computer processor all prescriptions for GHB only by the exclusive central pharmacy using only the central database; 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 particular medical doctor and based on filling of prescriptions by a particular patient, wherein said request data contain information identifying the patient, GHB as the drug prescribed, and credentials of the medical doctor; and 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 when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single

#	Claims of the '107 Patent
	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.
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; 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.
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.

B. LEVEL OF SKILL IN THE ART OF THE '107 PATENT

The subject matter of the '107 patent falls within the field of designing computer systems. Depending on the claim, the person of ordinary skill in this field would be a programmer, or a systems analyst/programmer. Such an individual would have a Bachelor's Degree in Computer Science and several years of experience in the field. *E.I. DuPont de Nemours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), *aff'd* 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein and would have the capability to draw inferences from them.

C. CLAIM CONSTRUCTION OF THE '107 PATENT

One of ordinary skill in the art and a court would interpret the claims of the '107 patent according to their plain and ordinary meaning unless otherwise specified herein.

On September 14, 2012, the U.S. District Court for the District of New Jersey issued a claim construction order for terms in the '730 patent family, which includes distribution patents, '106, '107, and '059, in the case of *Jazz Pharmaceuticals Inc. v. Roxane Laboratories Inc.,* No. 10-6108, D.I. 151 (D.N.J. Sept. 14, 2012). The district court's constructions for several relevant terms are briefly discussed below as well as in sections X(D) and XI(D), above. Par includes these constructions for informational purposes only and reserves its right to challenge these

constructions.

D. NONINFRINGEMENT OF THE '107 PATENT

Par does not directly infringe any claim of the '107 patent under 35 U.S.C. § 271(a) because Par does not perform the claimed method. Notably, independent claim 1 describes "a computerized method to control abuse of a prescription drug " which requires that "an exclusive central pharmacy" receive "all prescription requests, for any and all patients being prescribed the prescription drug ." Independent claim 4 also requires these two elements, but specifically names gamma hydroxyl butyrate as the "prescription drug." Par will not infringe these claims if granted approval for its generic product, because it will not control "an exclusive central pharmacy" that receives all of the prescriptions for the drug gamma hydroxyl butyrate or any other prescription drug.

Par further does not infringe claims 4-6, as they require the control of "gamma hydroxyl butyrate," whereas Par's proposed product contains sodium oxybate (sodium gamma-hydroxybutyrate).

Par also does not contributorily infringe under 35 U.S.C. § 271(c) because the claimed method has noninfringing uses. Furthermore, Par does not infringe claims 1-6 of the '107 patent under § 271(b) because the Par has a good faith belief that the '107 patent is invalid, which negates the requisite intent for induced infringement. *Commil USA, LLC v. Cisco Systems, Inc.*, 720 F.3d 1361, 1364 (Fed. Cir. Jun. 25, 2013) ("we find that Cisco's evidence of a good-faith belief of invalidity may negate the requisite intent for induced infringement.")

E. OBVIOUSNESS OF THE '107 PATENT

1. The Scope and Content of the Prior Art

The earliest possible effective U.S. filing date for the '107 patent is December 17, 2002, based on the filing date of U.S. Application 10/322,348 for the parent, '730 patent. The prior art is described in section X(E)(1), above.

2. Obviousness In Light Of Borsand (Claims 1)

Claim 1 of the '107 patent is obvious over Borsand, which describes each of the elements of claim 1. Claim 1 is directed to a computerized method for controlling abuse of a prescription drug. The claim essentially requires patients to obtain the prescription drug from a single, central pharmacy that maintains an exclusive computer database of information, thus allowing the pharmacy to perform checks of potential abuse before delivering the drug to the patient. The computerized method of claim 1 controls distribution by subjecting the single, central pharmacy to a multitude of controls before the drug is delivered.

Claim 1 of the '107 Patent	Borsand
A computerized method to control abuse of a prescription drug comprising:	Borsand discloses that the "invention relates to a computer based system for tracking information related to pharmaceutical prescriptions" and that this system reduces fraud, redundancy, pharmaceutical abuse, pharmaceutical misuse,

Claim 1 of the '107 Patent	Borsand
	and errors, with respect to prescription drugs. (Borsand ¶¶ 33; 38).
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;	A computer system or a computer, as described in Borsand, inherently includes a computer processor for processing data. Borsand teaches an exclusive computer database associated with an exclusive computer system. Borsand discloses a system that allows for "pharmaceutical information to be stored only once and in a centralized location accessible by the appropriate parties." (Borsand ¶ 3). Borsand teaches that all relevant data is housed in a computer that "can be a single centralized computer or server, a single network ..." (Borsand ¶ 31). Borsand discloses that the "system 20 provides functionality for tracking pharmaceutical 28, prescription 32, and related information," where such "[i]nformation tracking can be in a proactive and real-time manner, or in the form of reports and analysis 42 taking place after the events have already occurred. If a patient 22, provider 30, pharmacist 40, or PBM 50 attempts an action that not in accordance with the predefined rules 34 of the payor 60, the system 20 can be configured **to not allow the attempted conduct, or to allow the conduct, but generate a report 42 relating to the undesirable activity**." (Borsand ¶ 34).
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;	Borsand teaches that "[i]n 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." (Borsand ¶ 43). Borsand also teaches a prescription subsystem where "prescriptions are only issued by a certain subset of health care providers, such as physicians ...." Processing a prescription requires inputting "patient record which includes patient information relevant to pharmaceutical selection." Each doctor must use a unique "UserID" and a patient is assigned a unique "PatientID." (Borsand ¶ 3).
determining with the computer processor current and anticipated patterns of potential prescription abuse of said prescription drug from periodic reports generated only by the central database based on prescription request data from a particular medical doctor and further based on	The system of Borsand provides "functionality for tracking pharmaceutical, prescription and related information," where "tracking can be in a proactive and real-time manner, or in the form of reports and analysis ..." (Borsand ¶ 87). Any abuse or violation can be detected by the system

Claim 1 of the '107 Patent	Borsand
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	which "can be configured to not allow the attempted conduct, or to allow the conduct, but generate a report relating to the undesired activity." (*Id.).* Borsand discloses that the pharmaceutical subsystem (part of the overall exclusive central computer system) re-evaluates the prescription before the prescription is filled or sent to a payor, where "medical aspects of a prescription can also be reviewed, so that the appropriateness of the selected pharmaceutical can be confirmed as it relates to ... other patient attributes that could affect the desirability of filling a particular prescription." Borland discloses in multiple places that desirability of filling prescriptions may be tied to misuse of pharmaceuticals; for example, patient attributes includes patient's refill behavior. (Borsand ¶ 53).
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	Borsand discloses selecting at least some of the controls for distribution using Borsand's exclusive central computer system: Borsand's prescription subsystem, part of Borsand's overall system, requires a provider to communicate prescriptions thereto in order "to generate prescriptions for a patient" (Borsand ¶ 50); input "patient record which includes patient information relevant to pharmaceutical information" (*Id.* at ¶ 57); input a UserID which is unique to the provider, which necessarily includes physician identifying data (*Id.*); monitor whether prescription has been refilled (*Id.* at ¶ 56); and provide for automatic pre-certification of prescriptions to reduce "the likelihood of fraudulent or abusive behavior" (*Id.*); among others. Further, the system disclosed in Borsand includes a reimbursement system that communicates with the patient's insurance company (payor) and also prevents "[m]isuse of pharmaceuticals by redundant prescriptions, overuse ... and other forms of misuse can be reduced through use of the system. Fraud and error can also be reduced...." (*Id.* at ¶ 75).

Claim 1 of the '107 Patent	Borsand
checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;	

The examiner allowed claim 1 because the prior art considered by the examiner did not teach that all prescriptions will be received by an exclusive computer system/database.

> However, the closest prior art of record does not teach or fairly suggest receiving, **only into an exclusive central computer system/exclusive computer database, *all* prescriptions** for any and all patients being prescribed the prescription drug, 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, and authorizing the filling, using the exclusive central computer system/exclusive computer database, of a prescription for the prescription drug that has been subjected to multiple controls.

(Notice of Allowance, March 10, 2010). The examiner, however, never considered Borsand. Instead, the examiner found that "the closest prior art of record" was Moradi , Lilly et al. (, Melker et al., and Ukens. Notably, the examiner found that all the elements of claim 1 are disclosed in combination in the prior art of record rendering the alleged invention obvious, except an exclusive central computer system/database that receives all prescriptions from all patients, controls the distribution of the prescriptions, and authorizes distribution of the prescriptions. Furthermore, Borsand, alone, also teaches an exclusive computer system/database that performs the functions recited in claim 1.

It is the patentee's obligation to present evidence of secondary considerations, if any, to rebut a *prima facie* case of obviousness. The '106 patent provides no specific evidence of secondary considerations of non-obviousness. Any evidence of secondary considerations is insufficient to overcome the strong case of *prima facie* obviousness of the claimed subject matter.

3. Anticipation and/or Obviousness Over Briefing Booklet (Claim 1)

Claim 1 of the '107 patent is anticipated and/or obvious over the Briefing Booklet. See chart below for each disclosed element and analysis thereof.

Claim 1 of the '107 Patent	Briefing Booklet
A computerized method to control abuse of a prescription drug comprising:	The Briefing Booklet teaches use of a database using an exclusive specialty pharmacy. The reference to "real-time data" implies a computer processor managing the database. Further, the Briefing Booklet teaches the potential for abuse, misuse, or diversion of Xyrem (e.g., "They [law enforcement] continue to be very concerned, of course, about the use of illicit GHB and related

Claim 1 of the '107 Patent	Briefing Booklet
	chemicals and asked that Orphan Medical address both the potential for inappropriate prescribing of Xyrem and the potential for diversion...."). (Briefing Booklet at 7).
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;	Borsand teaches that "[b]ecause 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." (Briefing Booklet at 15). Further, Borsand teaches that "[t]he 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." (Briefing Booklet at 20).
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;	In Orphan Medical's Briefing Booklet, it teaches use of a database using an exclusive specialty pharmacy. The reference to "real-time data" implies a computer processor managing the database. In Orphan Medical's Briefing Booklet, it teaches use of a database using an exclusive specialty pharmacy. The reference to "real-time data" implies a computer processor managing the database. "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

Claim 1 of the '107 Patent	Briefing Booklet
	rapid identification in the rare case of diversion." (Briefing Booklet at 15). "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." (Briefing Booklet at 20).
determining with the computer processor current and anticipated patterns of potential prescription abuse of said prescription 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	The Briefing Booklet discloses that Orphan Medical's distribution system allows for determining abuse, misuse, or diversion of the prescription drug: "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." (Briefing Booklet at 20). The Briefing Booklet designates the central pharmacy as responsible for distribution of Xyrem® subjected to the multiple controls discussed *supra*. For example, the Briefing Booklet discloses, "[t]he Xyrem risk management system ensures that the centralized pharmacy will identify patients who are attempting to duplicate prescriptions." (Briefing Booklet at 16). The Briefing Booklet discloses that upon receipt of a prescription from the physician, the central pharmacy will "verify physician's eligibility by checking the AMA, DEA, or State Medical Board on-line databases" to ensure that "the prescription was written by a "real" physician with current privileges to prescribe controlled medications." (Briefing Booklet at 19).
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	The Briefing Booklet discloses multiple controls that are available in Orphan Medical's distribution system: the closed-loop distribution system "provides for the shipment and receipt of medicine" (Briefing Booklet at 13); verification of the physician's eligibility by checking AMA, DEA, or State Medical Board on-line databases (*Id.* at 19); verifying the prescription by contacting the physician's office to confirm patient information (*Id.*); collecting patient's specific information by the specialty pharmacy to assist "in the building of a patient registry which also aids in diversion prevention" (*Id.*); contacting the insurance company to obtain insurance reimbursement (*Id.*); providing the physician with printed educational materials via the "Physician

Claim 1 of the '107 Patent	Briefing Booklet
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.	Success Program" (*Id.*); providing the patient with printed educational materials via the "Patient Success Program" (*Id.* at 20); requiring the pharmacist at the specialty pharmacy to contact the patient to "confirm receipt of the Xyrem prescription and Patient Success Program" (*Id.*); shipping the prescription and the Patient Success Program via Federal Express (*Id.*); contacting the patient prior to shipping to "arrange a time for a next-day delivery when the patient or his designee is to be present," where the designee cannot be a minor (*Id.* at 19-20); contacting the "appropriate state/federal authorities" if a shipment is lost and attempting only one more "same-day redelivery attempt," after which the prescription "will be returned to the specialty pharmacy." (*Id.* at 20). The Briefing Booklet also discloses that "bulk drug for Xyrem will be 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." (*Id.* at 18). Further, the distribution system imposes inventory controls where "[r]eceiving, 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." (*Id.*). The Briefing Booklet also teaches that through the central pharmacy "all data collected will be available to state and federal authorities, on whatever timeframe they determine to be appropriate." (*Id.* at 16).

4. Anticipation and/or Obviousness in Light of the FDA Safety Review (Claim 1)

Claim 1 of the '107 patent is anticipated and/or obvious over the FDA Safety Review. See chart below for each disclosed element and analysis thereof.

Claim 1 of the '107 Patent	FDA Safety Review
A computerized method to control abuse of a prescription drug comprising:	The FDA Safety review discloses that "medically prescribed Xyrem may be diverted for illegal use." To control such abuse, the FDA Safety review proposed a closed-loop distribution system. (FDA Safety Review at 7; 108).
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	The FDA Safety Review teaches a method of distributing a prescription drug (Xyrem®) under exclusive control of an exclusive central pharmacy (or distributor). (FDA Safety Review at 108). Apparently, Orphan Medical proposed

Claim 1 of the '107 Patent	FDA Safety Review
abuse situations;	Nova Factor to be the central pharmacy. Further, the FDA Safety Review describes a "closed-loop distribution system," wherein "Xyrem® will NOT be placed in retail pharmacy outlets," and instead, the document describes a "primary and exclusive distributor of Xyrem®." (*Id.* at 108).
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;	The FDA Safety Review teaches that a single, sole, and secure database will store the relevant information. "Every patient and prescribing physician will be registered with [the exclusive distributor] in 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." (FDA Safety Review 110).
determining with the computer processor current and anticipated patterns of potential prescription abuse of said prescription 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	The FDA Safety review teaches that the secure database as described above will allow the DEA to review prescriptions by physician specialty, prescriptions by patient name, prescriptions by volume, and prescriptions by dose. Further, the FDA safety review teaches that repeat instances of lost, stolen, destroyed, or spilled prescription supplies will be flagged for monitoring and future instances thoroughly questioned. (FDA Safety Review at 108-10).
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	The FDA Safety review discloses multiple controls that will be exercised by the central pharmacy: identifying "physician name, address, telephone and facsimile, DEA and state license numbers" (FDA Safety Review at 110); verifying that "the physician is eligible to prescribe Xyrem [by checking] the National Practitioner Databank ... including confirming that the physician has an active DEA number and check on whether any actions are pending against the physician" (*Id.* at 109); shipping "comprehensive printed materials" to all first time physicians" (*Id.*); contacting "patient's insurance company" (*Id.*); shipping "comprehensive printed materials" to the patient that includes educational information, such as

Claim 1 of the '107 Patent	FDA Safety Review
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.	"proper handling of the drug and an outline of precautions to be taken against diversion" (*Id.*); verifying "patient's home address and [arrange] shipment (*Id.*); shipping Xyrem via a courier service (*Id.*); confirming receipt of the drug by "a phone call by the pharmacy to the patient, no more than 24 hours after the shipment is delivered" (*Id.*); returning the shipment if "patient is unavailable to accept a shipment of Xyrem and execute required receipt" (*Id.*); launching an investigation if a shipment is lost" (*Id.* at 20); shipping to another pharmacy "if required by the patient's insurance company" (*Id.*); flagging "repeat instances of lost, stolen, destroyed, or spilled prescriptions/supplies" (*Id.*); questioning when "a prescription refill is requested by the patient prior to the anticipated due date" (*Id.*); limiting shipment to "only one month's shipment at a time and never more than 3 months' supply per shipment." (*Id.*). Additionally, the FDA safety review discloses that the secure database discussed supra will be "made available for review by the DEA as well as other federal and state agencies upon request" (*Id.*) and the "bulk drug will be manufactured at a single site" (*Id.* at 108).

5. Obviousness Over the Video (Claim 1)

Claim 1 of the '107 patent is obvious over the Video. See chart below for each disclosed element and analysis thereof.

Claim 1 of the '107 Patent	Video
A computerized method to control abuse of a prescription drug comprising:	The Video shows a "shot of pharmacy employee picking up prescription fax and sitting down at a computer to verify physician's eligibility." (Video ¶ 21). The illustration of a computer in the Video teaches using a computer to control distribution. The Video teaches that the closed-loop distribution model minimizes opportunities for diversion of prescription drug Xyrem® to unauthorized individuals. (Video ¶¶ 4; 5.)
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;	The Video discloses a single, centrally-located specialty pharmacy that controls distribution, documentation, and security through a closed-loop distribution system. The prescriptions are sent to the central pharmacy, which verifies that the "physician is an Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data ... to check if there are any pending or

Claim 1 of the '107 Patent	Video
	previous actions against the physician." (Video ¶¶ 14; 21.) The single, specialty pharmacy stores data about prescriptions by patients; thus, it follows that the prescription sent by the physician includes patient identifying information. (*See, e.g.,* Video ¶ 24.)
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;	The Video teaches that all "data about inventory, physicians, reimbursements, patients, and delivery" is stored in one efficient and quickly-accessible location [single, specialty pharmacy]." (Video ¶ 24.) Further, the Video teaches that the "closed-loop distribution system … will 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." (Video ¶ 14.)
determining with the computer processor current and anticipated patterns of potential prescription abuse of said prescription 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	The Video discloses that the closed-loop distribution system "will 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." (Video ¶ 14.) Further, the Video discloses a single, centrally-located specialty pharmacy that controls distribution, documentation, and security through a closed-loop distribution system. The prescriptions are sent to the central pharmacy, which verifies that the "physician is an Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data ... to check if there are any pending or previous actions against the physician." (Video ¶¶ 14; 21.) The single, specialty pharmacy stores data about prescriptions by patients; thus, it follows that the prescription sent by the physician includes patient identifying information. (*See, e.g.,* Video ¶ 24.)
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	The Video teaches that multiple controls are selected by the single, central pharmacy to prevent abuse, misuse, or diversion. The video discloses that the physician sends the prescription directly to the specialty pharmacy; the specialty pharmacy then verifies if the prescribing physician is an "Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data from

Claim 1 of the '107 Patent	Video
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.	the physician's State Board of Health to determine if there are any pending or previous actions against the physician." (Video ¶ 21). The Video also teaches that physicians selected to prescribe Xyrem will "receive an educational module, in the mail, called the Physician Success Program." (Video ¶ 10). The video teaches that 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." (Video ¶26). The verification and documentation controls include contacting the patient directly to "make specific arrangements for the patient to the patient's authorized designee [designee would likely have to be over 18 years of age] to personally receive the package containing Xyrem." (Video ¶¶ 28; 32). The patient will be provided an educational package, Patient Success Program, along with Xyrem that will be "shipped overnight by Federal express utilizing a tracking system designed specifically for the specialty pharmacy." (Video ¶¶ 30-32). Receipt of Xyrem and educational materials is verified by a telephone call placed to the patient where "the specialty pharmacy will confirm receipt of the Xyrem prescription and the Patient Success program." (Video ¶¶ 34-35). If the patient or designee is unavailable to "receive or sign for the Xyrem, the package will be returned to the specialty pharmacy." (Video ¶ 33). If the package is lost, "the specialty pharmacy will initiate an immediate investigation." (Video ¶ 33). The inventory of Xyrem will be accessible only to qualified pharmacists and technicians and, "[b]oth Orphan and the pharmacy acknowledge and document every time any inventory is moved." (Video ¶¶ 16-17). Patients who inappropriately request refills are "flagged and their physician contacted. The physician verification process is repeated before every refill is sent." (Video ¶ 38.)

6. Application of the Prior Art to the '107 Patent (Claims 2 – 6)

Claim 2 of the '107 patent is directed to 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 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.

As discussed above, claim 1 is obvious in light of Borsand, the Briefing Book, the Video, and/or the FDA Safety review. The additional restrictions on the "controls," recited in claim 2, are taught by references that were not considered by the examiner. For example, the Briefing Booklet, Video, and FDA Safety Review disclose the controls recited in claim 2. (*See, e.g.,* Briefing Booklet at 19-20; Video at ¶¶ 14, 21, 24, 30-32, 34-35; Safety Review at 108-110). Similarly, Borsand discloses at least one of the recited controls, e.g., obtaining patient information. (*See, e.g.,* Borsand at ¶ 57). Thus, claim 2 is obvious.

Claim 3 is directed to the method of claim 1 and further comprises "consulting a separate database to verify that the medical doctor is eligible to prescribe the drug." References that were not considered by the examiner disclose consulting a separate database to verify physician eligibility. For example, the Briefing Booklet discloses that the central pharmacy will periodically check the AMA, NPD, and State Medical Boards databases to ensure physician eligibility to prescribe Xyrem. (Briefing Booklet at 15). The Video discloses that the specialty pharmacy verifies that the physician is eligible to prescribe Xyrem by checking a separate database of the physician's home State Board of Health. (Video at ¶ 21). The FDA Safety Review discloses that, upon receipt of a prescription, the specialty pharmacy will check the separate National Practitioner Databank to verify that the physician is eligible to prescribe Xyrem. (FDA Safety Review at 109). Similarly, Borsand discloses that in alternative embodiments, multiple databases may be used to store pharmaceutical information: "PBMs 50, payors 60, patients 22, providers 30, and prescriptions can each have their own separate databases 62, which can [be] interconnected or kept separate, but each are accessible from the computer housing 26 ...." (Borsand ¶ 43). Such a system would necessarily require checking a separate database to verify physician eligibility to prescribe a drug. Therefore, claim 3 is anticipated and/or rendered obvious as all of the recited elements are taught in the prior art.

Claim 4 is an independent claim that differs from claim 1 only by limiting the prescription drug to "gamma hydroxy butyrate (GHB)." At least the Briefing Booklet and the FDA Safety Review explicitly disclose that the prescription drug is GHB. (*See, e.g.,* Briefing Booklet at 7; FDA Safety Review at 7 (disclosing Xyrem®, which is a salt form of GHB)). Therefore, claim 4 is anticipated and/or rendered obvious by the prior art discussed above.

Claims 5 and 6 are similar to claims 2 and 3, except these claims are directed to independent claim 4. For the same reasons claims 2 and 3 are anticipated and/or rendered obvious, claims 5 and 6 are also either anticipated or rendered obvious by the same references.

F. INELIGIBLE SUBJECT MATTER UNDER 35 U.S.C. § 101

The claims of the '107 patent are invalid under 35 U.S.C. § 101 because the claimed subject matter is not patentable. The claims of the '107 patent do not satisfy the machine-or-transformation test, and are directed to algorithms and abstract ideas *Bilski v. Kappos*, 130 S.Ct. 3218, 3229-30 (2010); *In re Bilski*, 545 F.3d 943, 962-63 (Fed. Cir. 2008).

In the '107 patent, the process is not tied to a particular machine or apparatus. Although the claims include terms like "computerized method" and "computer processor," there is nothing in the specification indicating that a computer is integral to implementing the process. Further, while some of the steps require use of a "computer processor," 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, col. 3, lines 10-14.)[36]

The '107 patent claims do not transform an article into a different state or thing: They merely claim a method of distributing sensitive drugs that does not transform or make the drugs any less sensitive. Although some claims require 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. Although 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." *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, col. 1, lines 6- 7.)

The Federal Circuit has determined that patent claims are abstract when the "steps can be performed in the human mind, or by a human using a pen and paper." *CyberSource*, 654 F.3d at 1372. In the '107 patent, the process is similar to a clearing house in that the method merely requires collecting and organizing data of doctors who are able to prescribe, and the patients who are able to receive, the medication, and organizing the data describing shipments of the medication, and associated marketing material. This process could equally be performed by pencil, paper, and a traditional filing cabinet system.

The steps of the claims in the '107 patent represent common ways that people have used to restrict allocation of materials, where a central controlling entity confirms with a validated third-party authority whether a substance should be delivered to an individual. Without meaningful limits, the claims effectively preempt the fundamental concept itself and foreclose a

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[36] 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).

wide range of inventions that the patentee never conceived. For example, in *Dealertrack*, the Federal Circuit determined that the patentee's claimed process in its simplest form includes three steps: receiving data from one source (step A), selectively forwarding the data (step B, performed according to step D), and forwarding reply data to the first source (step C). *Dealertrack,* 674 F.3d at 1333. Because this claim "explain[s] the basic concept of processing information through a clearing-house . . . [t]he steps that constitute the method here do not impose meaningful limits on the claim's scope." *Id.* (citing *Bilski*, 130 S. Ct. at 3231; *Bilski*, 545 F.3d at 961-62) (quotations omitted). The Federal Circuit was "compelled to conclude that the claims are invalid as being directed to an abstract idea ***preemptive of a fundamental concept or idea*** that would foreclose innovation in this area." *Id.* at 1333 (emphasis added); *see also Mayo*, 132 S. Ct. at 1294 (the patent should not "risk disproportionately tying up the use of" the abstract idea in future discoveries). Similarly, here, the steps of the claims in the '107 are directed to a fundamental concept itself, thus are directed to an abstract idea.

In sum, the claims of the patent-in-suit fail to meet the requirements of § 101 because they: (1) fail the machine-or-transformation test and (2) are directed to the abstract idea of a centralized authorization center for prescriptions drugs , which is a fundamental principle that would be improperly preempted by the patent-in-suit. Here, the computer must be integral to the claimed invention, facilitating the process in a way that a person making calculations or computations could not." *Bancorp*, 687 F.3d at 1278. This method could be performed by someone using pencil, paper, and a standard records-keeping system. For these reasons, the claims of the '107 patent are invalid under 35 U.S.C. § 101.

G. CONCLUSION

For the reasons stated above, claims 1-6 of the '107 are anticipated and/or obvious over the prior art, and claims 1-6 are not patentable under 35 U.S.C. § 101. Further, Par will not infringe the claims of the '107 patent. Par reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these patents are invalid, unenforceable or not infringed.

XIII. THE '059 PATENT

A. OVERVIEW OF THE '059 PATENT

1. Specification of the '059 Patent

U.S. Patent No. 7,895,059 ("the '059 patent") issued on February 22, 2011, from U.S. Application 12/704,097, filed February 11, 2010, which is a continuation of U.S. Application 10/322,348 (filed December 17, 2002), which itself issued as U.S. Patent No. 7,668,730. The '059 patent listed three inventors: Dayton Reardon, Patti Engel, and Bob Gagne. It is assigned to Jazz.

The '059 patent is titled "Sensitive Drug Distribution System and Method," and is directed, *inter alia*, to computerized methods of distributing a prescription drug under control of an exclusive central pharmacy, including methods of distributing gamma hydroxy butyrate (GHB). According to the '059 patent, the "invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs." According to the '059 patent, sensitive drugs

requiring control of distribution include GHB. ('059 patent, col. 1, lines 17-35). The '059 patent indicates that there is a need for a distribution system to address abuse:

> 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.

('059 patent, col. 1, lines 36-39).

The invention purports to provide a drug distribution system and method utilizing 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 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. ('059 patent, col. 1, line 44 to col. 2, line 21.)

2. Prosecution History of the '059 Patent

On February 11, 2010, the applicants filed U.S. Application No. 12/704,097 ("the '097 application") with 16 total claims, including 6 independent claims.

On September 24, 2010, the USPTO issued a non-final rejection. Claims 1-16 were

rejected for non-statutory obviousness-type double patenting over claims 32, 35 and 37-42 of U.S. Patent No. 7,668,730 ("the '730 patent").

On December 21, 2010, the USPTO issued a Notice of Allowance, preliminarily determining PTA to be 0 days and providing the following reasons for allowance.

> Claims 1, 6, and 14 are directed to a computerized method of distributing a prescription drug 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 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/sent only if no potential abuse is found by the patient to whom the prescription drug is prescribed *and* the doctor/authorized prescriber prescribing the prescription drug.
>
> Dependent claims 2-5, 7, 8, 15, and 16 incorporate the allowable subject matter of their respective independent claims, through dependency, and are also allowable for the same reasons.
>
> Claims 9, 12, and 13 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/sent only if no potential abuse is found by the patient to whom GHB is prescribed *and* the doctor/authorized prescriber of the GHB.

Dependent claims 10 and 11 incorporate the allowable subject matter of claim 9, through dependency, and are also allowable for the same reasons.

On January 7, 2011, applicants paid the issue fee and filed a Rule 312 amendment after allowance with a Terminal Disclaimer to correct the assignee identified on the Terminal Disclaimer from Orphan Medical, Inc., to Jazz Pharmaceuticals, Inc.

On January 24, 2011, the USPTO approved the Terminal Disclaimer.

On February 22, 2010, the '059 patent issued with 16 claims. According to the face page of the '059 patent, no PTA was awarded.

3. Claims of the '059 Patent

The '059 patent issued with the following claims:

#	Claims of the '059 Patent
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 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 received and/or read prior to shipping the prescription drug; checking the exclusive computer database for potential abuse of the prescription drug; mailing or sending by courier 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;

#	Claims of the '059 Patent
	confirming receipt by the patient of the prescription drug; and generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.
2	The method of claim 1, wherein the exclusive central pharmacy controls the exclusive computer database.
3	The method of claim 1, comprising selectively blocking shipment of the prescription drug to a patient.
4	The method of claim 1, wherein an abuse pattern is associated with a patient, and shipment is blocked upon such association.
5	The method of claim 1, wherein the prescription drug comprises gamma hydroxy butyrate (GHB).
6	A computerized method of distributing a 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 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; 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; 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 received and/or read prior to providing the 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 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; confirming receipt by the patient of the prescription drug; and

#	Claims of the '059 Patent
	generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.
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.
8	The computerized method of claim 7, wherein the another pharmacy places controls on the distribution of the prescription drug, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of the prescription drug by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription drug, and limiting the prescription to a supply of limited duration.
9	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 received and/or 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.

#	Claims of the '059 Patent
10	The computerized method of claim 9, wherein providing GHB to the patient comprises the central pharmacy authorizing the prescription drug to be dispensed to the patient by another pharmacy.
11	The computerized method of claim 10, wherein the another pharmacy places controls on the distribution of GHB, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of GHB by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for GHB, flagging early requests to refill the GHB, and limiting the prescription to a supply of limited duration.
12	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 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 received and/or 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 or sending by courier 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.
13	A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:

#	Claims of the '059 Patent
	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 received and/or 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 or sending by courier 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.
14	A computerized method of distributing a 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 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; 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;

#	Claims of the '059 Patent
	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 received and/or read prior to providing the prescription drug to the patient; 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; 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 confirming receipt by the patient of the prescription drug.
15	The computerized method of claim 14, 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.
16	The computerized method of claim 15, wherein the another pharmacy places controls on the distribution of the prescription drug, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of the prescription drug by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription drug, and limiting the prescription to a supply of limited duration.

B. LEVEL OF SKILL IN THE ART OF THE '059 PATENT

The subject matter of the '059 patent falls within the field of designing computer systems. Depending on the claim, the person of ordinary skill in this field would be a programmer, or a systems analyst/programmer. Such an individual would have a Bachelor's Degree in Computer Science and several years of experience in the field. *E.I. DuPont de Nemours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), *aff'd* 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein and would have the capability to draw inferences from them.

C. CLAIM CONSTRUCTION OF THE '059 PATENT

One of ordinary skill in the art and a court would interpret the claims of the '059 patent according to their plain and ordinary meaning unless otherwise specified herein.

D. NONINFRINGEMENT OF THE '059 PATENT

Par does not directly infringe any claim of the '059 patent under 35 U.S.C. § 271(a) because Par does not perform the claimed method. Notably, independent claims 1, 6, and 14 describe "a computerized method of distributing a prescription drug " which requires that "an exclusive central pharmacy" receive "all prescription requests, for any and all patients being prescribed the prescription drug ." Independent claims 9, 12, and 13 are similar, describing "a computerized method of distributing gamma hydroxy butyrate (GHB)" which requires that "an exclusive central pharmacy" receive "prescription requests for GHB, for any and all patients being prescribed GHB." Par will not infringe these claims if granted approval for its generic product, because it will not control "an exclusive central pharmacy" that receives all of the prescriptions for the drug gamma hydroxyl butyrate or any other prescription drug.

Par further does not infringe claims 5, and 9-13, as they require the distribution of "gamma hydroxyl butyrate," whereas Par's proposed product contains sodium oxybate (sodium gamma-hydroxybutyrate).

Par also does not contributorily infringe under 35 U.S.C. § 271(c) because the claimed method has noninfringing uses. Furthermore, Par does not infringe claims 1-6 of the '107 patent under § 271(b) because the Par has a good faith belief that the '059 patent is invalid, which negates the requisite intent for induced infringement. *Commil USA, LLC v. Cisco Systems, Inc.*, 720 F.3d 1361, 1364 (Fed. Cir. Jun. 25, 2013) ("we find that Cisco's evidence of a good-faith belief of invalidity may negate the requisite intent for induced infringement.")

E. OBVIOUSNESS OF THE '059 PATENT

1. The Scope and Content of the Prior Art

The earliest possible effective U.S. filing date for the '059 patent is December 17, 2002, based on the filing date of U.S. Application 10/322,348 for the parent, '730 patent. The prior art is described in section X(E)(1), above.

2. Obviousness of the '059 Patent in Light of Borsand (Claim 1)

Claim 1 of the '059 patent is obvious over Borsand, which describes each of the elements of claim 1 in combination with other prior art references. Claim 1 is directed to a computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy. The claim essentially requires patients to obtain the prescription drug from a single, central pharmacy that maintains an exclusive computer database of information, thus allowing the pharmacy to perform checks of potential abuse before delivering the drug to the patient. The method of claim 1 controls distribution by subjecting the single, central pharmacy to a multitude of controls before the drug is delivered.

Claim 1 of the '059 Patent	Borsand
A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:	Borsand states that the "invention relates to a computer based system for tracking information related to pharmaceutical prescriptions." (Borsand ¶ 10.)

Claim 1 of the '059 Patent	Borsand
	Borsand further discloses a system that allows for "pharmaceutical information to be stored only once and in a centralized location accessible by the appropriate parties." (Borsand ¶ 3.)
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;	A computer system or a computer, as described in Borsand, inherently includes a computer processor for processing data. Borsand teaches an exclusive central computer system, which contains patient and doctor information. Borsand discloses a prescription subsystem where "prescriptions are only issued by a certain subset of health care providers, such as physicians ...." Processing a prescription requires inputting "patient record which includes patient information relevant to pharmaceutical selection." Each doctor must use a unique "UserID" and a patient is assigned a unique "PatientID." (Borsand ¶¶ 57-58; Figure 4b). Borsand addresses prior art deficiencies where "[i]t would be desirable for pharmaceutical information to be stored only once and in a **centralized location** accessible by the appropriate parties." (Borsand ¶ 3).
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;	Borsand teaches an exclusive computer database associated with an exclusive computer system. For example, Borsand discloses a system that allows for "pharmaceutical information to be stored only once and in a centralized location accessible by the appropriate parties." (Borsand ¶ 3). Borsand teaches that all relevant data is housed in a computer that "can be a single centralized computer or server, a single network ...." (Borsand ¶ 31.) According to Borsand, in the preferred embodiment, "all pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate regulations, policies, and guidelines." (Borsand ¶ 43.) Borsand also teaches that the relevant data must be entered in the system by the provider, *see, e.g.,* Borsand ¶¶ 58; 108, or the pharmacist. (*See* Borsand ¶ 86 ("If the pharmacist fills a pharmaceutical prescription, that information needs to be memorialized at 40.02 or its related pages.").)
processing with the computer processor all prescriptions for the prescription drug only by the exclusive central pharmacy using only the	Borsand teaches that the "invention relates to a computer based system for tracking information related to pharmaceutical prescriptions."

Claim 1 of the '059 Patent	Borsand
central database;	(Borsand ¶ 10). A computer inherently includes a computer processor for processing data. Borsand teaches that, in the preferred embodiment, "all pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate regulations, policies, and guidelines." (Borsand ¶ 43.)
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;	Borsand teaches that the "invention relates to a computer based system for tracking information related to pharmaceutical prescriptions." (Borsand ¶ 10). A computer inherently includes a computer processor for processing data. Borsand teaches a system that can "**check** of for unfavorable pharmaceutical interactions and allergic reactions, **prevent misuse of a prescription**, monitor the filling and re-filling of a prescription, as well as cancel a prescription after it has been issued by a provider." (Borsand Abstract.) According to Borsand's prescription subsystem, "prescriptions are only issued by a certain subset of health care providers, such as physicians ...." Processing a prescription requires inputting "patient record which includes patient information relevant to pharmaceutical selection." Each doctor must use a unique "UserID" and a patient is assigned a unique "PatientID." (*See* Borsand ¶¶ 57-58; Fig. 4b)
confirming with a patient that educational material has been received and/or read prior to shipping the prescription drug;	While Borsand does not explicitly require confirming that the patient has received and/or read the educational material "prior" to shipping the prescription drug, the FDA Safety Review (*See* obviousness analysis *supra*) and Califona cure this deficiency: Califano requires "confirming with the patient that educational material has been read prior to providing the drug to the patient." (*See* Califano ¶ 84; Examiner's Answer OA, dated 10/18/06.)
checking the exclusive computer database for potential abuse of the prescription drug;	The system of Borsand provides "functionality for tracking pharmaceutical, prescription and related information," where "tracking can be in a proactive and real-time manner, or in the form of reports and analysis ...." (Borsand ¶ 34). Any abuse or violation can be detected by the system which "can be configured to not allow the attempted conduct, or to allow the conduct,

Claim 1 of the '059 Patent	Borsand
	but generate a report relating to the undesired activity." *Id.* Further, Borsand discloses that the pharmaceutical subsystem (part of the overall exclusive central computer system) re-evaluates the prescription before the prescription is filled or sent to a payor, where "medical aspects of a prescription can also be reviewed, so that the appropriateness of the selected pharmaceutical can be confirmed as it relates to ... other patient attributes that could affect the desirability of filling a particular prescription." (Borsand ¶ 87). Borland discloses in multiple places that desirability of filling prescriptions may be tied to misuse of pharmaceuticals; for example, patient attributes includes patient's refill behavior. *Id.* at ¶ 53.
mailing or sending by courier 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;	Borsand discloses that in filling a prescription for a drug, an event can trigger a modification or cancellation of the prescription, where such an event includes "evidence of fraud, misuse, or redundancy on the part of a provider, pharmacist, or patient." (Borsand ¶ 120.) While Borsand does not explicitly disclose mailing or sending via courier the prescription drug, the Video, Briefing Booklet, FDA Safety Review, and Moradi disclose mailing or sending via courier the prescription drug if no abuse is found. (*See* obviousness analysis of the Video, Briefing Booklet, and the FDA Safety Review *infra*; Moradi ¶¶ 6, 43, 45; Examiner's Answer, OA dated 10/18/06.)
confirming receipt by the patient of the prescription drug; and	Borsand discloses that the system allows monitoring of whether or not a patient actually fills the prescription. (Borsand ¶ 56.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	Borsand discloses that "[i]f a patient 22, provider 30, pharmacist 40, or PBM 50 attempts an action that is not in accordance with the predefined rules 34 of the payor 60, the system 20 can be configured to not allow the attempted conduct, or to allow the conduct, but **generate a report** 42 relating to the undesirable activity." (Borsand ¶ 54.)

The examiner allowed claim 1 because the prior art considered by the examiner did not teach that all prescriptions will be received by an exclusive computer system/database.

> 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/sent only if no potential abuse is found by the patient to whom the prescription drug is prescribed *and* the doctor/authorized prescriber prescribing the prescription drug.

(Notice of Allowance, Dec. 21, 2010). The examiner, however, never considered Borsand. Instead, the examiner found that "the closest prior art of record" was Moradi (US 2004/0019794 A 1), Lilly et al. (US 2004/0176985 A1), Melker et al. (US 2002/0177232 A1), and Ukens ("Specialty Pharmacy"). Notably, the examiner found that all the elements of claim 1 are disclosed in combination in the prior art of record rendering the alleged invention obvious, except an exclusive central computer system/database that receives all prescriptions from all patients, controls the distribution of the prescriptions, and authorizes distribution of the prescriptions. Furthermore, Borsand, alone, also teaches an exclusive computer system/database that performs the functions recited in claim 1.

"[O]nce a challenger has presented a *prima facie* case of invalidity, the patentee has the burden of going forward with rebuttal evidence." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359–60 (Fed. Cir. 2007). It is the patentee's obligation to present evidence of secondary considerations, if any, to rebut a *prima facie* case of obviousness. The '059 patent provides no specific evidence of secondary considerations of non-obviousness. Secondary considerations of non-obviousness do not control the analysis where there is an otherwise strong case of obviousness, such as one based upon art not considered during prosecution. *Tokai Corp. v. Easton Enterprises, Inc.*, 632 F.3d 1358 (Fed. Cir. 2011) ("A strong case of prima facie obviousness, such as that presented here, cannot be overcome by a far weaker showing of objective indicia of nonobviousness."); *Sandt Tech. v. Resco Metal & Plastics*, 264 F.3d 1344, 1355 (Fed. Cir. 2001) ("We see no error in the district court's conclusion . . . that the secondary considerations cannot overcome the strong prima facie evidence of obviousness presented."). Any evidence of secondary considerations is insufficient to overcome the strong case of *prima facie* obviousness of the claimed subject matter.

3. Obviousness of the '059 Patent in Light of the Briefing Booklet (Claim 1)

Claim 1 of the '059 is obvious in light of the Briefing Booklet. See chart below for each disclosed element and analysis thereof.

Claim 1 of the '059 Patent	Briefing Booklet
A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:	The Briefing Booklet generally teaches use of a database using an exclusive specialty pharmacy. The reference to "real-time data" implies a computer processor managing the database. (Briefing Booklet at 20.)
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	In Orphan Medical's Briefing Booklet, it teaches use of a database using an exclusive specialty pharmacy. The reference to "real-time data" implies a computer processor managing the database.

Claim 1 of the '059 Patent	Briefing Booklet
information identifying patients, the prescription drug, and various credentials of the any and all medical doctors;	"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." (Briefing Booklet at 15). "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." (Briefing Booklet at 20.)
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;	The Briefing Booklet teaches data collection into the central database. The reference to "data collection" necessary includes entering the information into the central database. "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." (Briefing Booklet at 19.)
processing with the computer processor all prescriptions for the prescription drug only by the exclusive central pharmacy using only the central database;	The Briefing Booklet's reference to "real-time data" implies a computer processor processing the data.

Claim 1 of the '059 Patent	Briefing Booklet
	The Briefing Booklet teaches under the section entitled "Prescribing Options Selected" that the closed-loop distribution system controls distribution by controlling who prescribes Xyrem and controlling how it is prescribed. This, according to the Briefing Booklet, is achieved, in part, "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 of Xyrem. (Briefing Booklet at 14.)
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;	The Briefing Booklet discloses that "[t]he 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." The reference to real-time data implies a computer processor managing the data. (Briefing Booklet at 20.) The Briefing Booklet discloses that upon receipt of a prescription from the physician, the central pharmacy will "verify physician's eligibility by checking the AMA, DEA, or State Medical Board on-line databases" to ensure that "the prescription was written by a "real" physician with current privileges to prescribe controlled medications." (Briefing Booklet at 19.) The Briefing Booklet discloses that the collection of 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.**" (Briefing Booklet at 15).
confirming with a patient that educational material has been received and/or read prior to shipping the prescription drug;	The Briefing Booklet teaches that "[o]nce 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 point's in-between." (Briefing Booklet at 20.) While the Briefing Booklet does not explicitly require confirming that the patient has received and/or read the educational material "prior" to shipping the prescription drug, the FDA Safety Review (*See* obviousness analysis *infra*) and Califano cure this deficiency: Califano requires "confirming with the patient that educational

Claim 1 of the '059 Patent	Briefing Booklet
	material has been read prior to providing the drug to the patient." (*See* Califano ¶ 84; Examiner's Answer OA, dated 10/18/06.)
checking the exclusive computer database for potential abuse of the prescription drug;	The Briefing Booklet discloses that "[t]he 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." (Briefing Booklet at 20.)
mailing or sending by courier 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;	The Briefing Booklet discloses a distribution system that requires physician verification process "to catch any prescriptions written on stolen or counterfeit prescription pads" and entering patient information in a "patient registry which also aids in diversion prevention" before the Xyrem shipping process begins, where Xyrem is mailed via Federal Express. (Briefing Booklet at 19-20.)
confirming receipt by the patient of the prescription drug; and	The Briefing Booklet discloses a distribution system that requires the exclusive central pharmacy pharmacist to contact the patient to confirm receipt of the Xyrem prescription. (Briefing Booklet at 20.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	The Briefing Booklet teaches that "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." (Briefing Booklet at 16.) The Briefing Booklet further teaches that "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." (Briefing Booklet at 15.)

4. Obviousness of the '059 Patent in Light of the FDA Safety Review (Claim 1)

Claim 1 of the '059 is obvious in light of the Briefing Booklet. See chart below for each disclosed element and analysis thereof.

Claim 1 of the '059 Patent	FDA Safety Review

Claim 1 of the '059 Patent	FDA Safety Review
A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:	The FDA Safety Review teaches a method of distributing a prescription drug (Xyrem®) under exclusive control of an exclusive central pharmacy (or distributor). (FDA Safety Review at 108). Apparently, Orphan Medical proposed Nova Factor to be the central pharmacy.
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;	The FDA Safety Review describes a "closed-loop distribution system," wherein "Xyrem® will NOT be placed in retail pharmacy outlets," and instead, the document describes a "primary and exclusive distributor of Xyrem®." (*Id.* at 108). The FDA Safety Review teaches that every patient and physician allowed to prescribe the prescription drug (Xyrem®) will be registered into the exclusive central database. (FDA Safety Review at 110).
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;	The FDA Safety Review teaches that a single, sole, and secure database will store the relevant information. "Every patient and prescribing physician will be registered with [the exclusive distributor] in 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." (FDA Safety Review at 110.)
processing with the computer processor all prescriptions for the prescription drug only by the exclusive central pharmacy using only the central database;	FDA safety review teaches that the exclusive central pharmacy (or distributor) will control distribution by being the primary and exclusive distributor, maintaining inventory and distribution records, and maintaining patient registry. (FDA Safety Review 108-109.)
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;	The FDA Safety review teaches that the exclusive central pharmacy will verify that the physician is eligible to prescribe Xyrem®, including checking whether the physician has an active DEA number and whether any actions are pending against the physician. (FDA Safety Review at 109.)
confirming with a patient that educational material has been received and/or read prior to shipping the prescription drug;	The FDA Safety Review discloses that the Office of Post-Marketing Drug Risk assessment recommended that confirmation of whether the patient has read and fully understands the education material should be received by Nova

Claim 1 of the '059 Patent	FDA Safety Review
	Factor "**prior to the initial dispensing of the drug**." (FDA Safety Review at 114-115.)
checking the exclusive computer database for potential abuse of the prescription drug;	The FDA Safety Review notes in several in several places checking for potential for abuse, misuse, or diversion: prescriptions refills before anticipation date will be questioned (FDA Safety Review at 110); lost, stolen, destroyed, or spilled prescription/supply will be documented, flagged, and monitored (*Id.*); noting prescribing frequency (*Id.*); among others.
mailing or sending by courier 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;	The FDA Safety Review discloses that "once approval has been established, (b)(4) [exclusive specialty pharmacy] will … arrange shipment though (b)(4) or a similar carrier." (FDA Safety Review at 109.) The approval process requires verification of eligibility to prevent potential abuse. (*Id.*)
confirming receipt by the patient of the prescription drug; and	The FDA Safety Review discloses that "[r]eceipt of the drug by the patient will be ensured through … a phone call by the pharmacy to the patient." (FDA Safety Review at 109.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	The FDA Safety Review notes in several places potential for abuse, misuse, or diversion: prescriptions refills before anticipation date will be questioned (FDA Safety Review at 110); lost, stolen, destroyed, or spilled prescription/supply will be documented, flagged, and monitored (*Id.*); noting prescribing frequency (*Id.*); among others. While the FDA Safety Review does not explicitly disclose generating periodic reports, the Video, Borsand, Briefing Booklet, and Lilly, among others, disclose generating periodic reports to evaluate potential diversion patterns. (*See* obviousness analysis of the Video, Briefing Booklet, and the FDA Safety Review; Lilly ¶¶ 11, 33, 54, 57, 58, 61, 69; Examiner's Answer, OA dated 06/19/06.)

5. Obviousness of the '059 Patent in Light of the Video (Claim 1)

Claim 1 of the '059 patent is obvious over the Video.

Claim 1 of the '059 Patent	Video
A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:	The Video shows a "shot of pharmacy employee picking up prescription fax and sitting down at a computer to verify physician's eligibility." (Video ¶ 21). The illustration of a computer in the Video teaches using a computer to control distribution.

Claim 1 of the '059 Patent	Video
	The Video discloses a single, centrally-located specialty pharmacy that controls distribution, documentation, and security through a closed-loop distribution system. (Video ¶¶ 3-5.)
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;	The Video teaches using a computer to process prescription requests. A computer inherently includes a computer processor. The Video discloses a single, centrally-located specialty pharmacy that controls distribution, documentation, and security through a closed-loop distribution system. The prescriptions are sent to the central pharmacy, which verifies that the "physician is an Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data ... to check if there are any pending or previous actions against the physician." (Video ¶¶ 14; 21.) The single, specialty pharmacy stores data about prescriptions by patients; thus, it follows that the prescription sent by the physician includes patient identifying information. (*See, e.g.,* Video ¶ 24.)
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;	The Video teaches that all "data about inventory, physicians, reimbursements, patients, and delivery" is stored in one efficient and quickly-accessible location [single, specialty pharmacy]." (Video ¶ 24.) Further, the Video teaches that the "closed-loop distribution system … will 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." (Video ¶ 14.)
processing with the computer processor all prescriptions for the prescription drug only by the exclusive central pharmacy using only the central database;	The Video discloses that the secure distribution system of Xyrem® is achieved through a specialty pharmacy, which "is a single centrally located facility that stores "all the data about inventory, physicians, reimbursement, patients, and delivery in one efficient and quickly-accessible location." (Video ¶ 24). The Video teaches that the single, specialty pharmacy uses a computer, which inherently includes a computer processor.
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;	The Video teaches using a computer to process the specialty pharmacy prescription requests. A computer inherently includes a computer processor.

Claim 1 of the '059 Patent	Video
	The Video discloses that the prescriptions are sent to the central pharmacy, which verifies that the "physician is an Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data ... to check if there are any pending or previous actions against the physician."
confirming with a patient that educational material has been received and/or read prior to shipping the prescription drug;	The Video teaches sending a patient educational material, "Patient Success Program." (Video ¶ 31.) While the Video does not explicitly require confirming that the patient has received and/or read the educational material "prior" to shipping the prescription drug, the FDA Safety Review (*See* obviousness analysis *supra*) and Califano cure this deficiency: Califano requires "confirming with the patient that educational material has been read prior to providing the drug to the patient." (*See* Califano ¶ 84; Examiner's Answer OA, dated 10/18/06.)
checking the exclusive computer database for potential abuse of the prescription drug;	The Video discloses that the central pharmacy staff 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." (Video ¶ 14). The Video also discloses that the specialty pharmacy will keep track of anomalous patient requests to fill their prescriptions. (*Id.* at 38.)
mailing or sending by courier 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;	The Video discloses that Xyrem® will be "shipped overnight by Federal express utilizing a tracking system designed specifically for the specialty pharmacy." (Video ¶ 30.) The Video teaches that during "the process of verification and documentation, if any data or behavior suggest the possibility that Xyrem® may be used inappropriately, the specialty pharmacy is empowered to contact the appropriate authorities." (Video ¶ 29.)
confirming receipt by the patient of the prescription drug; and	The Video teaches that receipt of Xyrem® and educational materials is verified by a telephone call placed to the patient where "the specialty pharmacy will confirm receipt of the Xyrem prescription and the Patient Success program." (Video ¶ 35.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	The Video discloses that the closed-loop distribution system "will be able to **generate data**, recording prescribers, patients and dosing that could provide information for any possible investigations and prosecutions for state and

Claim 1 of the '059 Patent	Video
	federal authorities." (Video ¶ 14).

6. Application of the Prior Art (Claims 2-16)

Claim 2 of the '059 patent is directed to the method of claim 1 "wherein the exclusive central pharmacy controls the exclusive central database." References not considered by the Examiner disclose that the exclusive central pharmacy controls the exclusive central database. For example, the FDA Safety Review discloses that a method of distributing a prescription drug (Xyrem®) is under exclusive control of an exclusive central pharmacy (or distributor). (FDA Safety Review at 108). Similarly, Borsand discloses that, in the preferred embodiment, "all pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate regulations, policies, and guidelines," where the prescription subsystem limits issuance of prescriptions to certain subset of health providers. (Borsand ¶¶ 3; 50.)

Claim 3 of the '059 is directed to the method of claim 1 "comprising selectively blocking shipment of the prescription drug to a patient." References not considered by the Examiner disclose that shipments of the prescription drug may be selectively blocked. For Example, the FDA Safety Review discloses that if a patient is unavailable to accept a shipment of Xyrem® and execute the required receipt, the package will be returned to the pharmacy. (FDA Safety Review at 109). Similarly, The Briefing Booklet discloses that "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." (Briefing Booklet at 20.)

Claim 4 is directed to the method of claim 1 "wherein an abuse pattern is associated with a patient, and shipment is blocked upon such association." References not considered by the Examiner disclose that prior to shipment of the prescription drug, the verification process will prevent shipment to patients associated with an abuse pattern. For example, the Video teaches that prior to shipping the patient's medication overnight by Federal Express, a process of verification and documentation will allow the specialty pharmacy to determine "if any of the data or behavior suggests the possibility that Xyrem may be used inappropriately." (Video ¶¶ 29-30). Similarly, the FDA Safety Review teaches that Xyrem® will only be shipped once approval has been established, where approval requires verifying eligibility of the physician to prescribe the prescription drug and obtaining a certificate of medical necessity. (FDA Safety Review at 109.)

Claim 5 is directed to the method of claim 1 "wherein the prescription drug comprises gamma hydroxyl butyrate (GHB)." At least the Briefing Booklet and the FDA Safety Review explicitly disclose that the prescription drug is GHB.

Claim 6 is an independent claim, but is similar to claim 1. The preamble in claim 6 recites under "control," instead of under "exclusive control." Claim 6 recites "authorized prescribers" instead of "medical doctors." Clause 2 of claim 6 does not include "requiring entering," but only includes "entering" and additionally recites "wherein the use of the exclusive computer database is required for distribution of the prescription drug." Clause 5 includes "requiring checking" instead of "checking" and additionally recites "potential abuse associated with the patient and the authorized prescriber." Clause 6 recites "providing" instead of "mailing

or sending by courier." However, these differences do not add any limitation that overcomes any of the references discussed above.

For example, an "authorized prescriber" is broader than a "medical doctor." Similarly, "entering" is broader than "requiring entering" and "control" is broader than "exclusive control." Likewise, "providing" is broader than "mailing or sending by courier." Thus, to the extent the references discussed above with respect to claim 1 disclosed the recited limitations, they would also encompass these terms recited in claim 6.

The recitation "wherein the use of the exclusive computer database is required for distribution of the prescription drug" does not add any limitation that overcomes the references discussed with respect to claim 1. For example, Borsand teaches that, in the preferred embodiment, "***all*** pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate regulations, policies, and guidelines." (Borsand ¶ 43).

The differences in Clause 5 do not any add limitation that overcomes the references discussed above with respect to claim 1. For example, the Video discloses that, upon receipt of the prescription, the specialty pharmacy must first verify that the prescribing physician is an Orphan Medical's list of targeted physicians, has an active DEA and State license, and does not have any pending or previous actions. (Video ¶ 21). Similarly, the Briefing Booklet requires that, upon receipt of the prescription, the specialty pharmacy will verify the physician's eligibility to ensure the prescription was written by a "real-physician" and also call the physician's office to obtain patient information for diversion prevention. (Briefing Booklet at 19.)

Claim 7 is directed to the 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." References not considered by the Examiner disclose this limitation. For example, the FDA Safety Review teaches that the specialty pharmacy may ship the prescription to another pharmacy for patient pick-up. (FDA Safety Review at 110).

Claim 8 is directed to the method of claim 7 "wherein the another pharmacy places controls on the distribution of the prescription drug, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of the prescription drug by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription drug, and limiting the prescription to a supply of limited duration." References not considered by the Examiner disclose this limitation. For example, the FDA Safety Review discloses that, where the prescription will be picked up by another pharmacy, the specialty pharmacy must verify that there is a mechanism for the second pharmacy to protect against diversion of the prescription drug. (FDA Safety Review at 110). Further, the FDA Safety Review discloses diversion prevention mechanisms, which include, at least, some of the controls recited in claim 8 to protect against diversion. For example, the FDA Safety Review discloses identifying "physician name, address, telephone and facsimile, DEA and state license numbers" (FDA Safety Review at 110);

verifying that "the physician is eligible to prescribe Xyrem [by checking] the National Practitioner Databank ... including confirming that the physician has an active DEA number and check on whether any actions are pending against the physician" (*Id.* at 109); among others.

Claim 9 is an independent claim and is similar to claim 6. The only difference between claim 9 and claim 6 is that claim 9 is directed to GHB instead of a prescription drug. At least, the Briefing Booklet and FDA Safety Review, disclose that the prescription drug may be GHB. (*See, e.g.*, Briefing Booklet at 18; FDA Safety Review at 7). Thus, for the same reasons claim 6 is rendered obvious, claim 9 is also rendered obvious by the same references.

Claim 10 is directed to the method of claim 9 "wherein providing GHB to the patient comprises the central pharmacy authorizing the prescription drug to be dispensed to the patient by another pharmacy." Claim 10 is similar to claim 7, but is directed to GHB. Thus, for the same reasons claim 7 is rendered obvious, claim 10 is also rendered obvious by the same references.

Claim 11 is directed to the method of claim 9 "wherein the another pharmacy places controls on the distribution of GHB, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of GHB by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription drug, and limiting the prescription to a supply of limited duration." Claim 11 is similar to claim 8, but is directed to GHB. Thus, for the same reasons claim 8 is rendered obvious, claim 11 is also rendered obvious by the same references.

Claim 12 is an independent claim, but is similar to claim 6. Claim 12 is directed to GHB instead of a prescription drug. Clause 5 of claim 12 is limited to the patient, whereas clause 5 of claim 6 is directed to the patient and the authorized prescriber, thus is narrower. Thus, for the same reasons claim 6 is rendered obvious, claim 12 is also rendered obvious by the same references.

Claim 13 is an independent claim, but is similar to claim 9. The differences between claim 13 and claim 9 are that claim 13 includes additional clauses "manufacturing GHB" and "providing manufactured GHB only to the exclusive central pharmacy." However, adding these additional clauses does not overcome the references discussed above. For example, the FDA Safety Review discloses manufacturing GHB and providing the GHB to the central pharmacy (the primary and exclusive distributor of Xyrem®). (FDA Safety Review at 108). Clause 8 of claim 13 recites "mailing or sending by courier," as recited in claim 1, instead of "providing." Thus, for the same reasons claims 1 and 9 are rendered obvious, claim 13 is also rendered obvious by the same references.

Claim 14 is an independent claim, but is similar to claim 6. The differences between claim 14 and 6 are that in clause 5, claim 14 recites "potential abuse by the patient" instead of "potential abuse associated with the patient." In addition, claim 14 does not include the clause "generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns," thus making claim 14 broader than claim 6. Thus, for the

same reasons claim 6 is rendered obvious, claim 14 is also rendered obvious by the same references.

Claim 15 is directed to the method of claim 14 "wherein providing the prescription drug comprises the central pharmacy authorizing the prescription drug to be dispensed to the patient by another pharmacy." Claim 15 is similar to claims 7 and 10. Thus, for the same reasons claims 7 and 10 are rendered obvious, claim 15 is also rendered obvious by the same references.

Claim 16 is directed to the method of claim 14 "wherein the another pharmacy places controls on the distribution of GHB, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of GHB by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription drug, and limiting the prescription to a supply of limited duration." Claim 16 is similar to claims 8 and 11. Thus, for the same reasons claims 8 and 11 are rendered obvious, claim 16 is also rendered obvious by the same references.

F. INELIGIBLE SUBJECT MATTER UNDER 35 U.S.C. § 101

The claims of the '059 patent are invalid under 35 U.S.C. § 101 because the claimed subject matter is not patentable. The claims of the '059 patent do not satisfy the machine-or-transformation test, and are directed to algorithms and abstract ideas *Bilski v. Kappos*, 130 S.Ct. 3218, 3229-30 (2010); *In re Bilski*, 545 F.3d 943, 962-63 (Fed. Cir. 2008).

In the '059 patent, the process is not tied to a particular machine or apparatus. Although the claims include terms like "computerized method" and "computer processor," there is nothing in the specification indicating that a computer is integral to implementing the process. Further, while some of the steps require use of a "computer processor," 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.*, '059 patent, col. 3, lines 10-14.)[37]

The '059 patent claims do not transform an article into a different state or thing: They merely claim a method of distributing sensitive drugs that does not transform or make the drugs any less sensitive. Although some claims require 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. Although the claimed methods refer to periodic reports that are generated to evaluate

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[37] 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).

potential diversion patterns or potential for abuse, misuse, or diversion, this is merely an addition of "non-essential post-solution activity." *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.*, '059 patent, col. 1, lines 6- 7.)

The Federal Circuit has determined that patent claims are abstract when the "steps can be performed in the human mind, or by a human using a pen and paper." *CyberSource*, 654 F.3d at 1372. In the '059 patent, the process is similar to a clearing house in that the method merely requires collecting and organizing data of doctors who are able to prescribe, and the patients who are able to receive, the medication, and organizing the data describing shipments of the medication, and associated marketing material. This process could equally be performed by pencil, paper, and a traditional filing cabinet system.

The steps of the claims in the '059 patent represent common ways that people have used to restrict allocation of materials, where a central controlling entity confirms with a validated third-party authority whether a substance should be delivered to an individual. Without meaningful limits, the claims effectively preempt the fundamental concept itself and foreclose a wide range of inventions that the patentee never conceived. For example, in *Dealertrack*, the Federal Circuit determined that the patentee's claimed process in its simplest form includes three steps: receiving data from one source (step A), selectively forwarding the data (step B, performed according to step D), and forwarding reply data to the first source (step C). *Dealertrack,* 674 F.3d at 1333. Because this claim "explain[s] the basic concept of processing information through a clearing-house . . . [t]he steps that constitute the method here do not impose meaningful limits on the claim's scope." *Id.* (citing *Bilski*, 130 S. Ct. at 3231; *Bilski*, 545 F.3d at 961-62) (quotations omitted). The Federal Circuit was "compelled to conclude that the claims are invalid as being directed to an abstract idea ***preemptive of a fundamental concept or idea*** that would foreclose innovation in this area." *Id.* at 1333 (emphasis added); *see also Mayo*, 132 S. Ct. at 1294 (the patent should not "risk disproportionately tying up the use of" the abstract idea in future discoveries). Similarly, here, the steps of the claims in the '059 patent are directed to a fundamental concept itself, thus are directed to an abstract idea.

In sum, the claims of the patent-in-suit fail to meet the requirements of § 101 because they: (1) fail the machine-or-transformation test and (2) are directed to the abstract idea of a centralized authorization center for prescriptions drugs , which is a fundamental principle that would be improperly preempted by the patent-in-suit. Here, the computer must be integral to the claimed invention, facilitating the process in a way that a person making calculations or computations could not." *Bancorp*, 687 F.3d at 1278. This method could be performed by someone using pencil, paper, and a standard records-keeping system. For these reasons, the claims of the '059 patent are invalid under 35 U.S.C. § 101.

G. CONCLUSION

For the reasons stated above, claims 1-16 of the '059 patent are obvious over the prior art, and claims 1-16 are not patentable under 35 U.S.C. § 101. Par reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these patents are invalid, unenforceable or not infringed.

XIV. THE '988 PATENT

A. OVERVIEW OF THE '988 PATENT

1. Specification of the '988 Patent

The '988 patent issued from U.S. Application 13/013,680, filed August 27, 2012, which is a divisional of U.S. Application 13/013,680 (filed January 25, 2011, and now abandoned), which is a continuation of U.S. Application 12/704,097, which itself issued as U.S. Patent No. 7,895,059, which is a continuation of U.S. Application 10/322,348, which itself issued as U.S. Patent No. 7,668,730. The '988 patent lists three inventors: Dayton Reardon, Patti Engel, and Bob Gagne. It is assigned to Jazz. The '988 patent is titled "Sensitive Drug Distribution System and Method."

The '988 patent is directed, *inter alia*, to therapeutic methods of treating a patient with a prescription drug that is effective for therapeutic purposes but has the potential to be abused, the method including control of distribution by a central computer system and the drug including sodium oxybate/gamma hydroxyl butyrate (GHB). According to the '988 patent, the "invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs." ('988 patent, col. 1, lines 18-35). The '988 patent indicates that there is a need for a distribution system to address abuse. ('988 patent, col. 1, lines 36-39).

The invention purports to provide a drug distribution system and method utilizing 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 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. ('988 patent, col. 1, line 44 to col. 2, line 21.)

2. Prosecution History of the '988 Patent

On August 27, 2012, the applicants filed U.S. Application No. 13/595,757 ("the '757 application") with 15 total claims, including 2 independent claims. While filing the '757 application, the applicants filed a non-publication request under 35 U.S.C. § 122(b) and requested a Track I Prioritized Examination.

On October 10, 2012, applicants filed an IDS, listing documents related to office actions, amendments, appeal briefs of related patents, and documents related to *Jazz Pharmaceuticals Inc. v. Roxane Laboratories Inc.,* No. 10-6108, D.I. 151 (D.N.J. Sept. 14, 2012), such as the complaint, answer, counterclaims, and Markman briefs, among others.

On January 17, 2013, the USPTO issued a non-final rejection. Claims 1-15 were rejected for nonstatutory obviousness-type double patenting over claims 1-11 of the '730 patent and over claims 1-16 of the '059 patent. The USPTO also rejected claims 1-15 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.

('988 patent application, Jan. 17, 2013, Non-Final Rejection.)

On March 05, 2013, the applicants filed an IDS, listing documents related to a lawsuit *Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC*, *Jazz Pharmaceuticals Inc. v. Roxane Laboratories Inc.*, and other documents submitted to the FDA.

On March 07, 2013, the applicants filed an Amendment and Response. In response to the § 112 rejections, the applicants made the following amendment to claim 1:

> A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising:
>
> receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at ~~the~~ an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic 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, wherein the exclusive central pharmacy and the exclusive central database ~~are unique in that they~~ are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's 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 company's prescription drug;
>
> confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;
>
> checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the ~~uniqueness~~ of the exclusive central pharmacy and the exclusive central database facilitate[[s]] a determination of the potential abuse of the company's prescription drug;
>
> providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the

> company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;
>
> confirming receipt by the narcoleptic patient of the company's prescription drug; and
>
> generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

('988 patent application, Mar. 6, 2013, Response.)

In response to the § 112 rejections, the applicants made the following amendment to claim 5:

> The method of claim 1, wherein the exclusive central pharmacy enters data into ~~controls~~ the exclusive computer database.

In response to the § 112 rejections, the applicants made the following amendment to claim 9:

> A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising:
>
> receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug inventory is owned by a company, only at ~~the~~ an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic 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, wherein the exclusive central pharmacy and the exclusive central database ~~are unique in that~~ are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's 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 company's prescription drug;
>
> confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;

> checking the exclusive computer database for potential abuse of the company's prescription drug, wherein ~~the uniqueness of~~ the exclusive central pharmacy and the exclusive central database facilitate[[s]] a determination of the potential abuse of the company's prescription drug;
>
> providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;
>
> confirming receipt by the narcoleptic patient of the company's prescription drug; and
>
> generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

('988 patent application, Mar. 6, 2013, Response.)

In response to the § 112 rejections, the applicants made the following amendment to claim 13:

> The method of claim 9, wherein the exclusive central pharmacy enters data into ~~controls~~ the exclusive computer database.

('988 patent application, Mar. 6, 2013, Response.)

In regards to the nonstatutory obviousness-type double patenting rejection, the applicants filed two terminal disclaimers with the response filed on March 7, 2013.

On March 8, 2013, the USPTO approved the terminal disclaimers noted above.

On March 11, 2013, the applicants filed a supplemental IDS, filing a video entitled "Advisory Committee Video on Xyrem, Oral Solution."

On March 21, 2013, the USPTO issued a Notice of Allowance, allowing claims 1-15, and determining PTA to be 0 days. The USPTO also provided an initialed copy of an IDS listing non-patent literature.

On April 19, 2013, the USPTO initialed and returned the supplemental IDS filed on March 11, 2013.

On May 29, 2013, the applicants filed another supplemental IDS, listing additional documents related to the *Jazz v. Roxane* lawsuit.

On June 4, 2013, the '988 patent issued.

3. Claims of the '988 Patent

The '988 patent issued with the following claims:

#	Claims of the '988 Patent
1	A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising: receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic 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, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's 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 company's prescription drug; confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug; checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug; providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug; confirming receipt by the narcoleptic patient of the company's prescription drug; and generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.
2	The method of claim 1, wherein one or more of the exclusive central pharmacy and the exclusive central database are distributed over multiple computers, and wherein a query operates over all data in all the distributed databases relating to the prescriptions, the doctors, and the narcoleptic patients.
3	The method of claim 1, wherein the providing the company's prescription drug to the narcoleptic patient comprises the exclusive central pharmacy authorizing the company's prescription drug to be dispensed to the narcoleptic patient by another pharmacy.

#	Claims of the '988 Patent
4	The method of claim 1, comprising delivering the company's prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the company's prescription drug.
5	The method of claim 1, wherein the exclusive central pharmacy enters data into the exclusive computer database.
6	The method of claim 1, comprising selectively blocking shipment of the company's prescription drug to the narcoleptic patient.
7	The method of claim 1, wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the company's prescription drug is blocked based upon such association.
8	The computerized method of claim 1, wherein the company's prescription drug comprises a gamma hydroxyl butyrate (GHB) drug product.
9	A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising: receiving in a computer processor all prescription requests, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's 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 company's prescription drug; confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug; checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug; providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug; confirming receipt by the narcoleptic patient of the company's prescription drug; and generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.
10	The method of claim 9, wherein one or more of the exclusive central pharmacy and the exclusive central database are distributed over multiple computers, and wherein a

#	Claims of the '988 Patent
	query operates over all data in all the distributed databases relating to the prescriptions, the doctors, and the narcoleptic patients.
11	The method of claim 9, wherein the providing the company's prescription drug to the narcoleptic patient comprises the exclusive central pharmacy authorizing the company's prescription drug to be dispensed to the narcoleptic patient by another pharmacy.
12	The method of claim 9, comprising delivering the company's prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the company's prescription drug.
13	The method of claim 9, wherein the exclusive central pharmacy enters data into the exclusive computer database.
14	The method of claim 9, wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the company's prescription drug is blocked based upon such association.
15	The method of claim 9, wherein the company's prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

B. LEVEL OF SKILL IN THE ART OF THE '988 PATENT

The subject matter of the '988 patent falls within the field of designing computer systems. Depending on the claim, the person of ordinary skill in this field would be a programmer, or a systems analyst/programmer. Such an individual would have a Bachelor's Degree in Computer Science and several years of experience in the field. *E.I. DuPont de Nemours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), *aff'd* 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein and would have the capability to draw inferences from them.

C. CLAIM CONSTRUCTION OF THE '988 PATENT

One of ordinary skill in the art and a court would interpret the claims of the '988 patent according to their plain and ordinary meaning unless otherwise specified herein.

On September 14, 2012, the U.S. District Court for the District of New Jersey issued a claim construction order for terms in the '730 patent family, which includes distribution patents, '106, '107, and '059, in the case of *Jazz Pharmaceuticals Inc. v. Roxane Laboratories Inc.*, No. 10-6108, D.I. 151 (D.N.J. Sept. 14, 2012). While the '988 patent was not at issue at the time the court issued the claim construction order, the '988 patent stems from the same '730 distribution patent family, and shares many of the same terms. The district court's constructions for several relevant terms are briefly in sections X(D), XI(D), and XIII(D), above. Par includes these

constructions for informational purposes only and reserves its right to challenge these constructions.

D. NONINFRINGEMENT OF THE '988 PATENT

Par does not directly infringe any claim 1 of the '988 patent under 35 U.S.C. § 271(a) because Par does not perform the claimed method. Notably, independent claim 1 describes "a mtheod of treatment of a narcoleptic patient with a prescription drug while controlling potential misues, abuse or diversion" which requires that "an exclusive computer database" receive "all prescription requests, for any and all patients being prescribed the prescription drug ." Claims 2-8 are all dependant on claim 1. Par will not infringe these claims if granted approval for its generic product, because it will not control "an exclusive central pharmacy" that receives all of the prescriptions for sodium oxybate or any other prescription drug.

Par further does not infringe claims 8 or 15, as they require that the prescription drug comprises "a gamma hydroxyl butyrate (GHB) drug product," whereas Par's proposed product contains sodium oxybate (sodium gamma-hydroxybutyrate).

Par also does not contributorily infringe under 35 U.S.C. § 271(c) because the claimed method has noninfringing uses. Furthermore, Par does not infringe claims 1-6 of the '988 patent under § 271(b) because the Par has a good faith belief that the '988 patent is invalid, which negates the requisite intent for induced infringement. *Commil USA, LLC v. Cisco Systems, Inc.*, 720 F.3d 1361, 1364 (Fed. Cir. Jun. 25, 2013) ("we find that Cisco's evidence of a good-faith belief of invalidity may negate the requisite intent for induced infringement.")

E. OBVIOUSNESS OF THE '988 PATENT

1. The Scope and Content of the Prior Art

The earliest possible effective U.S. filing date for the '988 patent is December 17, 2002, based on the filing date of U.S. Application 10/322,348 for the grandparent, '730 patent. The prior art is described in section X(E)(1), above.

2. Obviousness in Light of Borsand (Claim 1)

Claim 1 of the '988 patent is obvious over Borsand, which describes each of the elements of claim 1 in combination with other prior art references. Claim 1 is directed to a method for treating patients with a prescription drug that has the potential to be abused, misused, or diverted. The claim essentially requires patients to obtain the prescription drug from a single, central pharmacy that maintains an exclusive computer database of information, thus allowing the pharmacy to perform checks of potential abuse before delivering the drug to the patient. The method of claim 1 controls distribution by subjecting the single, central pharmacy to a multitude of controls before the drug is delivered.

Claim 1 of the '988 Patent	Borsand
A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription	Borsand discloses that Borsand's system reduces fraud, redundancy, pharmaceutical abuse, pharmaceutical misuse, and errors, with respect to

Claim 1 of the '988 Patent	Borsand
drug, comprising:	prescription drugs. (Borsand ¶¶ 33; 38.)
receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic patients, the prescription drug, and various credentials of the any and all medical doctors;	A computer system or a computer, as described in Borsand, inherently includes a computer processor for processing data. Borsand teaches an exclusive central computer system, which contains patient and doctor information. Borsand discloses a prescription subsystem where "prescriptions are only issued by a certain subset of health care providers, such as physicians ...." Processing a prescription requires inputting "patient record which includes patient information relevant to pharmaceutical selection." Each doctor must use a unique "UserID" and a patient is assigned a unique "PatientID." (Borsand ¶¶ 57-58; Figure 4b). Borsand addresses prior art deficiencies where "[i]t would be desirable for pharmaceutical information to be stored only once and in a centralized location accessible by the appropriate parties." (Borsand ¶ 3). While Borsand may not explicitly teach that the prescription requests are for narcoleptic patients, the video, Briefing Booklet, and FDA Safety Review all disclose that the prescription drug is used to treat narcolepsy patients. Similarly, while Borsand may not explicitly teach distributing the prescription drug by a company that obtained approval, at least, the Briefing Booklet and FDA Safety Review cure this deficiency.
requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;	Borsand teaches an exclusive computer database associated with an exclusive computer system. For example, Borsand discloses a system that allows for "pharmaceutical information to be stored only once and in a centralized location accessible by the appropriate parties." (Borsand ¶ 3). Borsand teaches that all relevant data is housed in a computer that "can be a single centralized computer or server, a single network ...." (Borsand ¶ 31.) According to Borsand, in the preferred embodiment, "all pharmaceutical-related information is stored on a single database 62 that is accessible to any party subject to the appropriate regulations, policies, and guidelines." (Borsand ¶ 43.) Borsand also teaches that the relevant data must be entered in the system by the provider, *see, e.g.*, Borsand ¶¶ 58; 108, or the pharmacist. (*See* Borsand ¶ 86 ("If the pharmacist fills a

Claim 1 of the '988 Patent	Borsand
	pharmaceutical prescription, that information needs to be memorialized at 40.02 or its related pages.").)
checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the company's prescription drug;	Borsand teaches that the "invention relates to a computer based system for tracking information related to pharmaceutical prescriptions." (Borsand ¶ 10). A computer inherently includes a computer processor for processing data. Borsand teaches a system that can "check of for unfavorable pharmaceutical interactions and allergic reactions, prevent misuse of a prescription, monitor the filling and re-filling of a prescription, as well as cancel a prescription after it has been issued by a provider." (Borsand Abstract.) According to Borsand's prescription subsystem, "prescriptions are only issued by a certain subset of health care providers, such as physicians ...." Processing a prescription requires inputting "patient record which includes patient information relevant to pharmaceutical selection." Each doctor must use a unique "UserID" and a patient is assigned a unique "Patient*ID*." (*See* Borsand ¶¶ 57-58; Fig. 4b)
confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;	While Borsand does not explicitly require confirming that the patient has received and/or read the educational material "prior" to shipping the prescription drug, the FDA Safety Review (*See* obviousness analysis supra) and Califona cure this deficiency: Califano requires "confirming with the patient that educational material has been read prior to providing the drug to the patient." (*See* Califano ¶ 84; Examiner's Answer OA, dated 10/18/06.) Further, as noted above, the video, FDA Safety Review, and Briefing Booklet disclose that the prescription drug is for a narcoleptic patient.
checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug;	The system of Borsand provides "functionality for tracking pharmaceutical, prescription and related information," where "tracking can be in a proactive and real-time manner, or in the form of reports and analysis ...." (Borsand ¶ 34). Any abuse or violation can be detected by the system which "can be configured to not allow the attempted conduct, or to allow the conduct, but generate a report relating to the undesired activity." *Id.* Further, Borsand discloses that the pharmaceutical subsystem (part of the overall exclusive central computer system) re-evaluates the prescription before the prescription is filled or sent to a payor,

Claim 1 of the '988 Patent	Borsand
	where "medical aspects of a prescription can also be reviewed, so that the appropriateness of the selected pharmaceutical can be confirmed as it relates to ... other patient attributes that could affect the desirability of filling a particular prescription." (Borsand ¶ 87). Borland discloses in multiple places that desirability of filling prescriptions may be tied to misuse of pharmaceuticals; for example, patient attributes includes patient's refill behavior. (*Id.* at ¶ 53.)
providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;	Borsand discloses that in filling a prescription for a drug, an event can trigger a modification or cancellation of the prescription, where such an event includes "evidence of fraud, misuse, or redundancy on the part of a provider, pharmacist, or patient." (Borsand ¶ 120.)
confirming receipt by the narcoleptic patient of the company's prescription drug; and	Borsand discloses that the system allows monitoring of whether or not a patient actually fills the prescription. (Borsand ¶ 56.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	Borsand discloses that "[i]f a patient 22, provider 30, pharmacist 40, or PBM 50 attempts an action that is not in accordance with the predefined rules 34 of the payor 60, the system 20 can be configured to not allow the attempted conduct, or to allow the conduct, but **generate a report** 42 relating to the undesirable activity." (Borsand ¶ 54.)

It is the patentee's obligation to present evidence of secondary considerations, if any, to rebut a *prima facie* case of obviousness. The '988 patent provides no specific evidence of secondary considerations of non-obviousness. Any evidence of secondary considerations is insufficient to overcome the strong case of *prima facie* obviousness of the claimed subject matter.[38]

3. Obviousness in Light of the Briefing Booklet (Claim 1)

Claim 1 of the '988 patent is obvious over the Briefing Booklet.

Claim 1 of the '988 Patent	Briefing Booklet
A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising:	The Briefing Booklet generally teaches the therapeutic benefits of Xyrem® in treating narcolepsy. (*See* generally Briefing Booklet (e.g., "upon learning about narcolepsy and the clinical results of Xyrem, these parties agreed that the therapeutic need for Xyrem was

[38] Secondary considerations of non-obviousness do not control the analysis where there is an otherwise strong case of obviousness, such as one based upon art not considered during prosecution. *Tokai Corp. v. Easton Enterprises, Inc.*, 632 F.3d 1358 (Fed. Cir. 2011) ("A strong case of prima facie obviousness, such as that presented here, cannot be overcome by a far weaker showing of objective indicia of nonobviousness."); *Sandt Tech. v. Resco Metal & Plastics*, 264 F.3d 1344, 1355 (Fed. Cir. 2001) ("We see no error in the district court's conclusion . . . that the secondary considerations cannot overcome the strong prima facie evidence of obviousness presented.").

Claim 1 of the '988 Patent	Briefing Booklet
	compelling.")). Further, the Briefing Booklet teaches the potential for abuse, misuse, or diversion of Xyrem (e.g., "They [law enforcement] 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...." (Briefing Booklet, at 7.)
receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic patients, the prescription drug, and various credentials of the any and all medical doctors;	"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." (Briefing Booklet at 306). "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." (Briefing Booklet at 311.) The Briefing Booklet teaches that the bulk drug is manufactured at a single site and is formulated into a finished product at a separate site, and each of these sites must be approved by meeting "FDA and DEA requirements for controlled substances." Briefing Booklet at 18.
requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;	The Briefing Booklet teaches data collection into the central database. The reference to "data collection" necessary includes entering the information into the central database. "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

Claim 1 of the '988 Patent	Briefing Booklet
	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." (Briefing Booklet at 19)
checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the company's prescription drug;	The Briefing Booklet discloses that "[t]he 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." The reference to real-time data implies a computer processor managing the data. (Briefing Booklet at 20.) The Briefing Booklet discloses that upon receipt of a prescription from the physician, the central pharmacy will "verify physician's eligibility by checking the AMA, DEA, or State Medical Board on-line databases" to ensure that "the prescription was written by a "real" physician with current privileges to prescribe controlled medications." (Briefing Booklet at 19.) The Briefing Booklet discloses that the collection of 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." (Briefing Booklet at 15).
confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;	The Briefing Booklet teaches that "[o]nce 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." (Briefing Booklet at 20.) While the Briefing Booklet does not explicitly require confirming that the patient has received and/or read the educational material "prior" to shipping the prescription drug, the FDA Safety Review (*See* obviousness analysis infra) and Califano cure this deficiency: Califano requires "confirming with the patient that educational material has been read prior to providing the

Claim 1 of the '988 Patent	Briefing Booklet
	drug to the patient." (*See* Califano ¶ 84; Examiner's Answer OA, dated 10/18/06.)
checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug;	The Briefing Booklet discloses that "[t]he 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." (Briefing Booklet at 20.)
providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;	The Briefing Booklet discloses a distribution system that requires physician verification process "to catch any prescriptions written on stolen or counterfeit prescription pads" and entering patient information in a "patient registry which also aids in diversion prevention" before the Xyrem shipping process begins, where Xyrem is mailed via Federal Express. (Briefing Booklet at 19-20.)
confirming receipt by the narcoleptic patient of the company's prescription drug; and	The Briefing Booklet discloses a distribution system that requires the exclusive central pharmacy pharmacist to contact the patient to confirm receipt of the Xyrem prescription. (Briefing Booklet at 20.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	The Briefing Booklet teaches that "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." (Briefing Booklet at 16.) The Briefing Booklet further teaches that "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." (Briefing Booklet at 15.)

4. Obviousness in Light of the FDA Safety Review (Claim 1)

Claim 1 of the '988 patent is obvious over the FDA Safety Review.

Claim 1 of the '988 Patent	FDA Safety Review
A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising:	The FDA Safety Review teaches a method of distributing a prescription drug (Xyrem®) under exclusive control of an exclusive central pharmacy (or distributor). (FDA Safety Review

Claim 1 of the '988 Patent	FDA Safety Review
	at 108). The FDA Safety review discloses that Xyrem is effective for treating narcolepsy, but also that "medically prescribed Xyrem may be diverted for illegal use." (FDA Safety Review at 7; 108)
receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic patients, the prescription drug, and various credentials of the any and all medical doctors;	The FDA Safety Review teaches a method of distributing a prescription drug (Xyrem®) under exclusive control of an exclusive central pharmacy (or distributor). (FDA Safety Review at 108). Apparently, Orphan Medical proposed Nova Factor to be the central pharmacy. It describes a "closed-loop distribution system," wherein "Xyrem® will NOT be placed in retail pharmacy outlets," and instead, the document describes a "primary and exclusive distributor of Xyrem®." *Id.* at 108. The FDA Safety Review teaches that the prescription drug will be manufactured by two different companies that will be approved for distribution, as these companies would have to be "FDA and DEA-compliant, 'fill-finish' facilities." FDA Safety Review at 108. In addition, the FDA Safety Review teaches that the "drug product will be stored at a facility compliant with Schedule III regulations, where a consignment inventory will be maintained." *Id.*
requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;	The FDA Safety Review teaches that a single, sole, and secure database will store the relevant information. "Every patient and prescribing physician will be registered with [the exclusive distributor] in 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." (FDA Safety Review at 110.)
checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the company's prescription drug;	The FDA Safety review teaches that the exclusive central pharmacy will verify that the physician is eligible to prescribe Xyrem®, including checking whether the physician has an active DEA number and whether any actions are pending against the physician.

Claim 1 of the '988 Patent	FDA Safety Review
	(FDA Safety Review at 109.)
confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;	The FDA Safety Review discloses that the Office of Post-Marketing Drug Risk assessment recommended that confirmation of whether the patient has read and fully understands the education material should be received by Nova Factor "prior to the initial dispensing of the drug." (FDA Safety Review at 114-115.)
checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug;	The FDA Safety Review notes in several in several places checking for potential for abuse, misuse, or diversion: prescriptions refills before anticipation date will be questioned (FDA Safety Review at 110); lost, stolen, destroyed, or spilled prescription/supply will be documented, flagged, and monitored (*Id.*); noting prescribing frequency (*Id.*); among others.
providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;	The FDA Safety Review discloses that "once approval has been established, (b)(4) [exclusive specialty pharmacy] will … arrange shipment though (b)(4) or a similar carrier." (FDA Safety Review at 109.) The approval process requires verification of eligibility to prevent potential abuse. *Id.*
confirming receipt by the narcoleptic patient of the company's prescription drug; and	The FDA Safety Review discloses that "[r]eceipt of the drug by the patient will be ensured through … a phone call by the pharmacy to the patient." (FDA Safety Review at 109.)
generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	The FDA Safety Review notes in several places potential for abuse, misuse, or diversion: prescriptions refills before anticipation date will be questioned (FDA Safety Review at 110); lost, stolen, destroyed, or spilled prescription/supply will be documented, flagged, and monitored (*Id.*); noting prescribing frequency (*Id.*); among others. While the FDA Safety Review does not explicitly disclose generating periodic reports, the Video, Borsand, Briefing Booklet, and Lilly, among others, disclose generating periodic reports to evaluate potential diversion patterns. (*See* obviousness analysis of the Video, Briefing Booklet, and the FDA Safety Review; Lilly ¶¶ 11, 33, 54, 57, 58, 61, 69; Examiner's Answer , OA dated 06/19/06.)

5. Obviousness in Light of the Video (Claim 1)

Claim 1 of the '988 patent is obvious over the Video.

Claim 1 of the '988 Patent	Video
A method of treatment of a narcoleptic patient	The Video teaches using a method that includes

Claim 1 of the '988 Patent	Video
with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising:	a single, centrally-located specialty pharmacy that controls distribution, documentation, and security of prescription drugs, such as Xyrem® to treat narcolepsy, through a closed-loop distribution system in order to minimize abuse, misuse, diversion. (Video, ¶¶ 2-5; 13.)
receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic patients, the prescription drug, and various credentials of the any and all medical doctors;	The Video shows a "shot of pharmacy employee picking up prescription fax and sitting down at a computer to verify physician's eligibility." (Video ¶ 21). The illustration of a computer in the Video teaches using a computer to control distribution. The Video teaches using a computer to process prescription requests. A computer inherently includes a computer processor. The Video discloses a single, centrally-located specialty pharmacy that controls distribution, documentation, and security through a closed-loop distribution system. The prescriptions are sent to the central pharmacy, which verifies that the "physician is an Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data ... to check if there are any pending or previous actions against the physician." (Video ¶¶ 14; 21.) The single, specialty pharmacy stores data about prescriptions by patients; thus, it follows that the prescription sent by the physician includes patient identifying information. (*See, e.g.,* Video ¶ 24.) To the extent the video does not explicitly teach distribution by an approved company, the Briefing Booklet and FDA Safety Review cure this deficiency.
requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;	The Video teaches that all "data about inventory, physicians, reimbursements, patients, and delivery" is stored in one efficient and quickly-accessible location [single, specialty pharmacy]." (Video ¶ 24.) Further, the Video teaches that the "closed-loop distribution system … will 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." (Video ¶ 14.)
checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to	The Video teaches using a computer to process the specialty pharmacy prescription requests. A computer inherently includes a

Claim 1 of the '988 Patent	Video
prescribe the company's prescription drug;	computer processor. The Video discloses that the prescriptions are sent to the central pharmacy, which verifies that the "physician is an Orphan Medical's list of targeted physicians and has active DEA and State License. Additionally, the pharmacy checks data ... to check if there are any pending or previous actions against the physician." (Video ¶ 24.)
confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;	The Video teaches sending a patient educational material, "Patient Success Program." (Video ¶ 31.) While the Video does not explicitly require confirming that the patient has received and/or read the educational material "prior" to shipping the prescription drug, the FDA Safety Review (*See* obviousness analysis supra) and Califano cure this deficiency: Califano requires "confirming with the patient that educational material has been read prior to providing the drug to the patient." (*See* Califano ¶ 84; Examiner's Answer OA, dated 10/18/06.)
checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug;	The Video discloses that the central pharmacy staff 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." (Video ¶ 14). The Video also discloses that the specialty pharmacy will keep track of anomalous patient requests to fill their prescriptions. (*Id.* at 38.)
providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;	The Video discloses that Xyrem® will be "shipped overnight by Federal express utilizing a tracking system designed specifically for the specialty pharmacy." (Video ¶ 30.) The Video teaches that during "the process of verification and documentation, if any data or behavior suggest the possibility that Xyrem® may be used inappropriately, the specialty pharmacy is empowered to contact the appropriate authorities." (Video ¶ 29.)
confirming receipt by the narcoleptic patient of the company's prescription drug; and	The Video teaches that receipt of Xyrem® and educational materials is verified by a telephone call placed to the patient where "the specialty pharmacy will confirm receipt of the Xyrem prescription and the Patient Success program." (Video ¶ 35.)
generating with the computer processor periodic reports via the exclusive computer database to	The Video discloses that the closed-loop distribution system "will be able to **generate**

Claim 1 of the '988 Patent	Video
evaluate potential diversion patterns.	**data**, recording prescribers, patients and dosing that could provide information for any possible investigations and prosecutions for state and federal authorities." (Video ¶ 14).

6. Application of the Prior Art (Claims 2-15)

Claim 2 of the '988 patent is directed to the method of claim 1 "wherein one or more of the exclusive central pharmacy and the exclusive central database are distributed over multiple computers, and wherein a query operates over all data in all the databases relating to the prescriptions, the doctors, and the narcoleptic patients." Borsand teaches that "[i]n alternative embodiments of the invention, multiple databases are used to store pharmaceutical information. PBMs 50, payors 60, patients 22, providers 30, and prescriptions can each have their own databases 62, which can in [*sic*] interconnected or kept separate, but each are accessible from the [main] computer 26 housing the computer programs used by the system 20." (Borsand ¶ 43). Accordingly, Borsand teaches using multiple databases, which naturally would be housed in multiple computers, in relation to the prescriptions, the doctors, and the patients. Further, as noted above, while Borsand does not explicitly teach that the patients are narcoleptic patients, the Video, Briefing Booklet, and the FDA Safety Review disclose that the prescription drugs are for narcoleptic patients.

Claim 3 is directed to the method of claim 1, "wherein the providing company's prescription drug to the narcoleptic patient comprises the exclusive central pharmacy authorizing the company's prescription drug to be dispensed to the narcoleptic patient by another pharmacy." The FDA Safety Review teaches that the specialty pharmacy may ship the prescription to another pharmacy for patient pick-up. (FDA Safety Review at 110). The FDA Safety Review also discloses that, where the prescription will be picked up by another pharmacy, the specialty pharmacy must verify that there is a mechanism for the second pharmacy to protect against diversion of the prescription drug. (FDA Safety Review at 110).

Claim 4 is directed to the method of claim 1, "comprising delivering the company's prescription to the narcoleptic patient in order to treat the narcoleptic patient with the company's prescription drug." The FDA Safety Review discloses that Xyrem will be delivered to the narcoleptic patient by the central pharmacy [(b)(4)]using a courier service. (FDA Safety Review at 109). Similarly, the Briefing Booklet discloses that the "specialty pharmacy will contact the patient … and arrange a time for a next-day delivery…." (Briefing Booklet at 19.)

Claim 5 is directed to the method of claim 1, "wherein the exclusive central pharmacy enters data into the exclusive computer database." The prior art references teach that the central pharmacy enters data into an exclusive central database. For example, the Video teaches that all "data about inventory, physicians, reimbursements, patients, and delivery" is stored in one efficient and quickly-accessible location [single, specialty pharmacy]." (Video ¶ 24). Similarly, the Briefing Booklet teaches data collection into the central database. The reference to "data collection" necessary includes entering the information into the central database. "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." (Briefing Booklet at 19.)

Claim 6 is directed to the method of claim 1, "comprising selectively blocking shipment of the company's prescription drug to the narcoleptic patient." The prior art references disclose that shipments of the prescription drug may be selectively blocked. For Example, the FDA Safety Review discloses that if a patient is unavailable to accept a shipment of Xyrem® and execute the required receipt, the package will be returned to the pharmacy. (FDA Safety Review at 109). Similarly, The Briefing Booklet discloses that "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." (Briefing Booklet at 20.)

Claim 7 is directed the method of claim 1, "wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the company's prescription drug is blocked based upon such association." The prior art references disclose that prior to shipment of the prescription drug, the verification process will prevent shipment to patients associated with an abuse pattern. For example, the Video teaches that prior to shipping the patient's medication overnight by Federal Express, a process of verification and documentation will allow the specialty pharmacy to determine "if any of the data or behavior suggests the possibility that Xyrem may be used inappropriately." (Video ¶¶ 29-30). Similarly, the FDA Safety Review teaches that Xyrem® will only be shipped once approval has been established, where approval requires verifying eligibility of the physician to prescribe the prescription drug and obtaining a certificate of medical necessity. (FDA Safety Review at 109.)

Claim 8 is directed to the "computerized" method of claim 1, "wherein the company's prescription drug comprises a gamma hydroxyl butyrate (GHB) drug product." As an initial matter, the method of claim 1 is not a "computerized" method, and appears to be an error that the Examiner failed to observe or require correction. Nonetheless, substantively, at least the Briefing Booklet and the FDA Safety Review explicitly disclose that the prescription drug is GHB.

Claim 9 is an independent claim, but is similar to claim 1. The difference between claim 9 and claim 1 is that claim 9 recites "the prescription drug inventory is owned by a company," whereas, claim 1 recites "the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug." This difference does not overcome the prior art references. For example, the FDA Safety Review discloses that the distributing company will own the inventory (e.g., "The inventory will be owned by Orphan Medical, Inc., and the facility will be managed by (b)(4).") (FDA Safety Review at 108.)

Claim 10 is directed to the method of claim 9 and includes the same limitation as claim 2. Thus, for the same reasons claim 2 is rendered obvious, claim 10 is also rendered obvious by the same references.

Claim 11 is directed to the method of claim 9 and includes the same limitation as claim 3. Thus, for the same reasons claim 3 is rendered obvious, claim 11 is also rendered obvious by the same references.

Claim 12 is directed to the method of claim 9 and includes the same limitation as claim 4. Thus, for the same reasons claim 4 is rendered obvious, claim 12 is also rendered obvious by the same references.

Claim 13 is directed to the method of claim 9 and includes the same limitation as claim 5. Thus, for the same reasons claim 5 is rendered obvious, claim 13 is also rendered obvious by the same references.

Claim 14 is directed to the method of claim 9 and includes the same limitation as claim 7. Thus, for the same reasons claim 7 is rendered obvious, claim 14 is also rendered obvious by the same references.

Claim 15 is directed to the method of claim 9 and includes the same limitation as claim 8. Thus, for the same reasons claim 8 is rendered obvious, claim 15 is also rendered obvious by the same references.

F. INELIGIBLE SUBJECT MATTER UNDER 35 U.S.C. § 101

The claims of the '988 patent are invalid under 35 U.S.C. § 101 because the claimed subject matter is not patentable. The claims of the '988 patent do not satisfy the machine-or-transformation test, and are directed to algorithms and abstract ideas *Bilski v. Kappos*, 130 S.Ct. 3218, 3229-30 (2010); *In re Bilski*, 545 F.3d 943, 962-63 (Fed. Cir. 2008).

In the '988 patent, the process is not tied to a particular machine or apparatus. Although the claims include terms like "computerized method" and "computer processor," there is nothing in the specification indicating that a computer is integral to implementing the process. Further, while some of the steps require use of a "computer processor," 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.*, '988 patent, col. 3, lines 10-14.)[39]

The '988 patent claims do not transform an article into a different state or thing: They merely claim a method of distributing sensitive drugs that does not transform or make the drugs

[39] 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).

any less sensitive. Although some claims require 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. Although 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." *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.*, '988 patent, col. 1, lines 6- 7.)

The Federal Circuit has determined that patent claims are abstract when the "steps can be performed in the human mind, or by a human using a pen and paper." *CyberSource*, 654 F.3d at 1372. In the '988 patent, the process is similar to a clearing house in that the method merely requires collecting and organizing data of doctors who are able to prescribe, and the patients who are able to receive, the medication, and organizing the data describing shipments of the medication, and associated marketing material. This process could equally be performed by pencil, paper, and a traditional filing cabinet system.

The steps of the claims in the '988 patent represent common ways that people have used to restrict allocation of materials, where a central controlling entity confirms with a validated third-party authority whether a substance should be delivered to an individual. Without meaningful limits, the claims effectively preempt the fundamental concept itself and foreclose a wide range of inventions that the patentee never conceived. For example, in *Dealertrack*, the Federal Circuit determined that the patentee's claimed process in its simplest form includes three steps: receiving data from one source (step A), selectively forwarding the data (step B, performed according to step D), and forwarding reply data to the first source (step C). *Dealertrack,* 674 F.3d at 1333. Because this claim "explain[s] the basic concept of processing information through a clearing-house . . . [t]he steps that constitute the method here do not impose meaningful limits on the claim's scope." *Id.* (citing *Bilski*, 130 S. Ct. at 3231; *Bilski*, 545 F.3d at 961-62) (quotations omitted). The Federal Circuit was "compelled to conclude that the claims are invalid as being directed to an abstract idea ***preemptive of a fundamental concept or idea*** that would foreclose innovation in this area." *Id.* at 1333 (emphasis added); *see also Mayo*, 132 S. Ct. at 1294 (the patent should not "risk disproportionately tying up the use of" the abstract idea in future discoveries). Similarly, here, the steps of the claims in the '988 patent are directed to a fundamental concept itself, thus are directed to an abstract idea.

In sum, the claims of the patent-in-suit fail to meet the requirements of § 101 because they: (1) fail the machine-or-transformation test and (2) are directed to the abstract idea of a centralized authorization center for prescriptions drugs , which is a fundamental principle that would be improperly preempted by the patent-in-suit. Here, the computer must be integral to the claimed invention, facilitating the process in a way that a person making calculations or computations could not." *Bancorp*, 687 F.3d at 1278. This method could be performed by someone using pencil, paper, and a standard records-keeping system. For these reasons, the claims of the '988 patent are invalid under 35 U.S.C. § 101.

G. CONCLUSION

For the reasons stated above, claims 1-15 of the '988 patent are obvious over the prior art, and claims 1-15 are invalid 35 U.S.C. § 101. Par reserves the right to develop additional grounds, reasons and authorities that any or all of the claims of these patents are invalid, unenforceable or not infringed.

Xyrem® (sodium oxybate) oral solution

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

June 6, 2001

Orphan Medical Inc.

Agenda

♦ Introduction	Dayton Reardan, Ph.D., VP of Regulatory Affairs
♦ Medical Need	Emmanuel Mignot, M.D., Stanford University
♦ Efficacy	William Houghton, M.D., COO, Medical Officer
♦ Polysomnographic Effects of Xyrem	Jed Black, M.D., Stanford University
♦ Safety	William Houghton, M.D., COO, Medical Officer
♦ Summary of Risks Versus Benefits	William Houghton, M.D., COO, Medical Officer

11:00 a.m.

♦ Abuse Liability	Robert Balster, Ph.D., Medical College of Virginia
♦ Risk Management	Patti Engel, R.N., B.S.N., VP Marketing & Sales

Experts Available for the Committee

Helene Emsellem, M.D.
Center for Sleep and Wake Disorders,
Chevy Chase, MD

Martha Hagaman, M.D.
Sleep Medicine Associate
St. Thomas Hospital, Nashville, TN

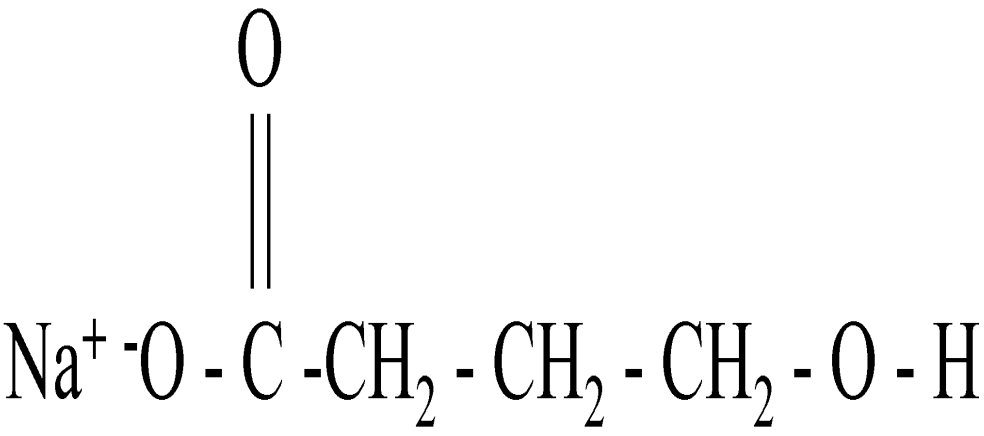
Ruzica Ristanovic, M.D.
Sleep Disorders Center
Evanston Hospital
Evanston, Illinois

Richard Okerholm, Ph.D.
Pharmacokinetic and Drug Metabolism
Consultant

Frederick E. Reno, Ph.D.
Preclinical Toxicology Consultant

Richard Trout, Ph.D.
Statistician
Department of Statistics
Professor (Emeritus)
Rutgers University
New Jersey

Chemical Structure



sodium oxybate

Xyrem

Regulatory Overview

- 1960s discovery of GHB, approval as an anesthetic in France
- 1970s initial clinical narcolepsy evaluation
- 1978 GHB was used as an example for the need of an Orphan Drug Act
- 1980s two independent controlled studies
- 1994 FDA approached Orphan Medical to develop
- 1995 pre-IND meeting with FDA
- 1998 Treatment IND approved
- 2000 Orphan Medical submitted this NDA
  - Priority review

Recognition of Abuse

- Xyrem is not the problem
- Ease of synthesis
- Initial availability of internet GHB kits
- Current availability of precursor GHB substitutes
  - Gammabutyrolactone (GBL)
  - 1,4-butanediol (1,4-BD)
- Federal legislation in 2000 controls only GHB

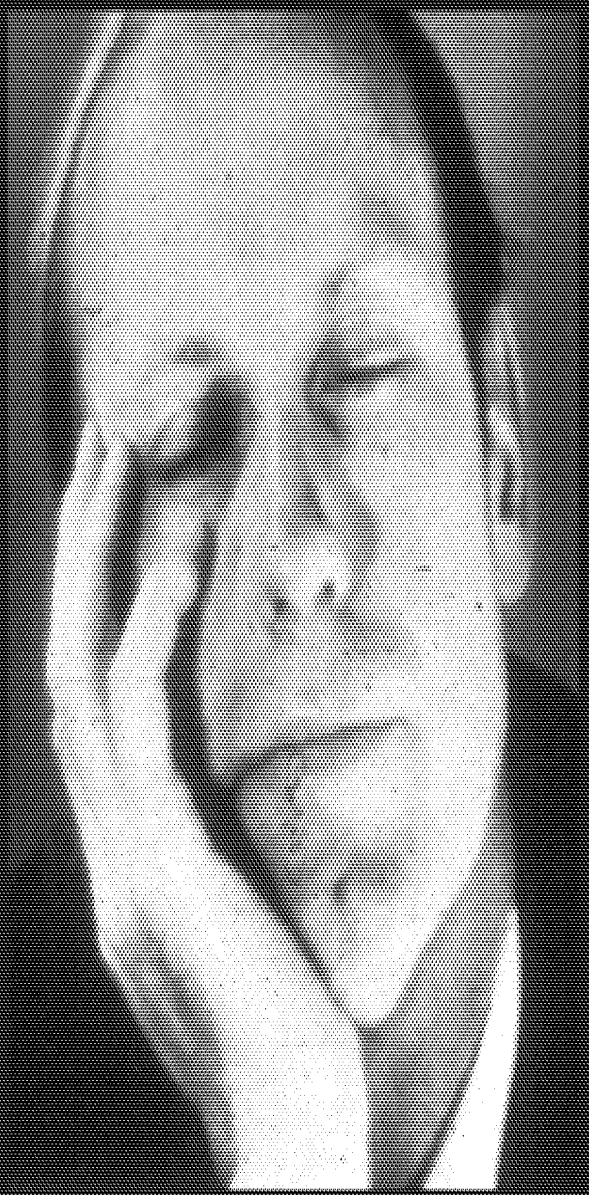
Proposed Indication

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.

Prevalence of Narcolepsy in the U.S.

- Narcolepsy is an orphan disease
- Epidemiology estimates 135,000 patients
- 55% are diagnosed (75,000)
- 32% of those have cataplexy for which they seek treatment (24,000)

Narcolepsy - Medical Need



Emmanuel Mignot
M.D., Ph.D.

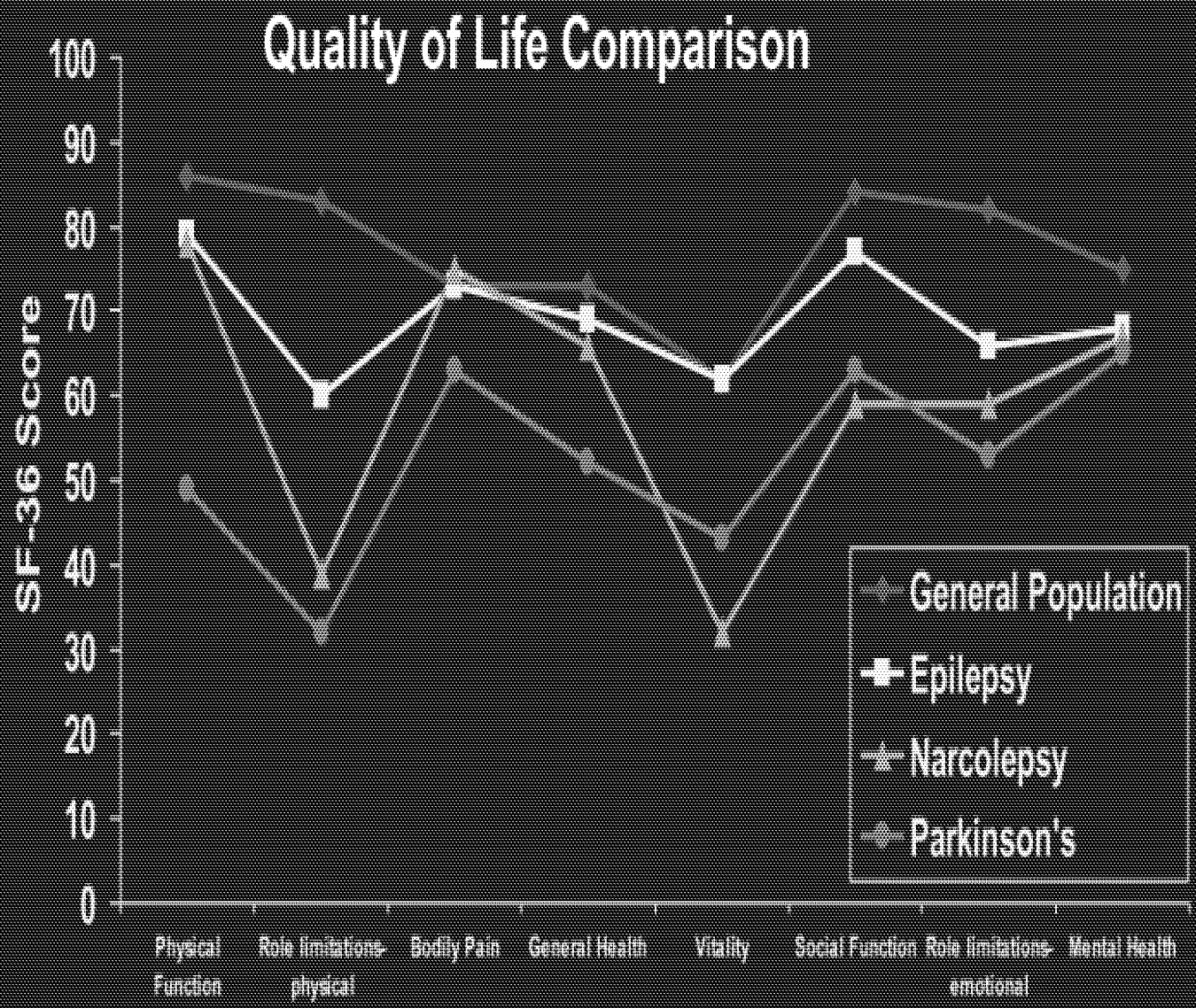
Director
Center for Narcolepsy
Stanford University

Washington, D.C.
June 6th, 2001

Narcolepsy - Cataplexy

- Excessive daytime sleepiness
- Cataplexy
- Hypnagogic hallucinations
- Sleep paralysis
- Disturbed nocturnal sleep

Narcolepsy - A Disabling Disorder



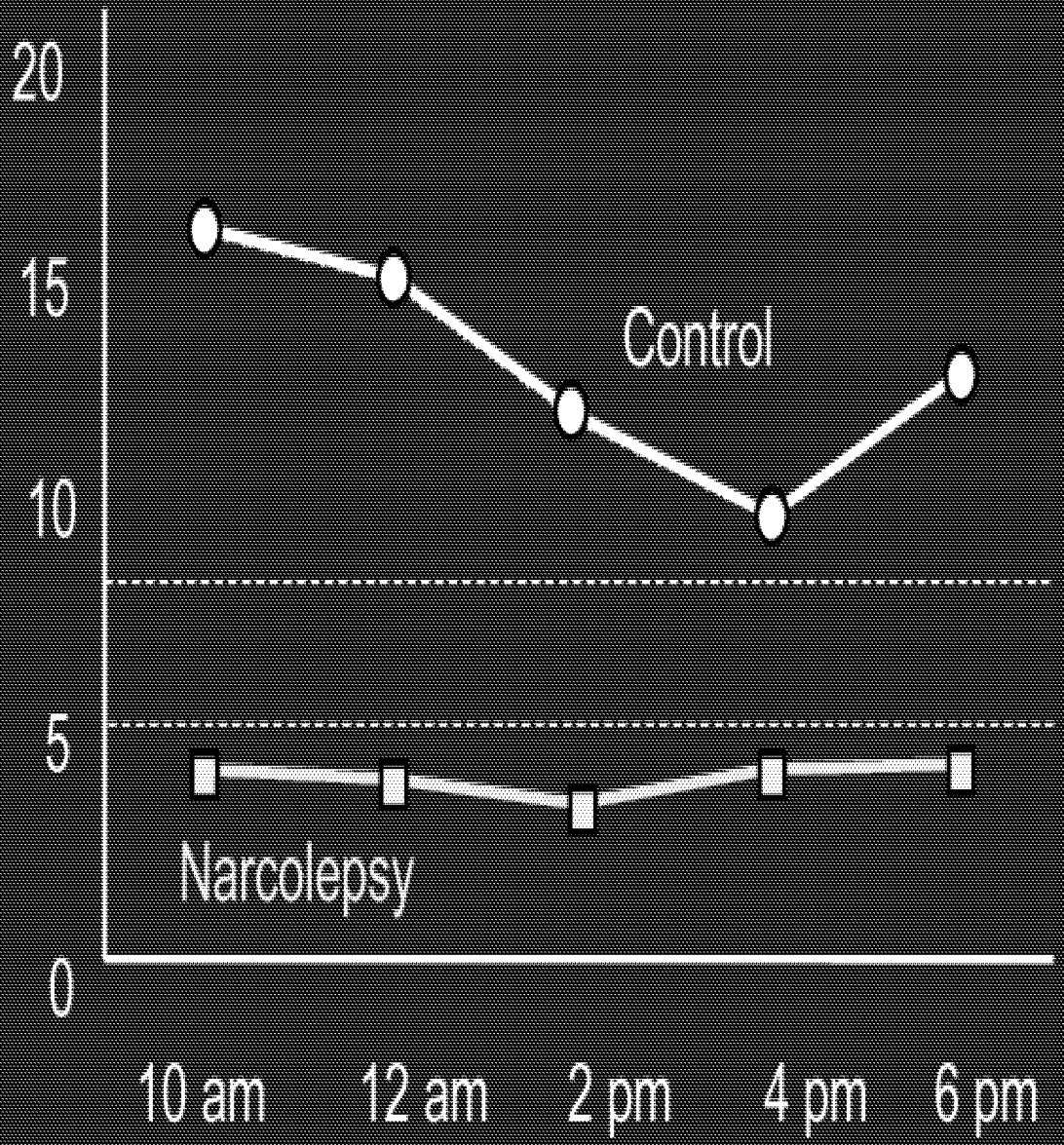
Adapted from Beusterien et al. SLEEP 1999; 22

Driving Effects and Accidents

	Narcolepsy	Controls
♦Do you drive?	48%	63%
♦Fall asleep driving	66	6
♦Cataplexy driving	29	0
♦Sleep paralysis driving	12	0
♦Frequent near accidents	67	0
♦Led to accidents	37	5
♦Higher insurance	16	1
♦Suspended license	7	4

From: Broughton et al. Psychophysiological aspects of sleep. Park Ridge, NJ: Noyes Medical Publ, 1981.

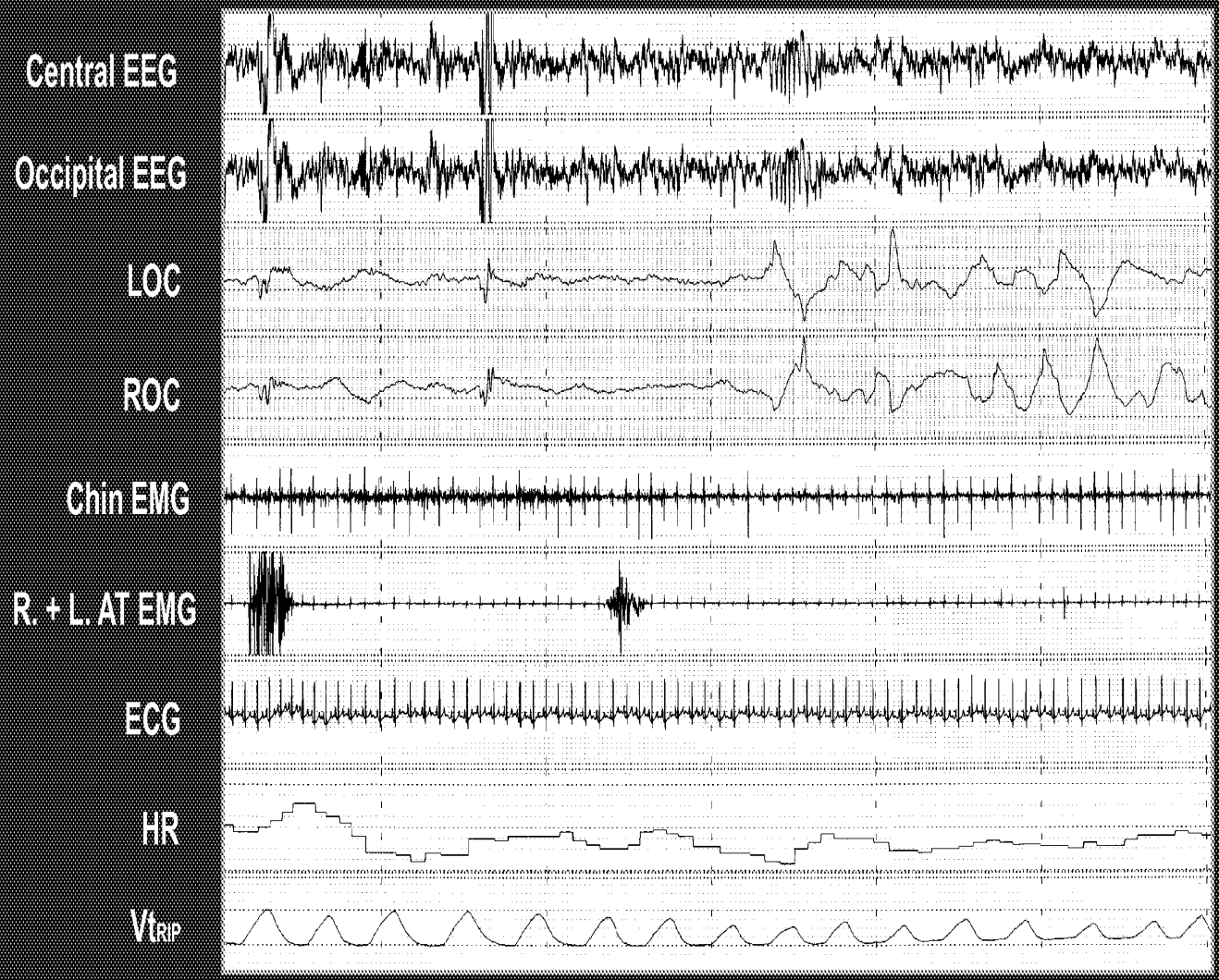
Objective Measurement of EDS



13

Abnormal Regulation of REM Sleep

Sudden transition from wakefulness to REM sleep



≥ 2 SOREMPs is typical for narcolepsy

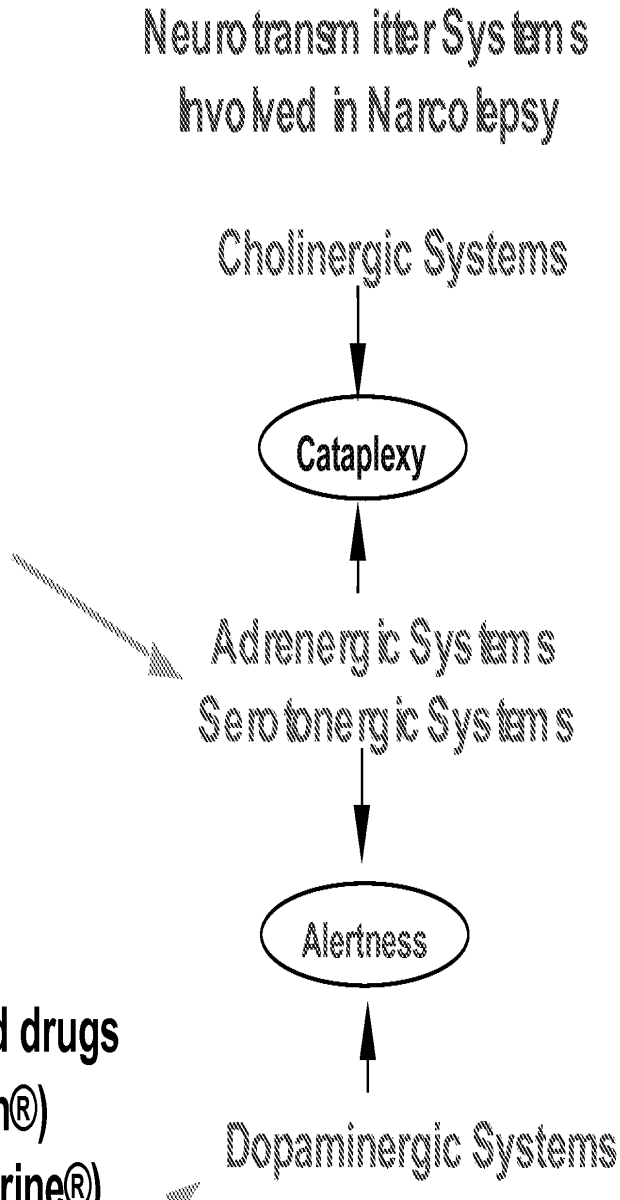
ANTI-NARCOLEPSY-DRUGS

Antidepressants

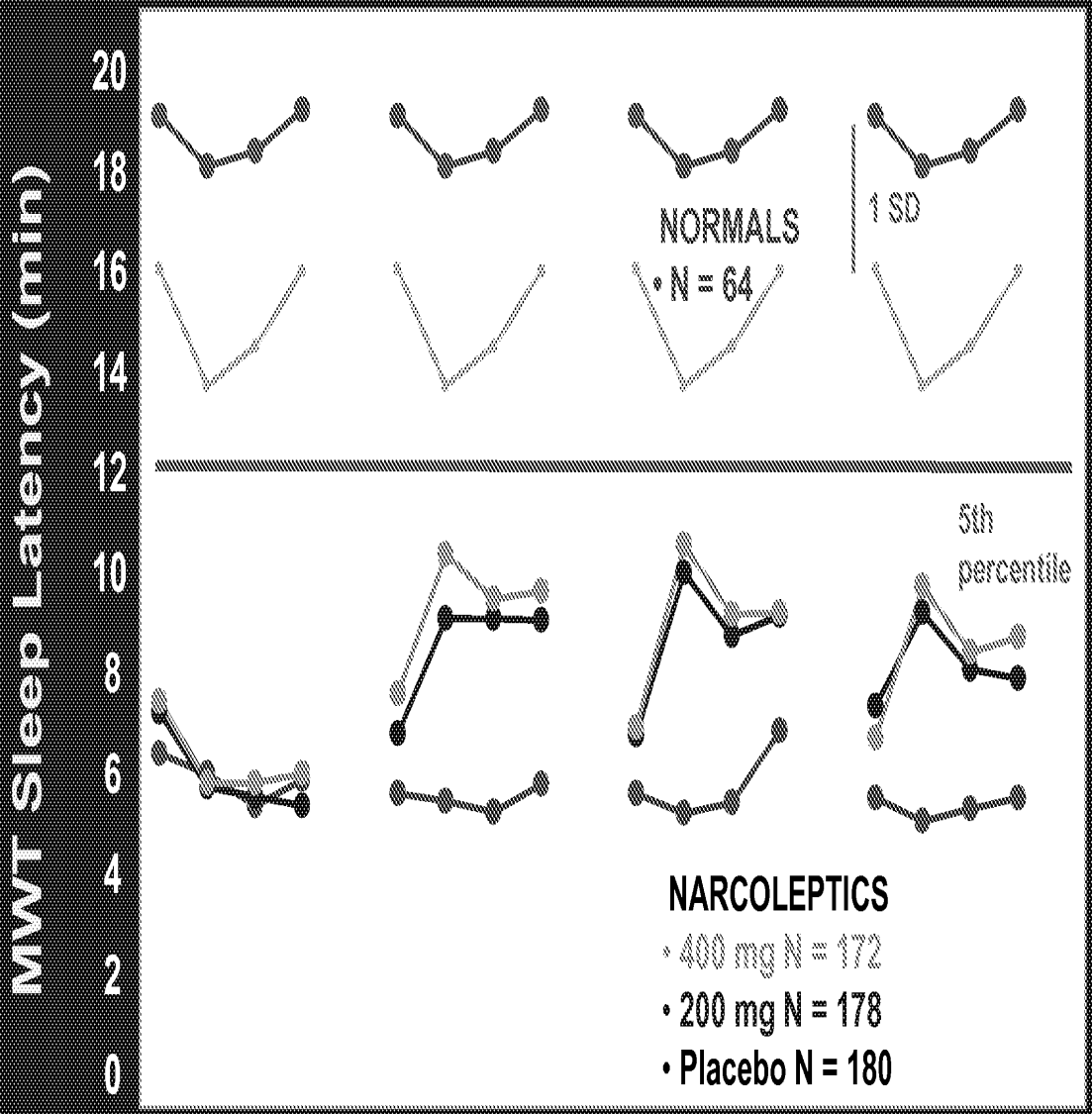
- Imipramine (Tofranil®)
- Clomipramine (Anafranil®)
- Protryptiline (Vivactil®)
- Fluoxetine (Prozac®)

Stimulants - All are scheduled drugs

- Methamphetamine (Desoxyn®)
- Dextroamphetamine (Dexedrine®)
- Methylphenidate (Ritalin®)
- Pemoline (Cylert®)
- Modafinil (Provigil®)



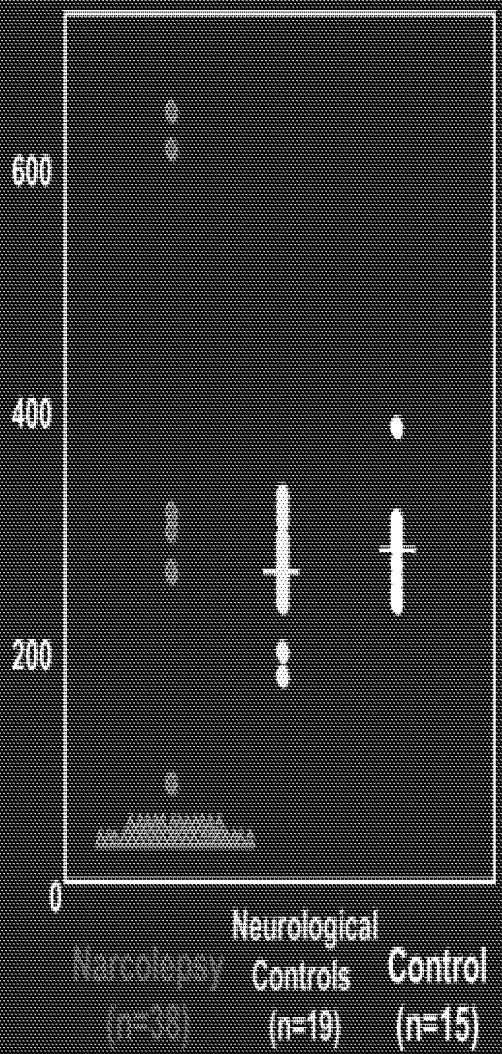
Partial Efficacy of Treatments: MWT



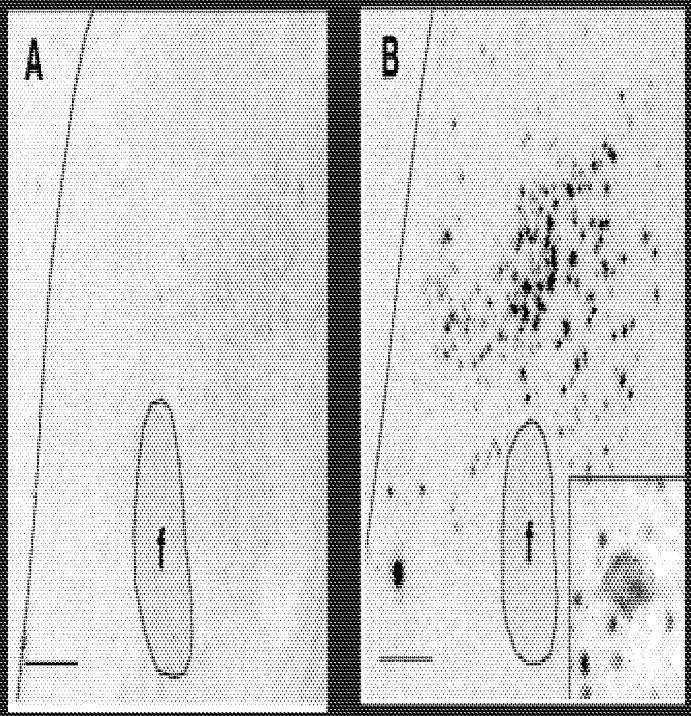
US Modafinil in Narcolepsy Multicenter Study Group. Ann Neurol 1998;43 and Neurology 2000;54.

Hypocretin Deficiency in Narcolepsy

Cerebrospinal Fluid



Lateral Hypothalamic brain tissue



Nishino et al. Lancet, 355:39-40, 2000; Peyron et al., Nature Med, 6: 991-7, 2000

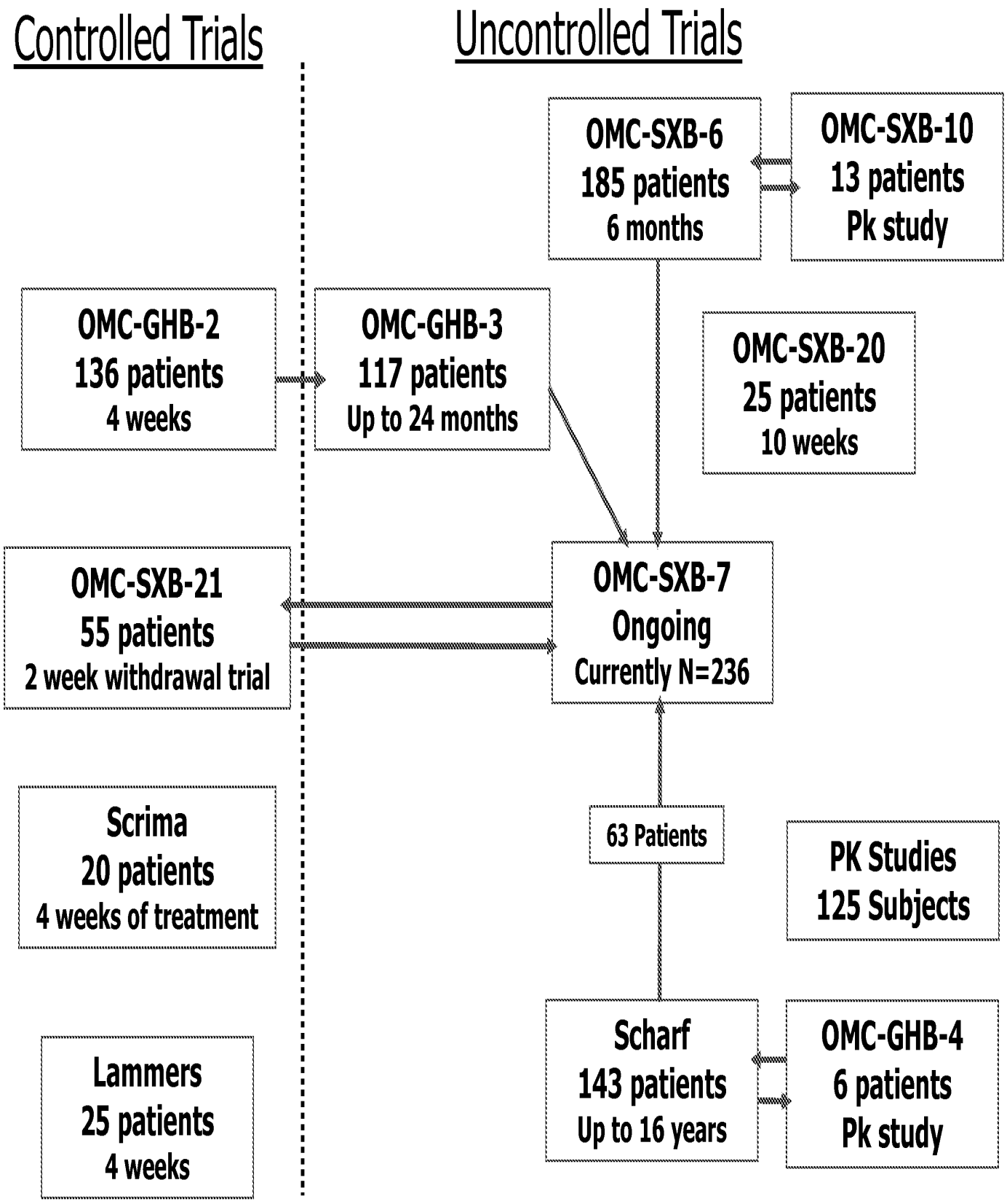
Need for New Treatments

- Narcolepsy is serious and disabling
- Current treatments are unsatisfactory in term of side effects and efficacy
- Current treatments all have a similar mode of action and act symptomatically
- Future treatments that may involve hypocretin agonists are years away

Xyrem® Clinical Data: Efficacy

William Houghton, M.D.

Chief Operating Officer & Medical Officer,
Orphan Medical, Inc.



Xyrem

OMC-GHB-2 Study

- Randomized, double-blind, placebo-controlled, parallel-group, multi-center trial comparing the effects of three doses (3g, 6g, 9g) of orally administered Xyrem with placebo for the treatment of narcolepsy

OMC-GHB-2

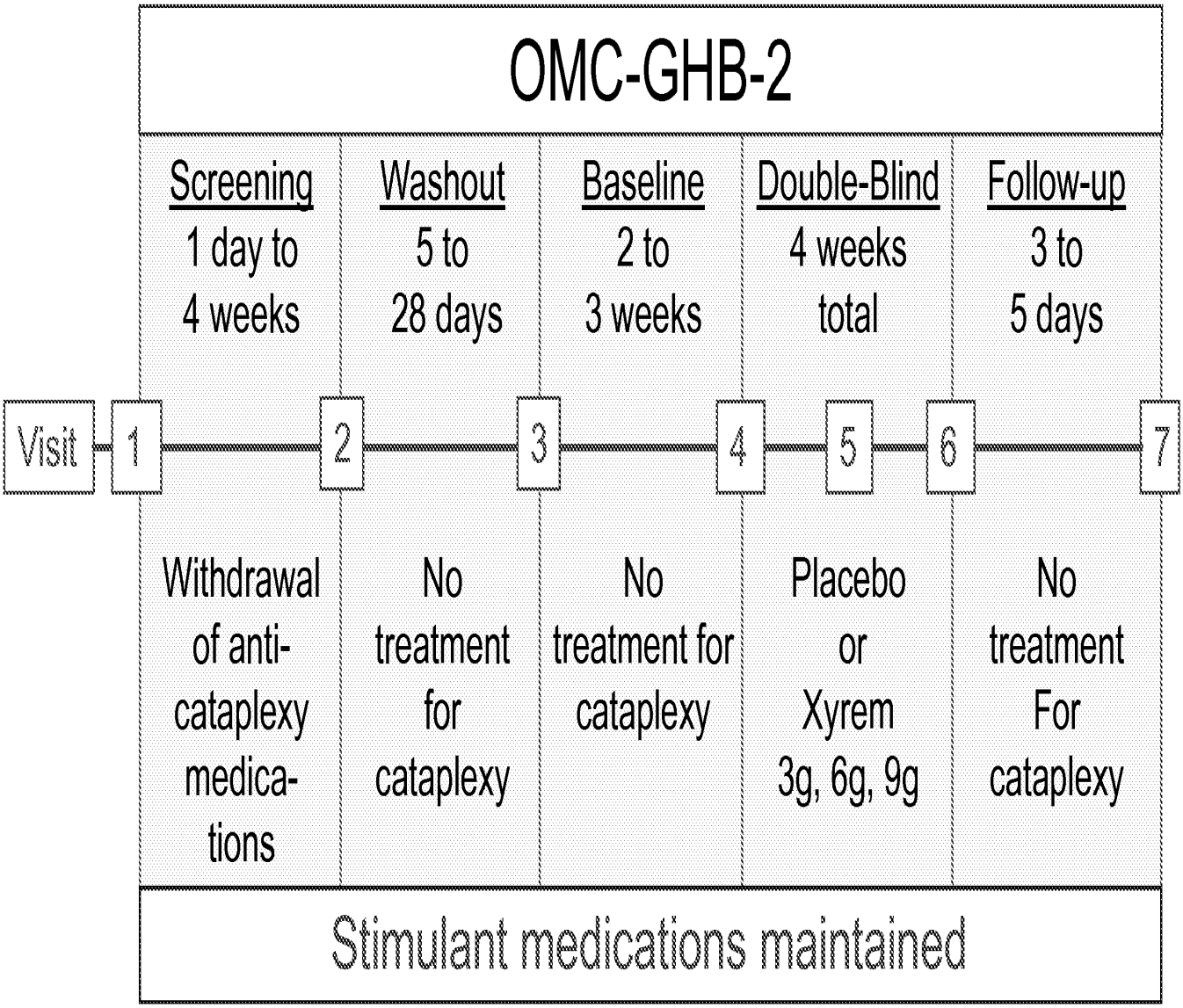
Efficacy Parameters

- Primary efficacy parameter
  - Total number of cataplexy attacks/week versus baseline
- Secondary efficacy parameters
  - Complete and partial cataplexy attacks
  - Daytime sleepiness / Inadvertent naps
  - Hypnagogic hallucinations
  - Sleep paralysis
  - CGI—Clinical Global Impression

OMC-GHB-2
Inclusion Criteria

- Diagnosis of narcolepsy
  - Polysomnography (PSG) and Multiple Sleep Latency Test (MSLT) within the last 5 years
    - Excluding sleep apnea or other causes of daytime sleepiness
  - History of Excessive Daytime Sleepiness (EDS) and cataplexy for at least 6 months
    - Recurrent daytime naps that occur almost daily for at least 3 months

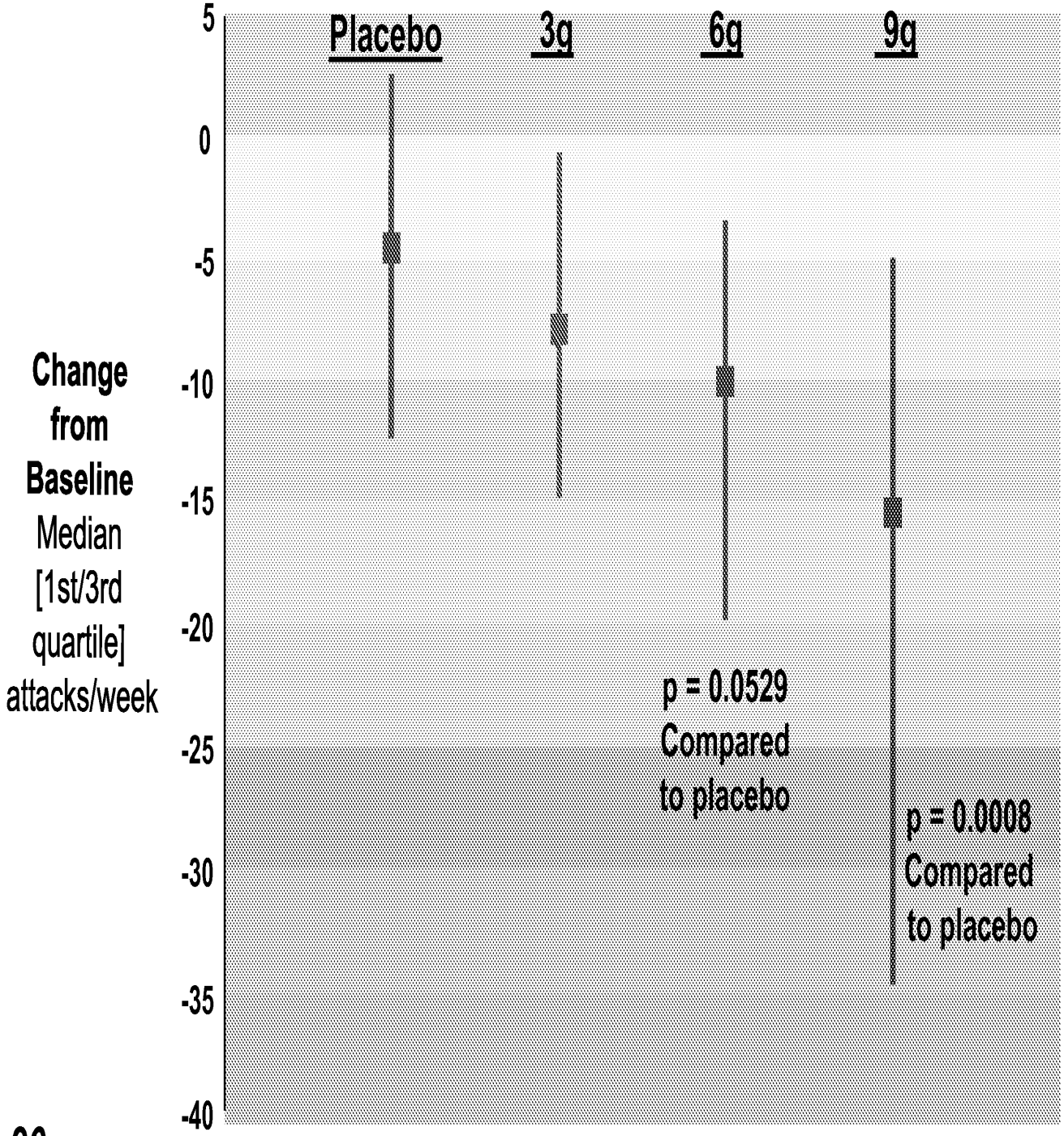
OMC-GHB-2
Overall Study Design



Cataplexy Attacks per Week

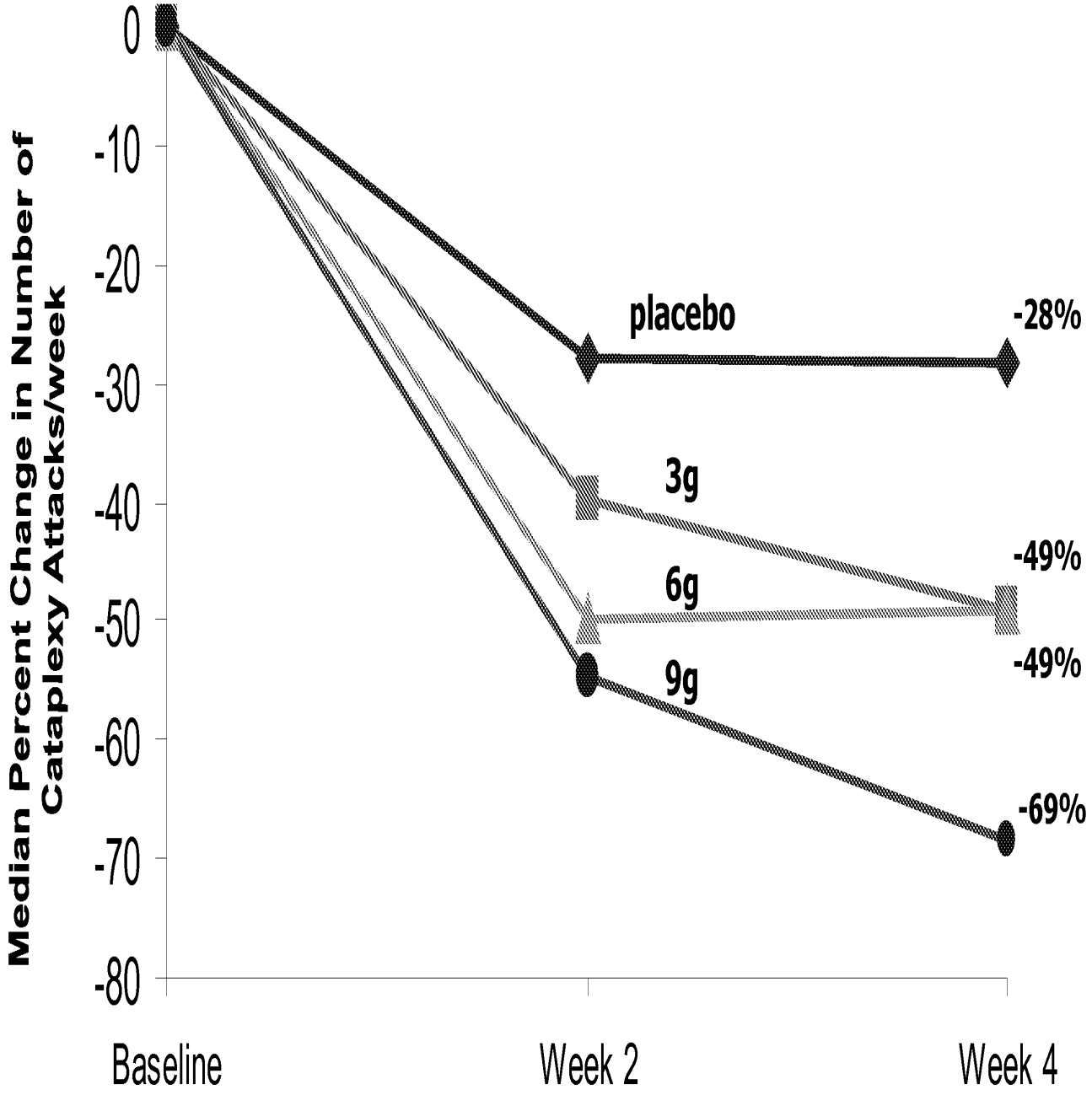
Dose Group	Statistic	Observed		Change from BL to EP	Comparison with placebo (p-value)
		Baseline(BL)	Endpoint(EP)		
Placebo	N=33				
	Mean(SD)	35.1 (47.1)	24.0 (28.4)	-11.1 (27.7)	
	Median	20.5	16.3	-4.3	---
	P-value	--	--	**0.028**	
3g	N=33				
	Mean(SD)	28.6 (30.5)	19.5 (27.5)	-9.1 (22.4)	
	Median	20.0	9.5	-7.0	0.5235
	P-value	--	--	**0.026**	
6g	N=31				
	Mean(SD)	33.8 (45.6)	24.6 (62.9)	-9.2 (27.3)	
	Median	23.0	8.0	-9.9	0.0529
	P-value	--	--	**0.070**	
9g	N=33				
	Mean(SD)	35.7 (34.5)	14.4 (19.3)	-21.3 (29.8)	
	Median	23.5	8.7	-16.1	**0.0008**
	P-value	--	--	**<0.001**	

OMC-GHB-2 Primary Efficacy
Total Cataplexy



Xyrem

OMC-GHB-2 Primary Efficacy
Cataplexy (Median Percent Change)



Xyrem

Secondary Efficacy
Epworth Sleepiness Scale

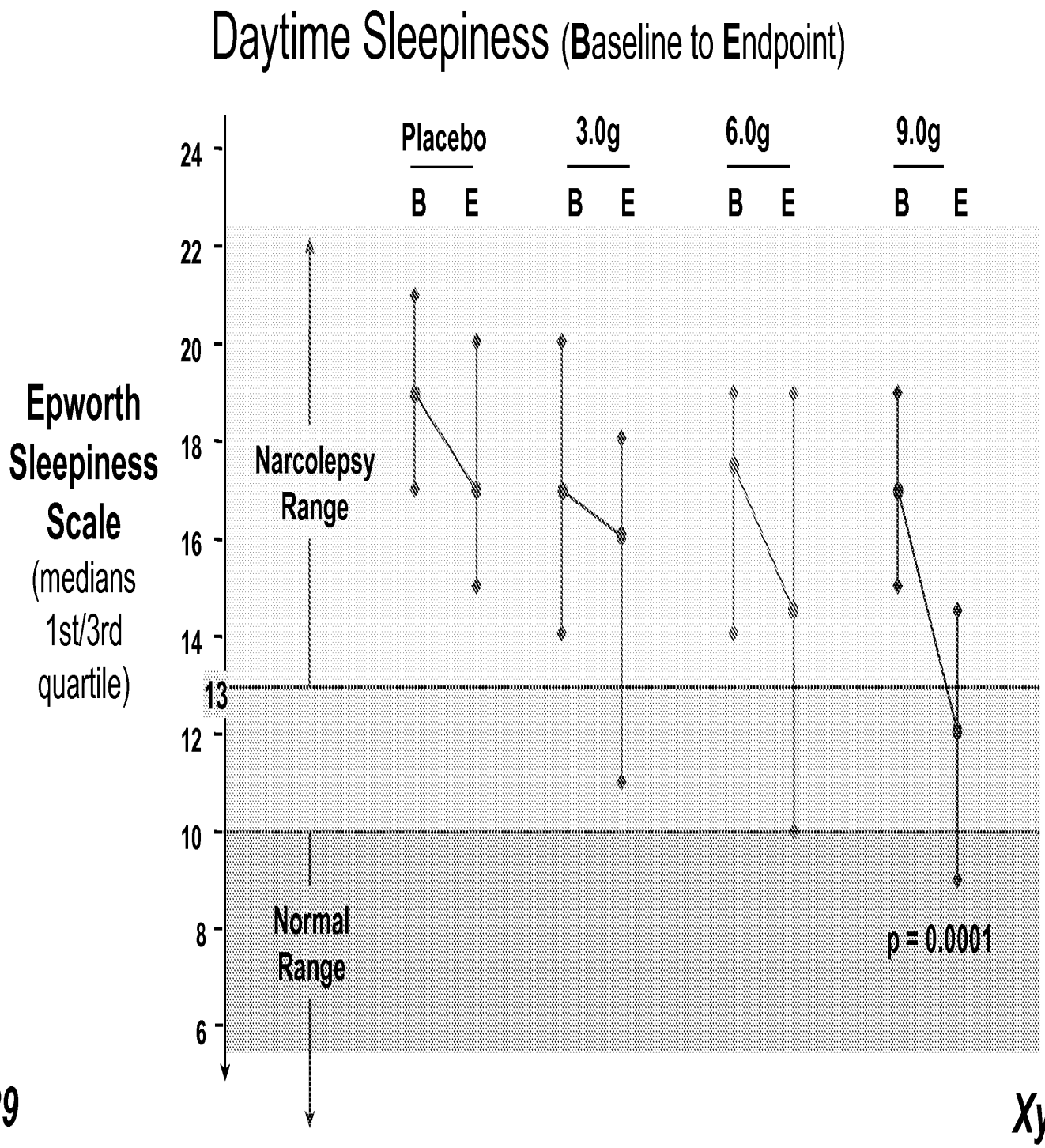
	Situation
1.	Sitting and reading
2.	Watching TV
3.	Sitting, inactive in a public place (e.g. a theater or a meeting)
4.	As a passenger in a car for an hour without a break
5.	Lying down to rest in the afternoon when circumstances permit
6.	Sitting and talking to someone
7.	Sitting quietly after lunch without alcohol
8.	In a car, while stopped for a few minutes in the traffic

Response: Range: 0-24

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Xyrem

OMC-GHB-2 Secondary Efficacy Daytime Sleepiness (medians)



Xyrem

OMC-GHB-2 Other Daytime Sleepiness Parameters

Parameters	Treatment	p-value (vs. placebo)
Inadvertent Naps/Sleep Attacks/	Placebo	--
Daytime Sleep Attacks	3g	n.s.
	6g	**0.0497**
(baseline median = 1.50)	9g	**0.0122**

Clinical Global Impression (CGI)

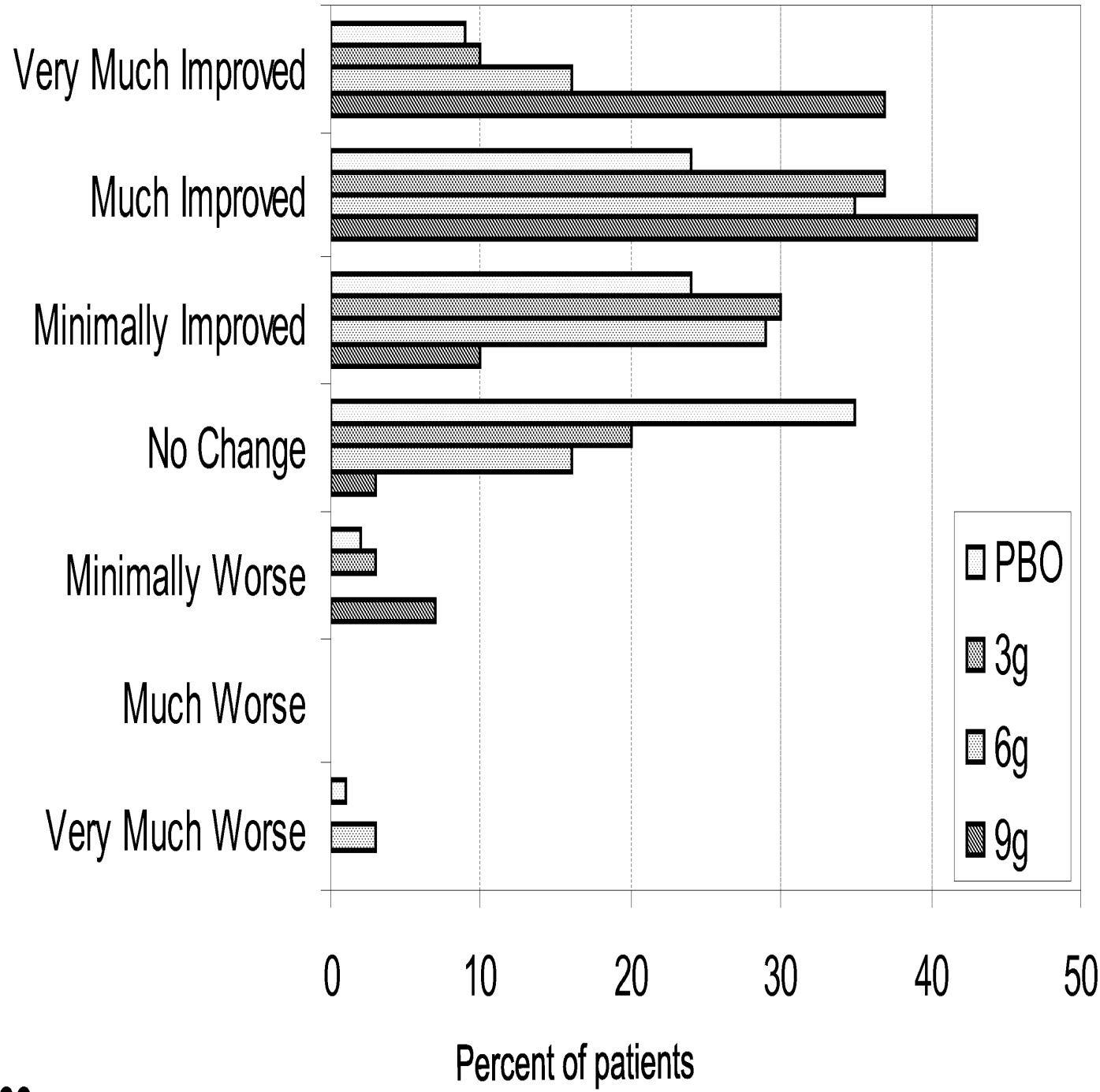
CGI-Severity (Baseline)

1. Normal – shows no signs of illness
2. Borderline ill
3. Slightly ill
4. Moderately ill
5. Markedly ill
6. Among the most extremely ill of patients

CGI-Change (Endpoint)

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

Clinical Global Impression of Change at Endpoint OMC-GHB-2 – By Dose Group



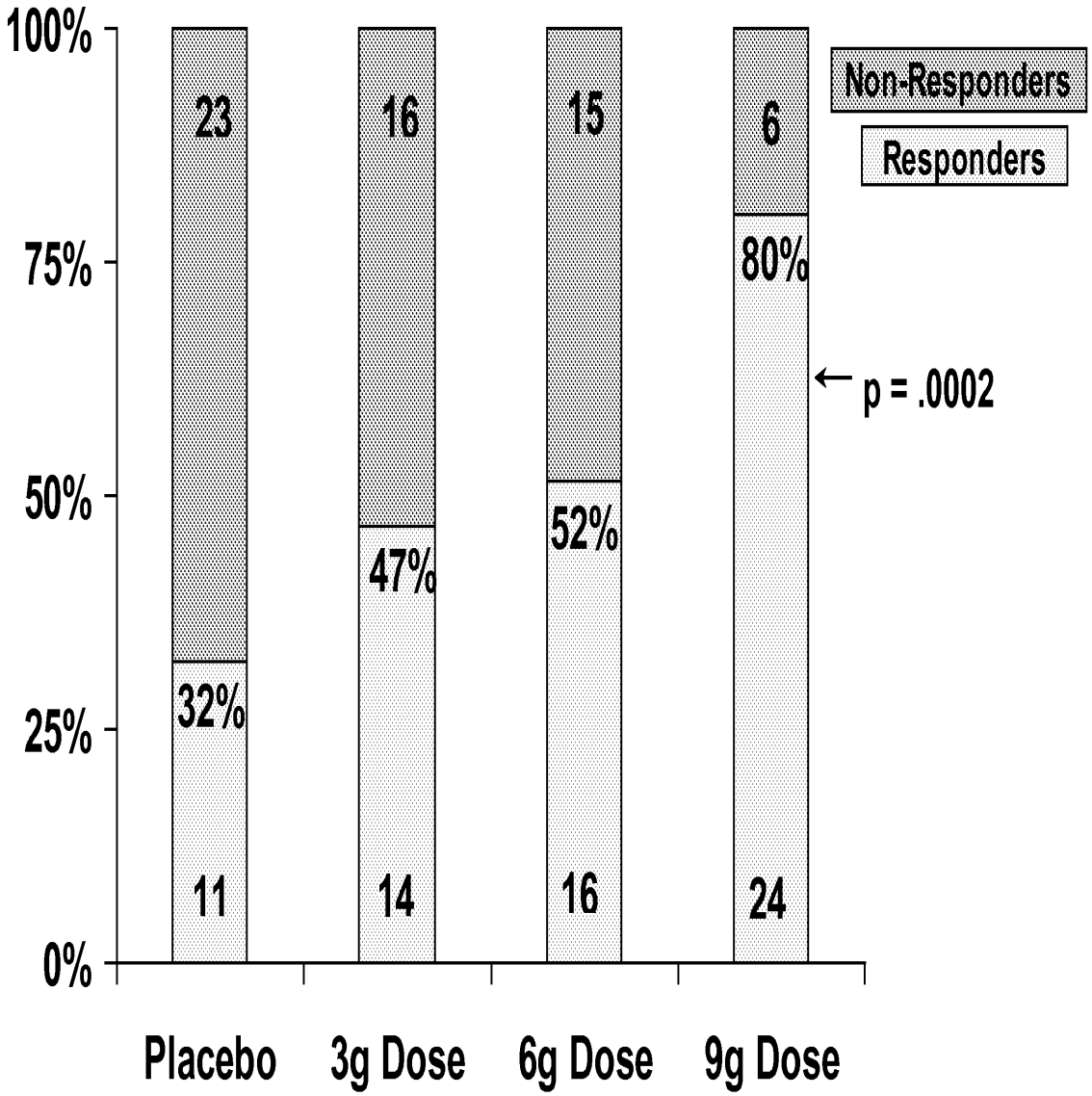
Xyrem

Post-Hoc Responder/Non-Responder Analysis

- Responder
  - Very much improved
  - Much improved
- Non-Responder
  - Minimally improved
  - No-change
  - Minimally worse
  - Much worse
  - Very much worse

OMC-GHB-2 Secondary Efficacy CGIc

Investigator's Clinical Global Impressions of Change



Xyrem

OMC-GHB-2
Other Variables

Parameters	Treatment	P-value (vs. placebo)
Awakenings at Night	Placebo	--
	3g	n.s.
	6g	n.s.
Baseline median = 2.27/day	9g	**0.0035**
Sleep Paralysis Episodes		
Baseline median = 0.14/day		n.s.
Hypnagogic Hallucinations		
Baseline median = 0.30/day		n.s.

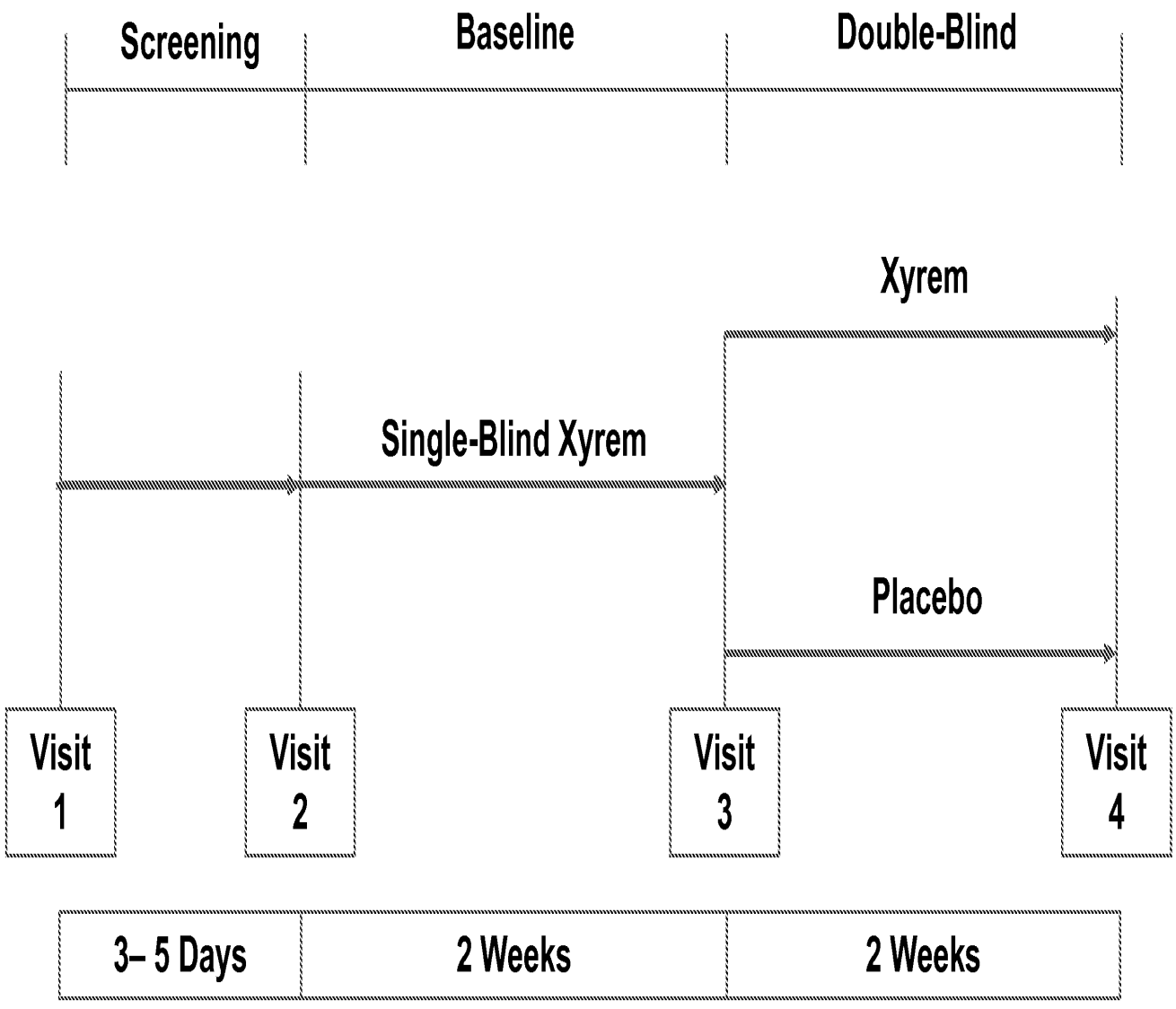
Xyrem® Clinical Data: Efficacy

OMC-SXB-21

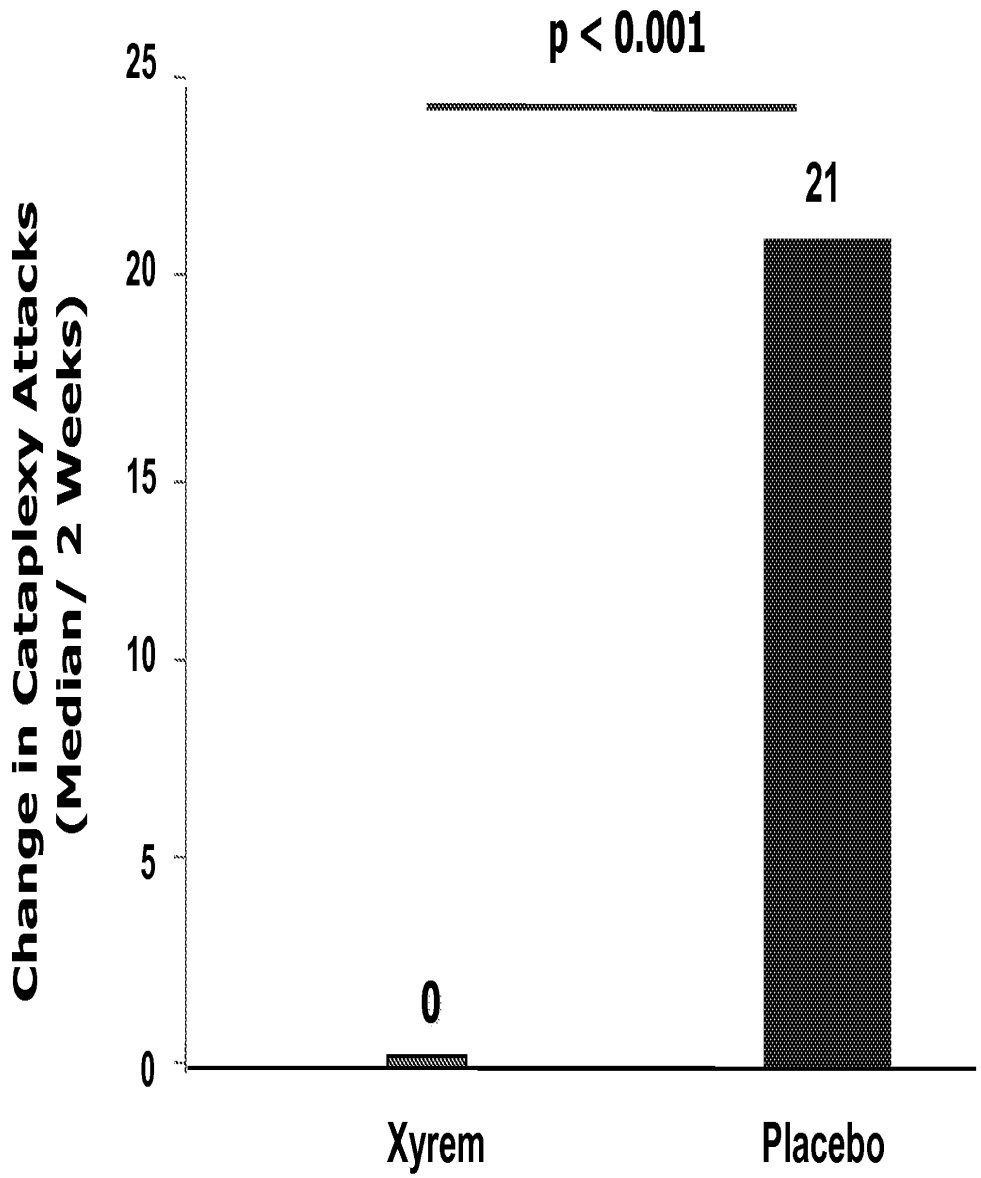
OMC-SXB-21
Objective

- Provide evidence for the long-term efficacy of Xyrem based on the return of cataplexy symptoms upon cessation of a minimum of 6 months of open-label treatment with active drug.

OMC-SXB-21
Study Design

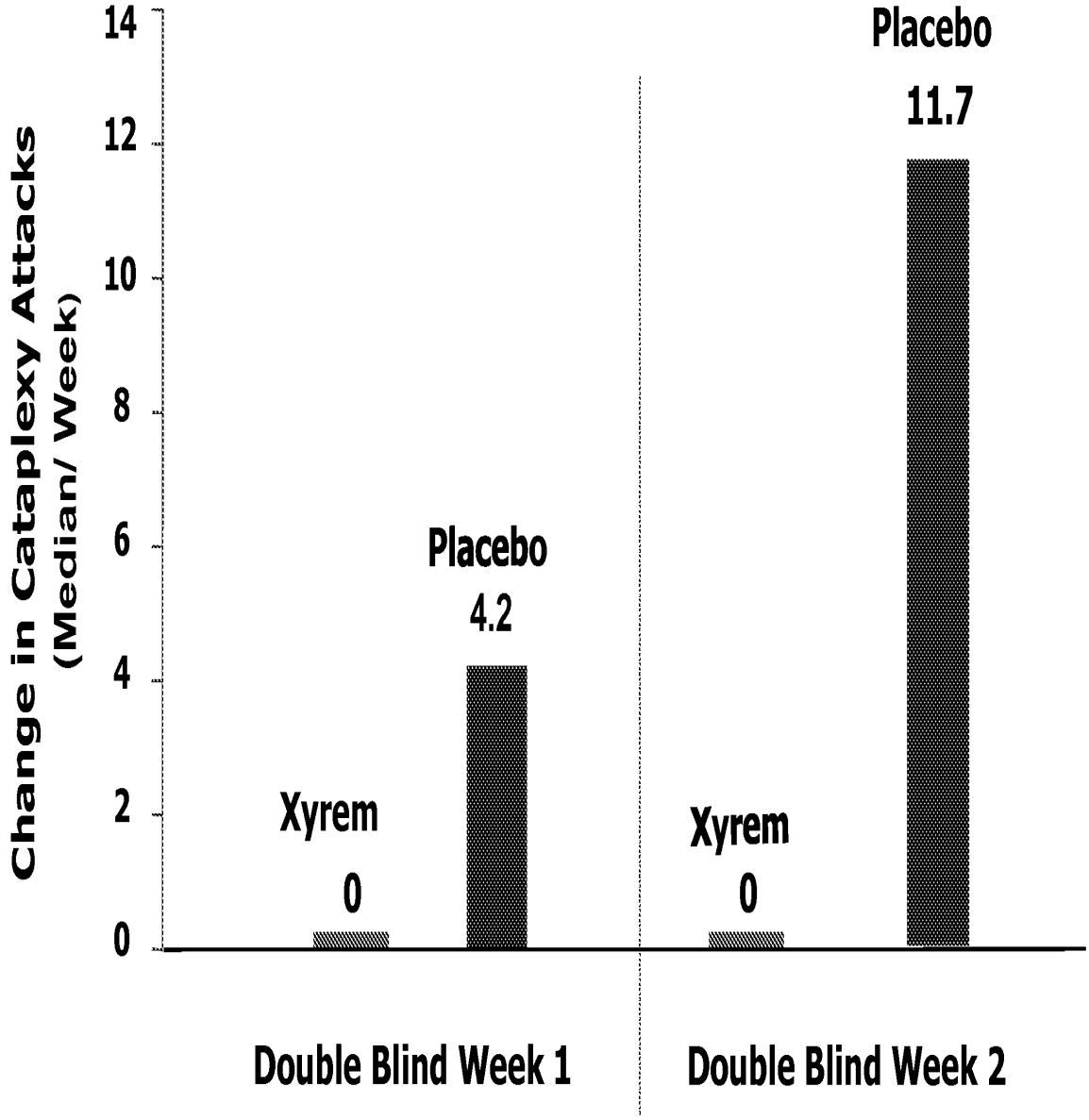


OMC-SXB-21 Cataplexy
Median Change from Baseline



Xyrem

OMC-SXB-21 Cataplexy
Median Change from Baseline



Xyrem® Clinical Data: Efficacy

Other Double-Blind Placebo-Controlled Clinical Trials

Scrima Trial

Lammers Trial

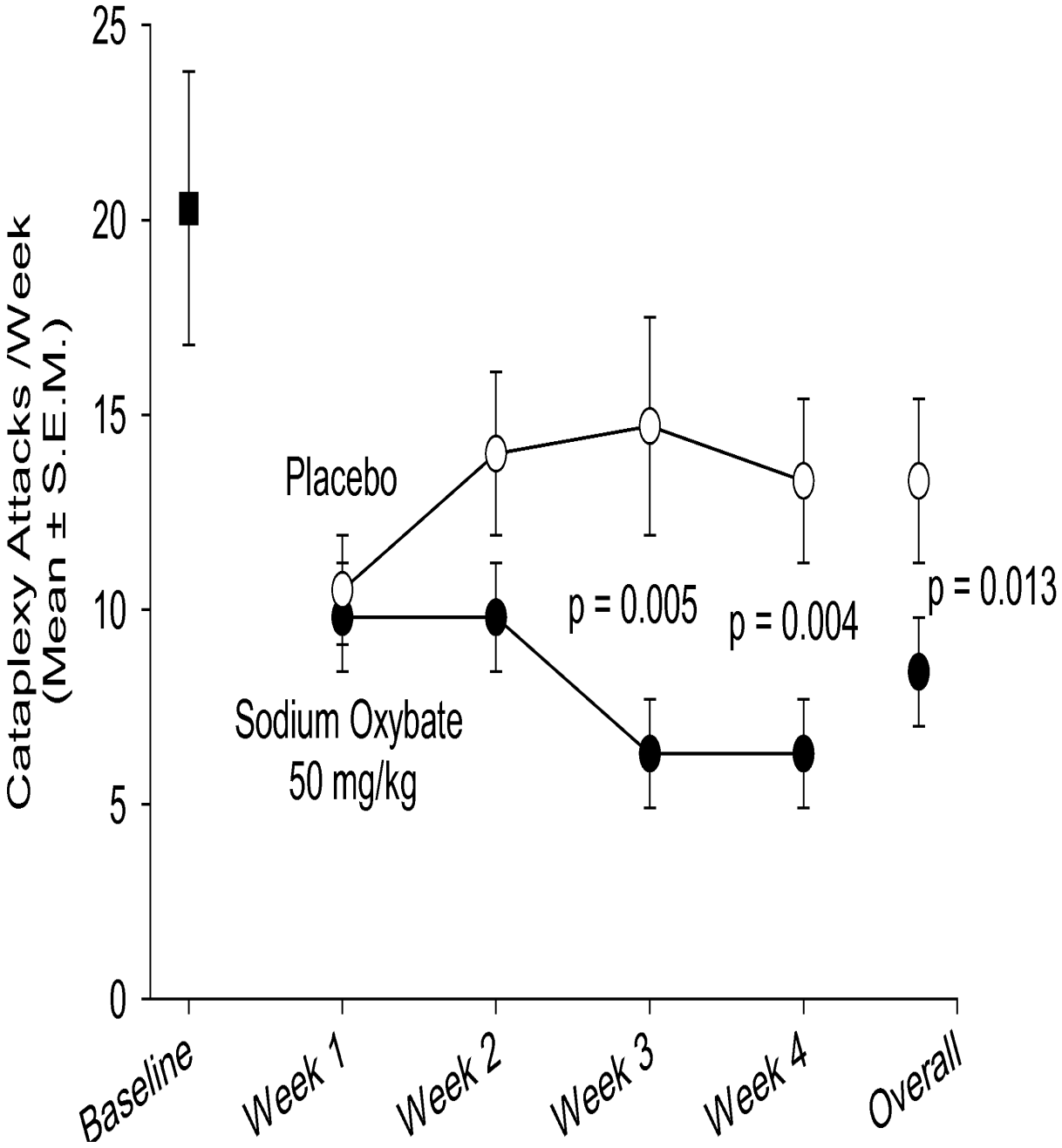
Scrima Cross-over Trial Study Design

N=20

	Baseline 14 Days	Treatment 1 29 Days	Washout 6 Days	Treatment 2 29 Days	Washout 6 Days
Withdrawal of Cataplexy Meds	X	Sodium oxybate	X	Placebo	X
	X	Placebo	X	Sodium oxybate	X
Stimulants continued throughout study					

Xyrem

Scrima Trial
Number of Cataplexy Attacks / Week



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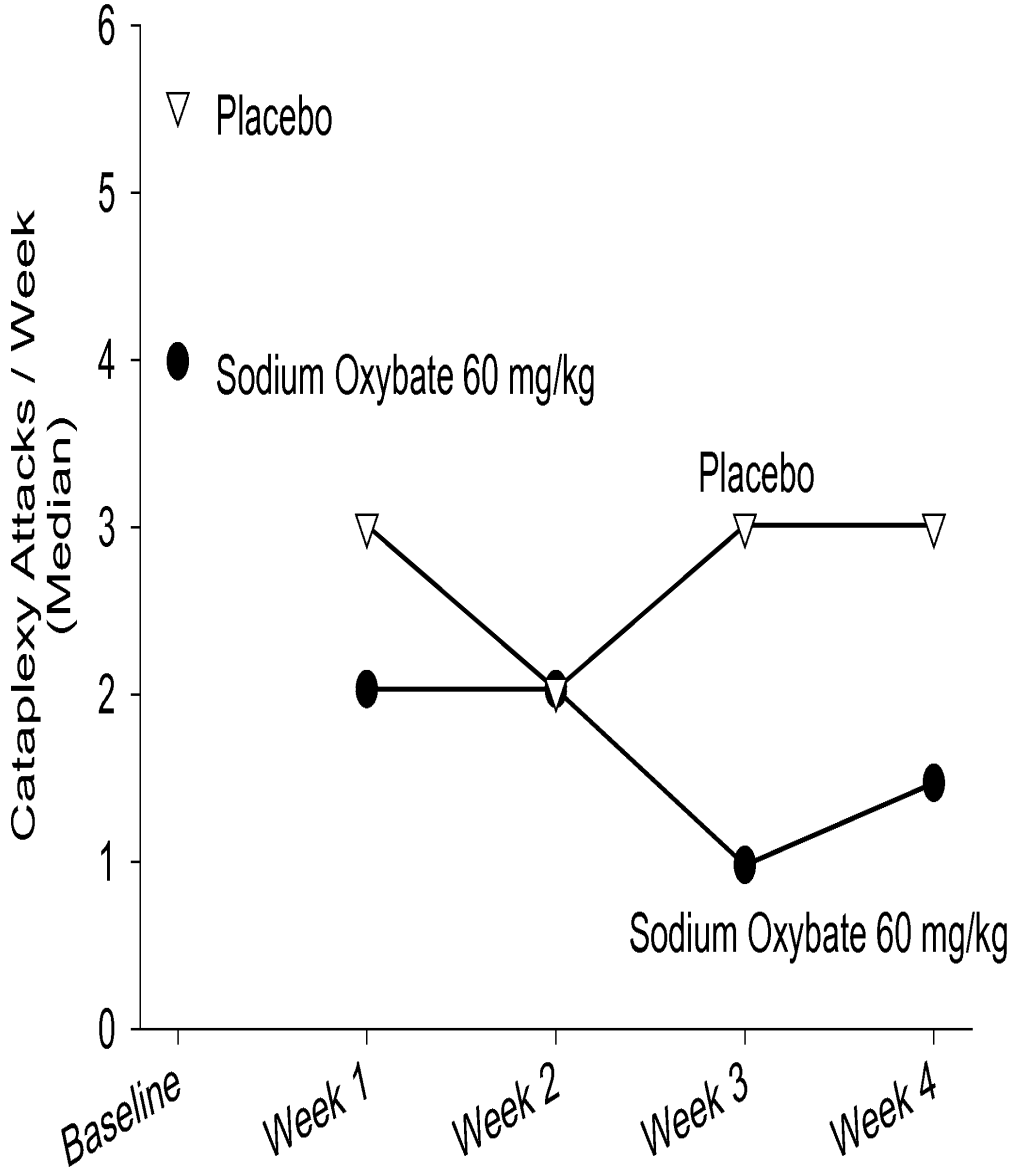
Lammers Trial
Study Design

N=24

Baseline 1 1 Week	Treatment 1 4 Weeks	Washout 3 Weeks	Baseline 2 1 Week	Treatment 2 4 Weeks
X	Sodium Oxybate (60mg/kg)	X	X	Placebo
X	Placebo	X	X	Sodium Oxybate (60 mg/kg)
Concomitant treatment for cataplexy and EDS continued throughout				

Xyrem

Lammers Trial
Cataplexy



Xyrem

Lammers Trial
Other Measures

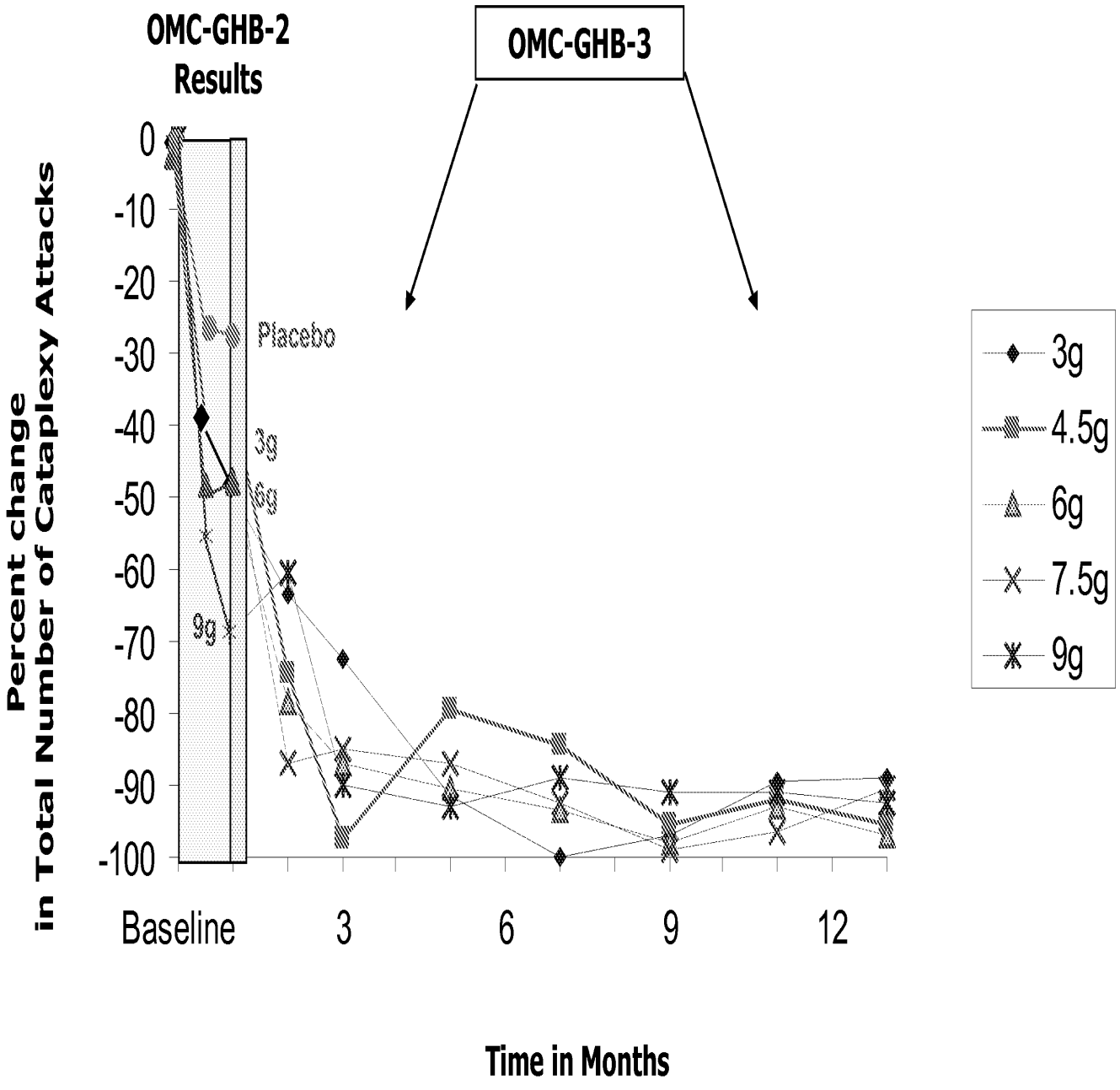
Efficacy Parameter	Change	Significance p-value
Hypnagogic Hallucinations	Reduction from 0.87 to 0.28	**0.008**
Daytime Sleep Attacks	Reduction from 2.27 to 1.40	**0.001**

Xyrem® Clinical Data: Efficacy

OMC-GHB-3

OMC-GHB-3

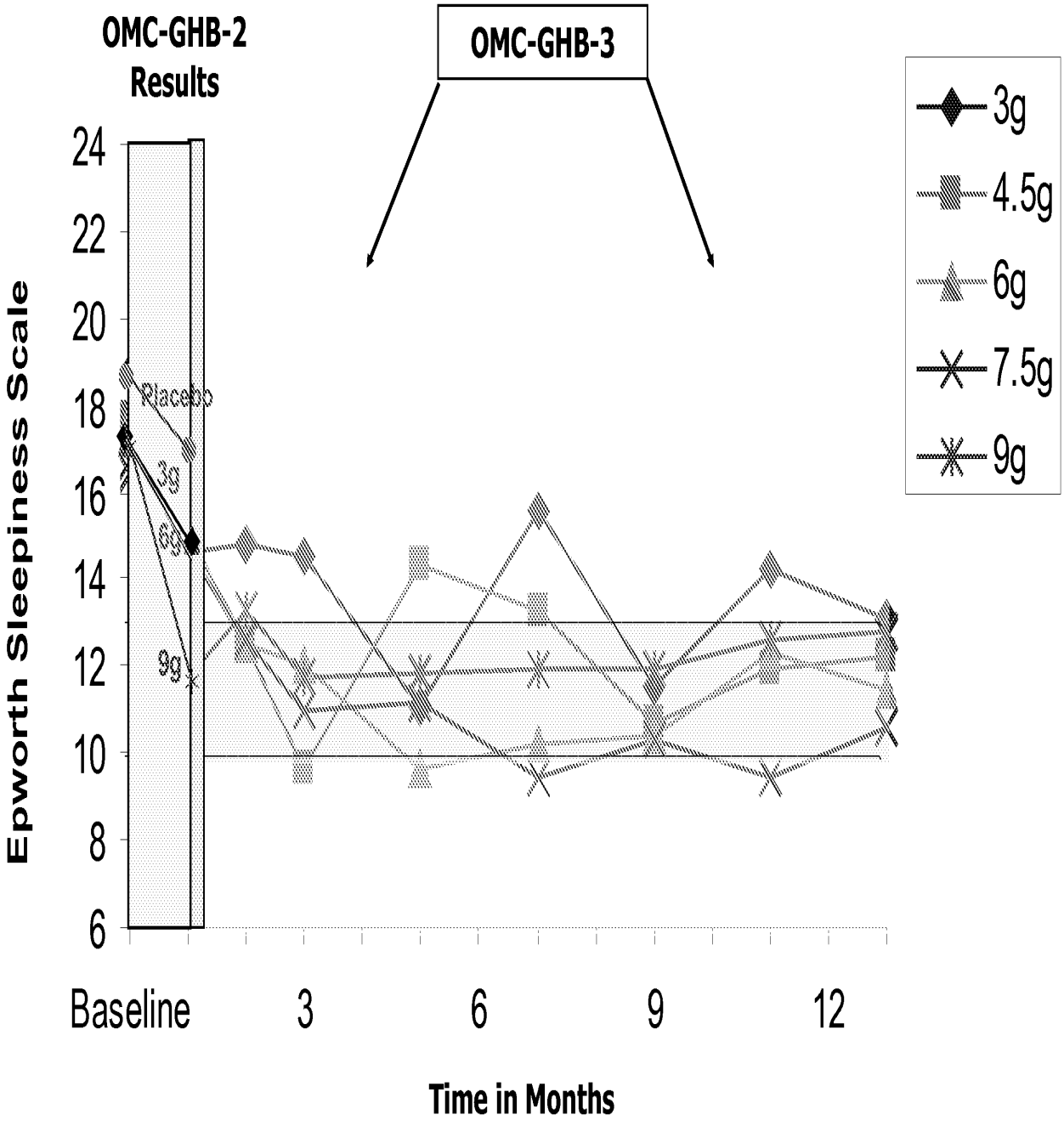
Cataplexy – Median Percent Change



Xyrem

OMC-GHB-3

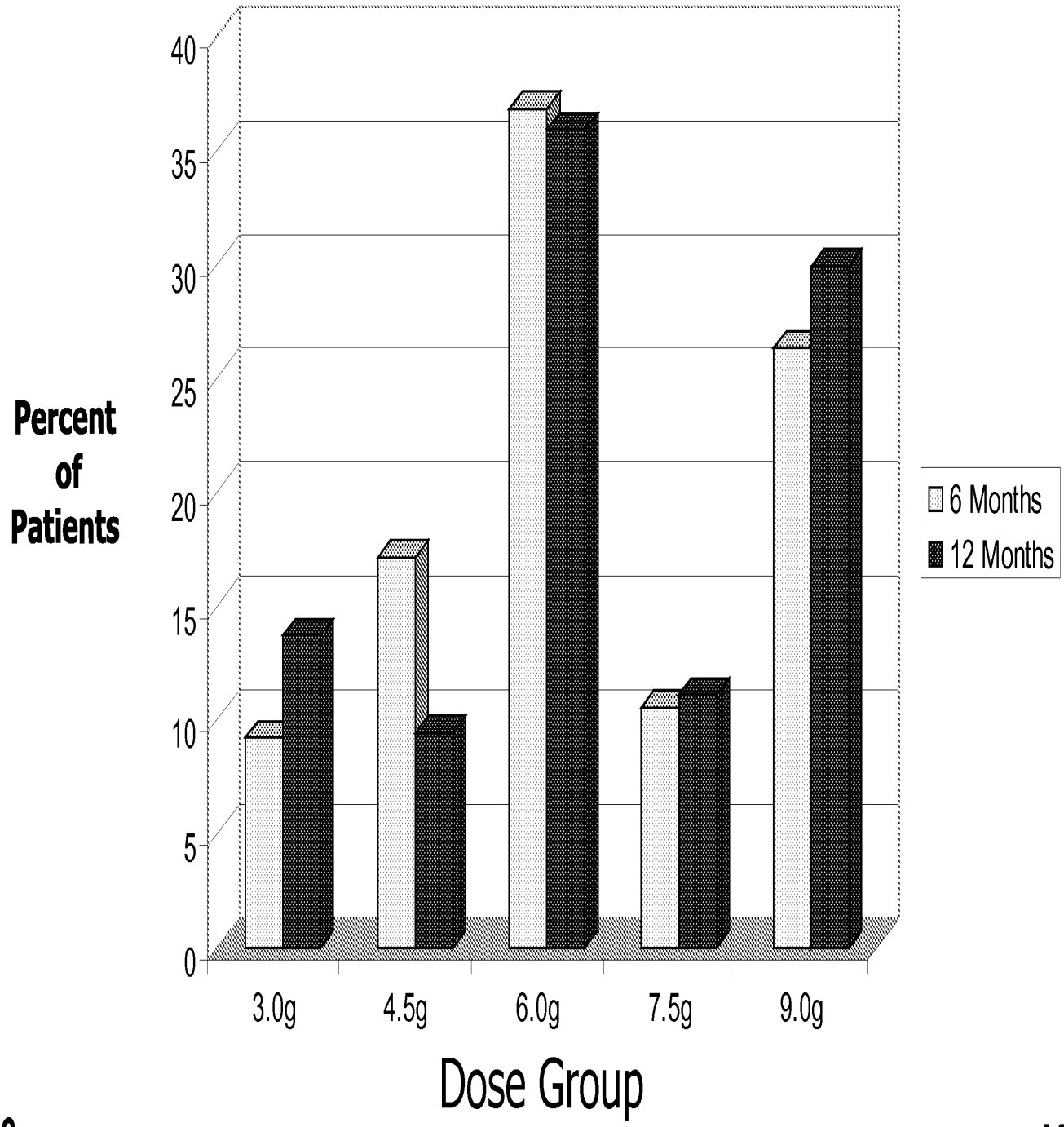
Mean ESS for All Dose Groups



Xyrem

OMC-GHB-3

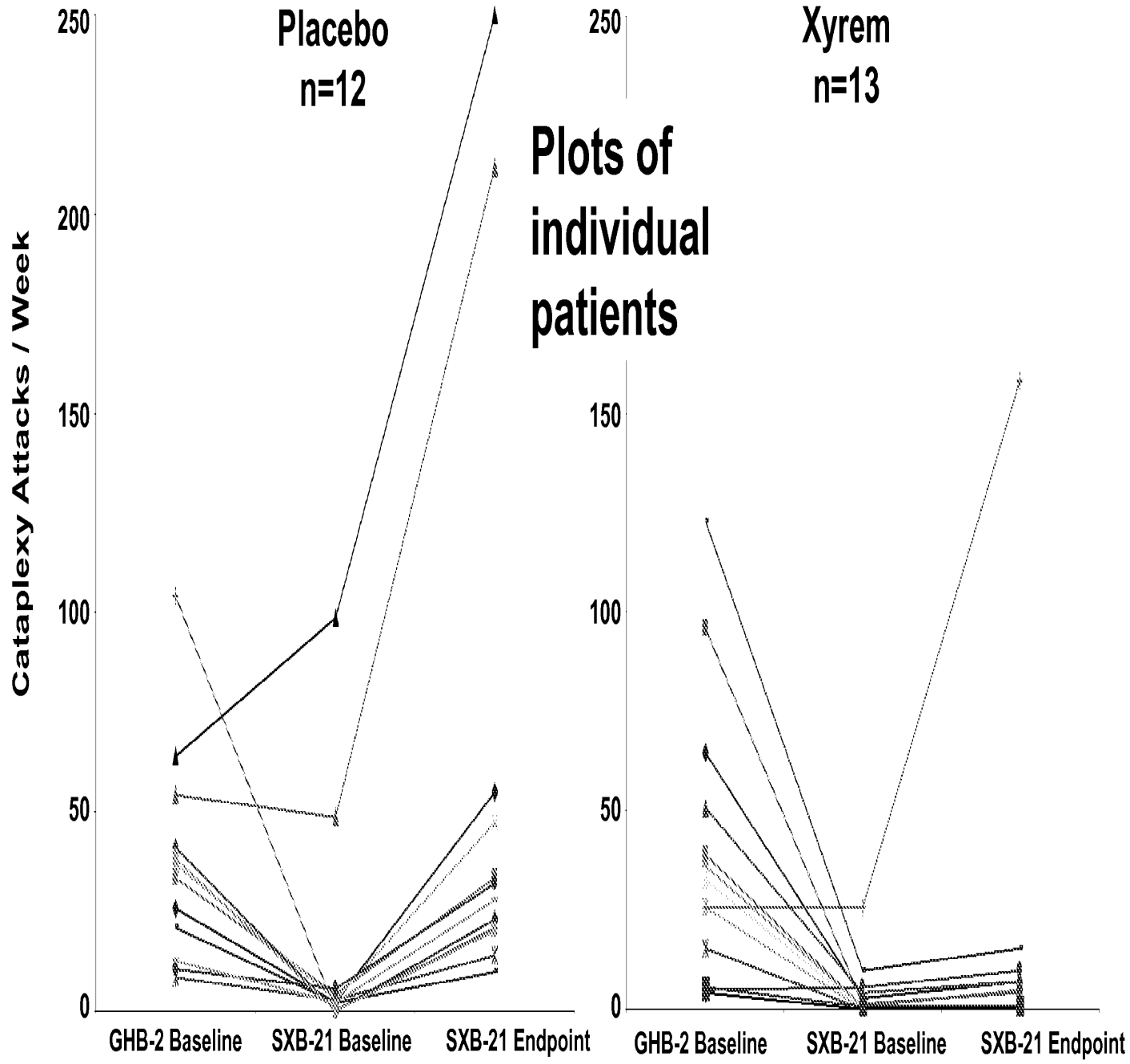
Dose Distribution – 6 & 12 Months



Xyrem

OMC-SXB-21 Supports Efficacy in OMC-GHB-3

Cataplexy Attacks / Week: OMC-GHB-2/3 Patients in OMC-SXB-21



Xyrem

Summary of Efficacy

Trial/Dose	Change in Cataplexy	Daytime Sleepiness
OMC-GHB-2		
3g	0.5235	0.1137
6g	0.0529	0.1860
9g	**0.0008**	**0.0001**
OMC-SXB-21	**0.001**	--
SUPPORTIVE STUDIES		
LAMMERS--60 mg/kg (4.75g)	**0.002**	**0.028**
SCRIMA--50 mg/kg (3.5g)	**0.022**	n.s.

Clinical Pharmacokinetics, Drug Interactions, and Pharmacodynamics

William Houghton, M.D.

Chief Operating Officer & Medical Officer,
Orphan Medical, Inc.

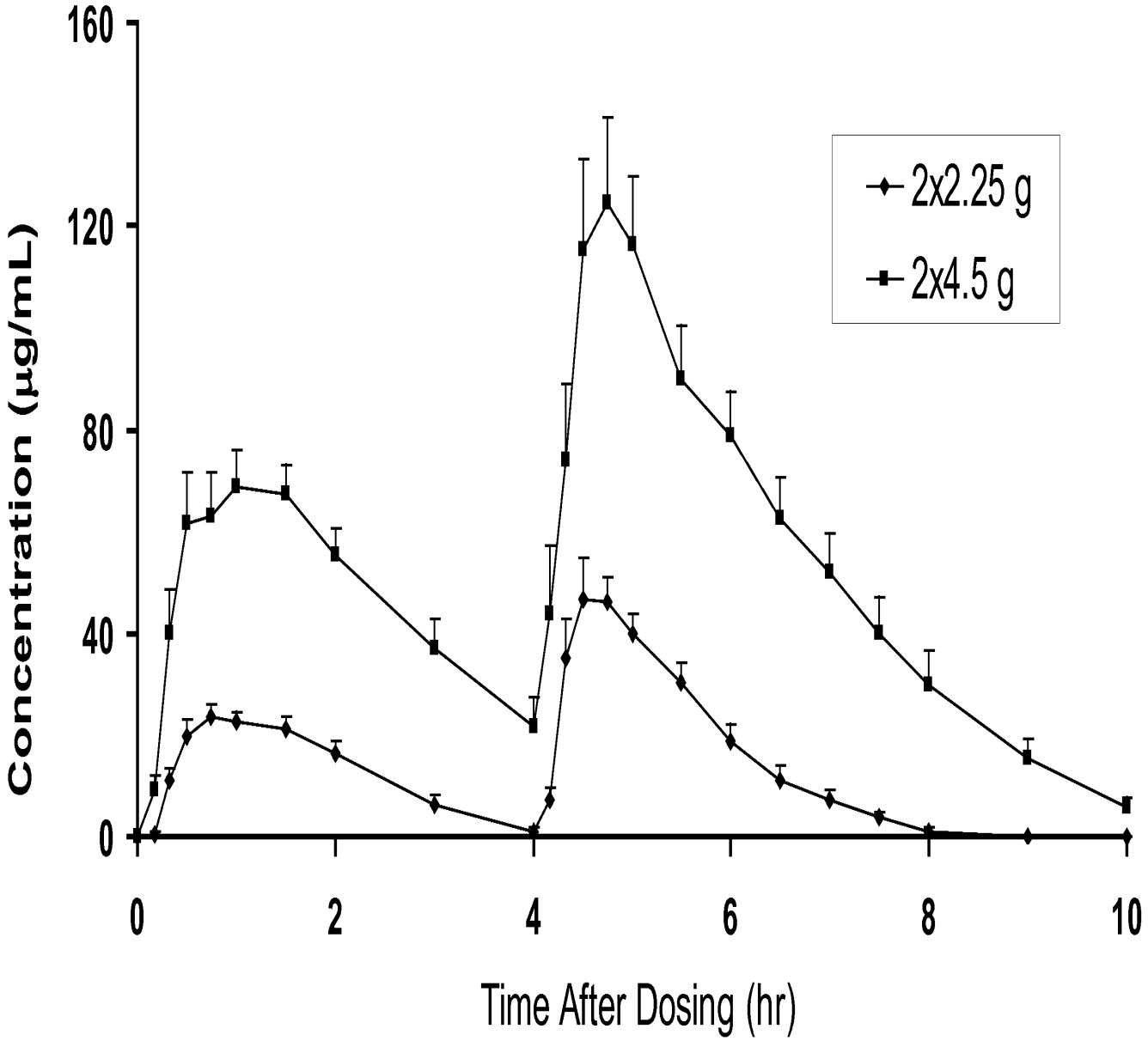
Xyrem Pharmacokinetic Studies

1. Pilot PK study in narcoleptic patients
2. Acute versus chronic dosing in patients
3. Study of gender differences
4. Dose proportionality study
5. Food effect study

6-8. Three drug interaction studies
(zolpidem, protriptyline, modafinil)

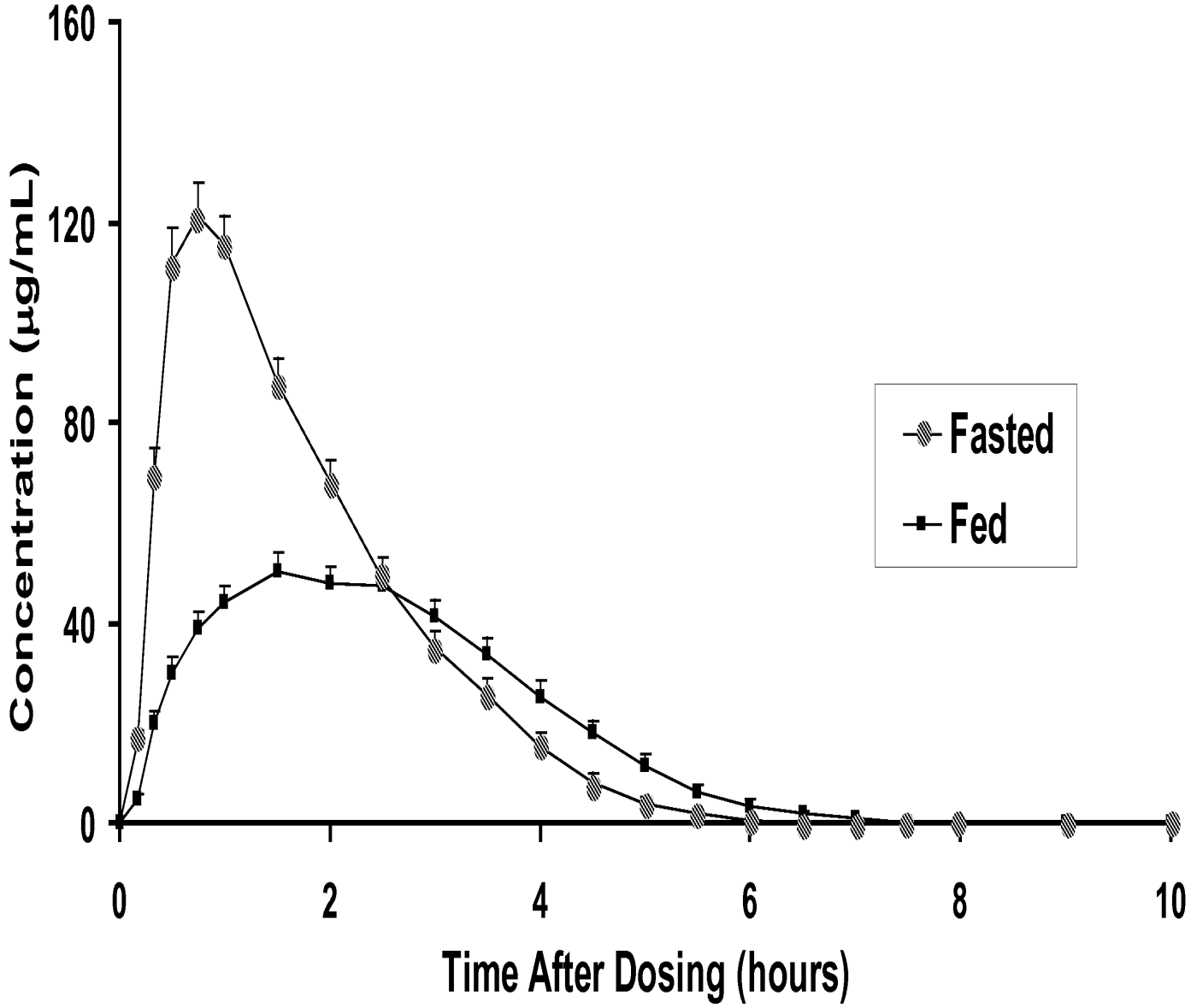
In vitro cytochrome p450 study: negative

Plasma Concentrations of Oxybate (GHB) After 4.5 Grams (2x2.25) or 9.0 Grams (2x4.5) of Xyrem to Normal Volunteers (Mean, Standard Error)

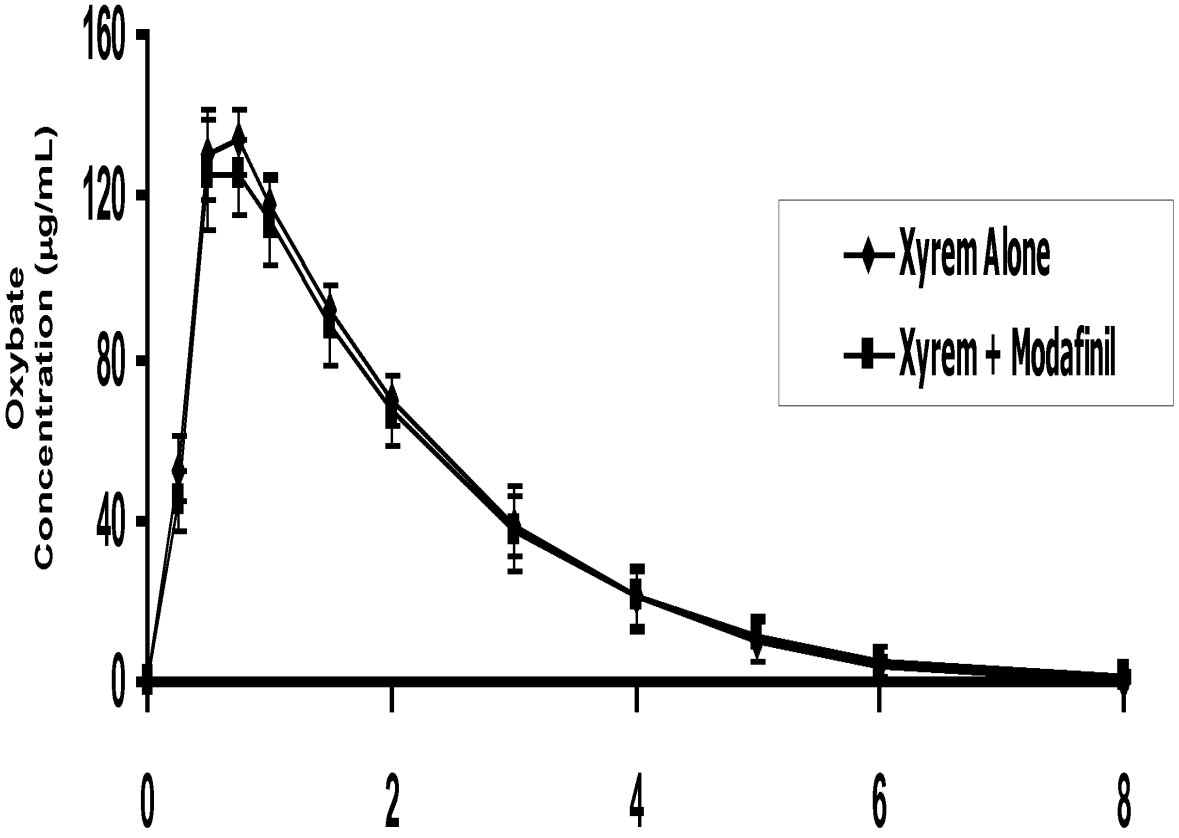


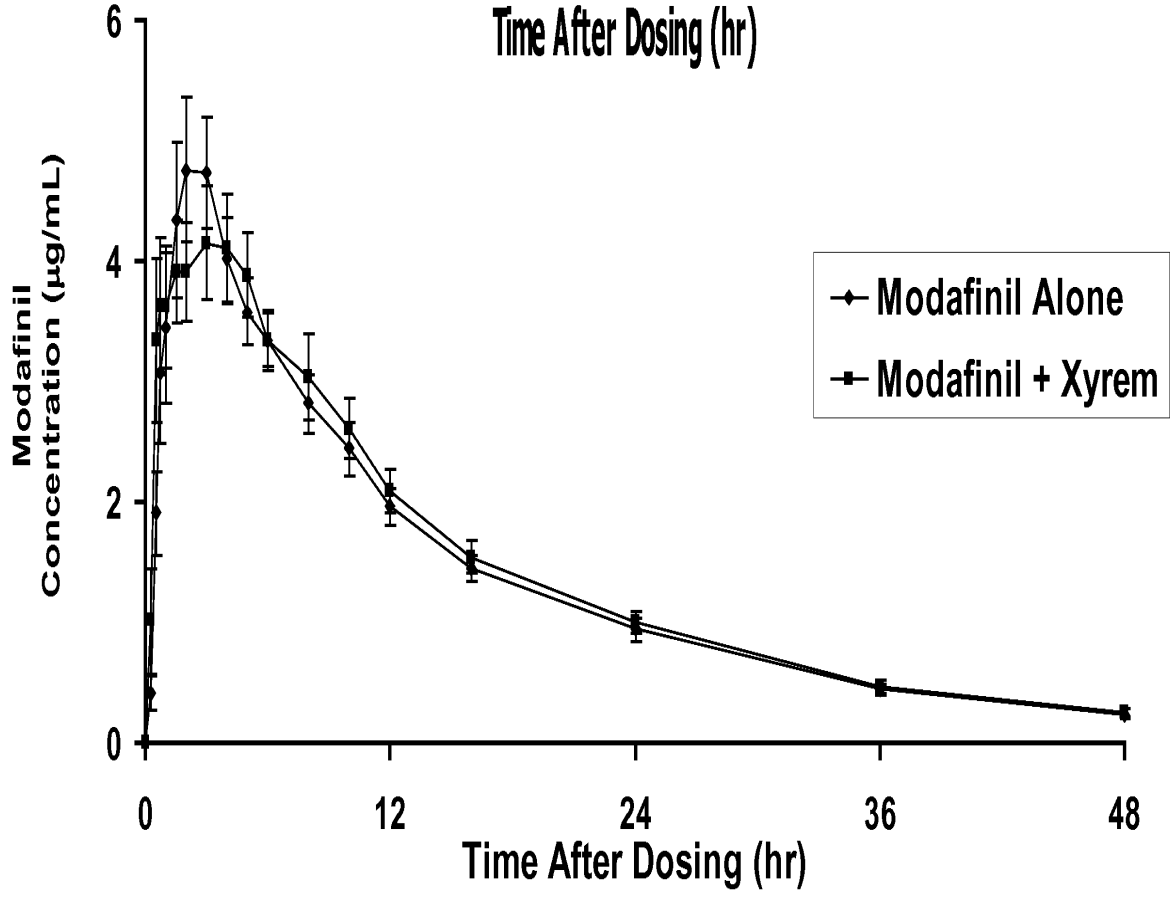
Xyrem

Plasma Oxybate (GHB) Concentration After an Oral Dose of 4.5 Grams of Xyrem to Normal Volunteers Following a High Fat Meal or after an Overnight Fast



Xyrem – Modafinil Interaction Study





Xyrem Pharmacokinetics: Summary

- Rapid absorption (T_{max} = 30-75 min) and elimination ($T_{1/2}$ = 40-60 min) from plasma
- Non-linear, dose-dependent kinetics
- Capacity limited absorption & elimination
- No gender differences
- No difference between acute and chronic dosing

Xyrem Pharmacokinetics: Summary

- Chronic dosing does not change kinetics
- Food delays absorption and reduces systemic exposure
- No kinetic interactions with 3 other classes of drugs
- No cytochrome p450 effects found

Polysomnographic Effects of Xyrem

Jed Black, M.D.

Director of the Stanford Sleep Clinic
Stanford University

Effects of Sodium Oxybate on Quantitative EEG Parameters in Narcoleptics

- Initial research in narcolepsy (1977+)
  - Broughton and Mamelak (1979)
  - Mamelak (1981, 1977)
  - Modified sleep patterns
    - increase in slow-wave sleep
    - reduced awakenings
- Scrima (1989, PSG and MSLT)
- Lammers (1993, PSG and MSLT)
- OMC-SXB-20 (PSG and MWT)

Scrima and Lammers Trials
Nocturnal PSG Data

		Scrima Trial	Lammers Trial
Variable	Result	p-value	p-value
Stage 1 Sleep	Decreased	0.026	n.s.
Stages 3 & 4	Increased	0.001	0.053
Awakenings	Decreased	0.042	0.016
% wake time	Decreased	n.s.	0.007

Xyrem

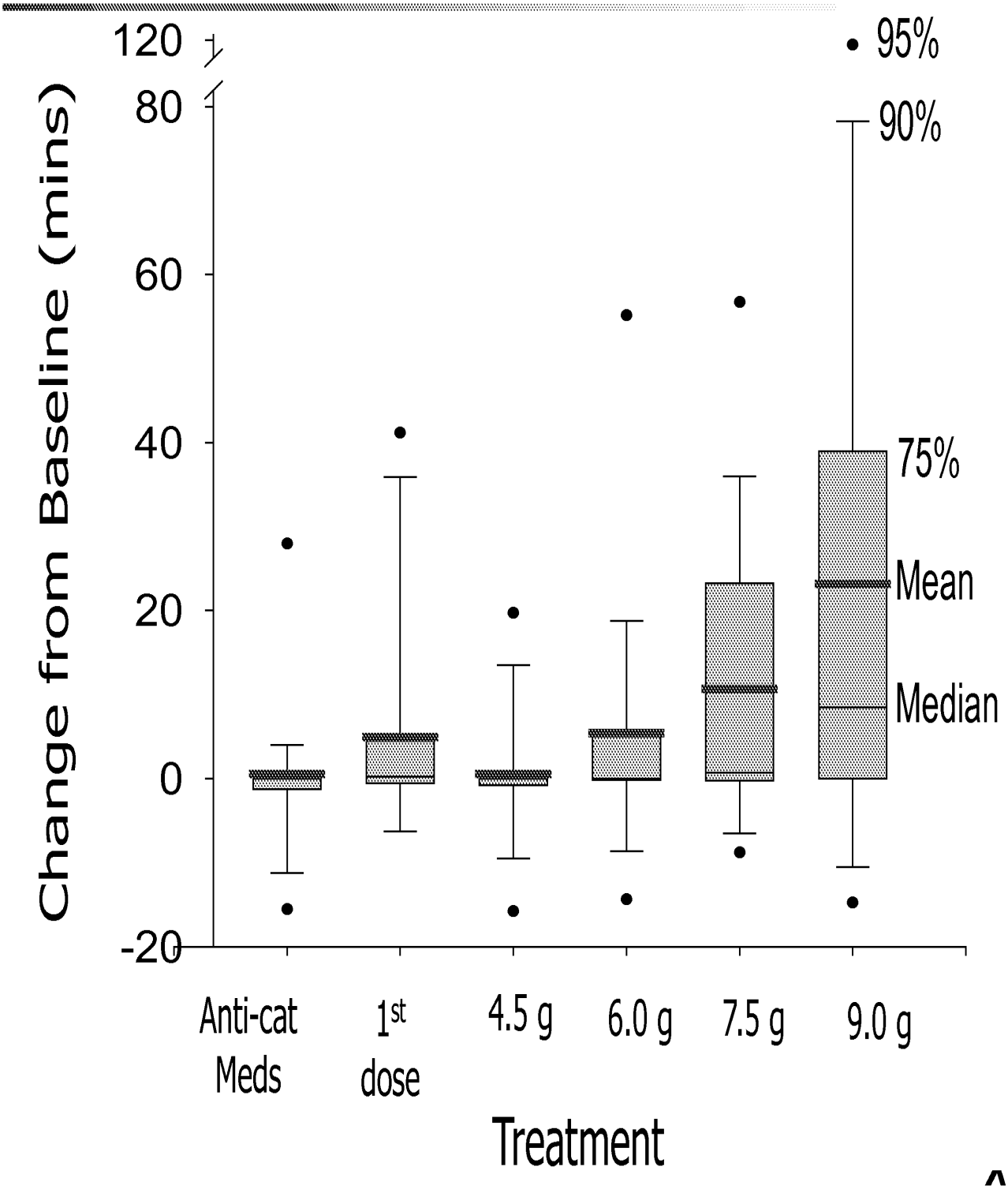
OMC-SXB-20
Study Design

- Open-label, dose-escalation (4.5 g – 9 g)
  - Stimulants continued at stable dose
  - 2 week anti-cataplectic taper
  - 2 week washout
  - 4 weeks 4.5 g Xyrem
  - 2 weeks 6 g, 7.5 g, and 9 g each
- PSG obtained:
  - Prior meds
  - Baseline
  - 4.5 g (1st night)
  - 4.5 g, 6 g, 7.5 g, 9 g (last night)
- MWT obtained: prior meds, baseline, 4.5 g (after 4 weeks),and 9 g

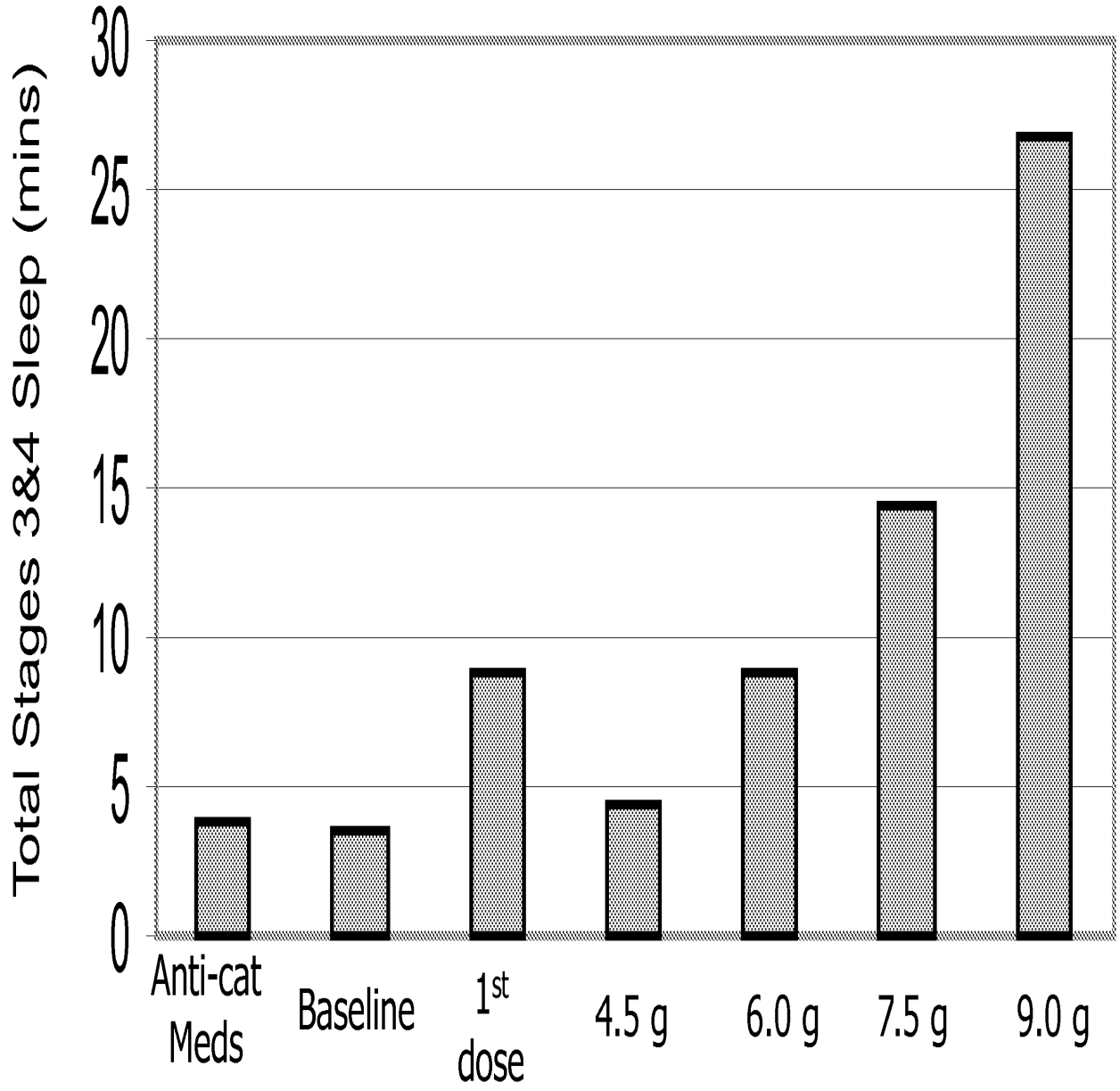
OMC-SXB-20
Study Results

- PSG
  - Dose-related increase in Stage 3 & 4 sleep
  - Dose-related increase in Delta Power
- Daytime measures
  - Dose-related increase in daytime alertness
  - Dose-related reduction in subjective sleepiness

Change in Slow Wave (Stages 3&4) Sleep Duration

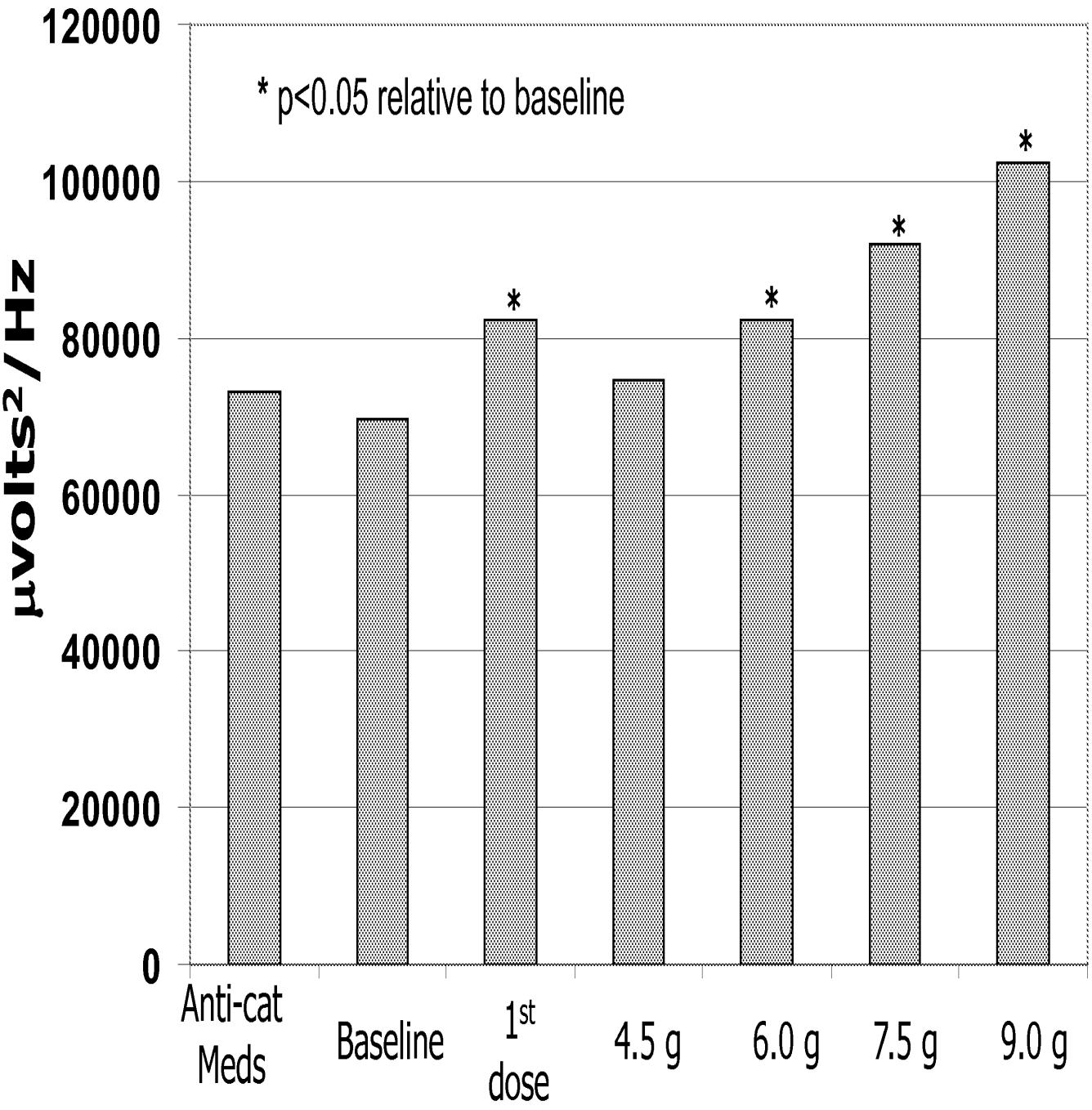


Total Slow Wave (Stages 3&4) Sleep Duration



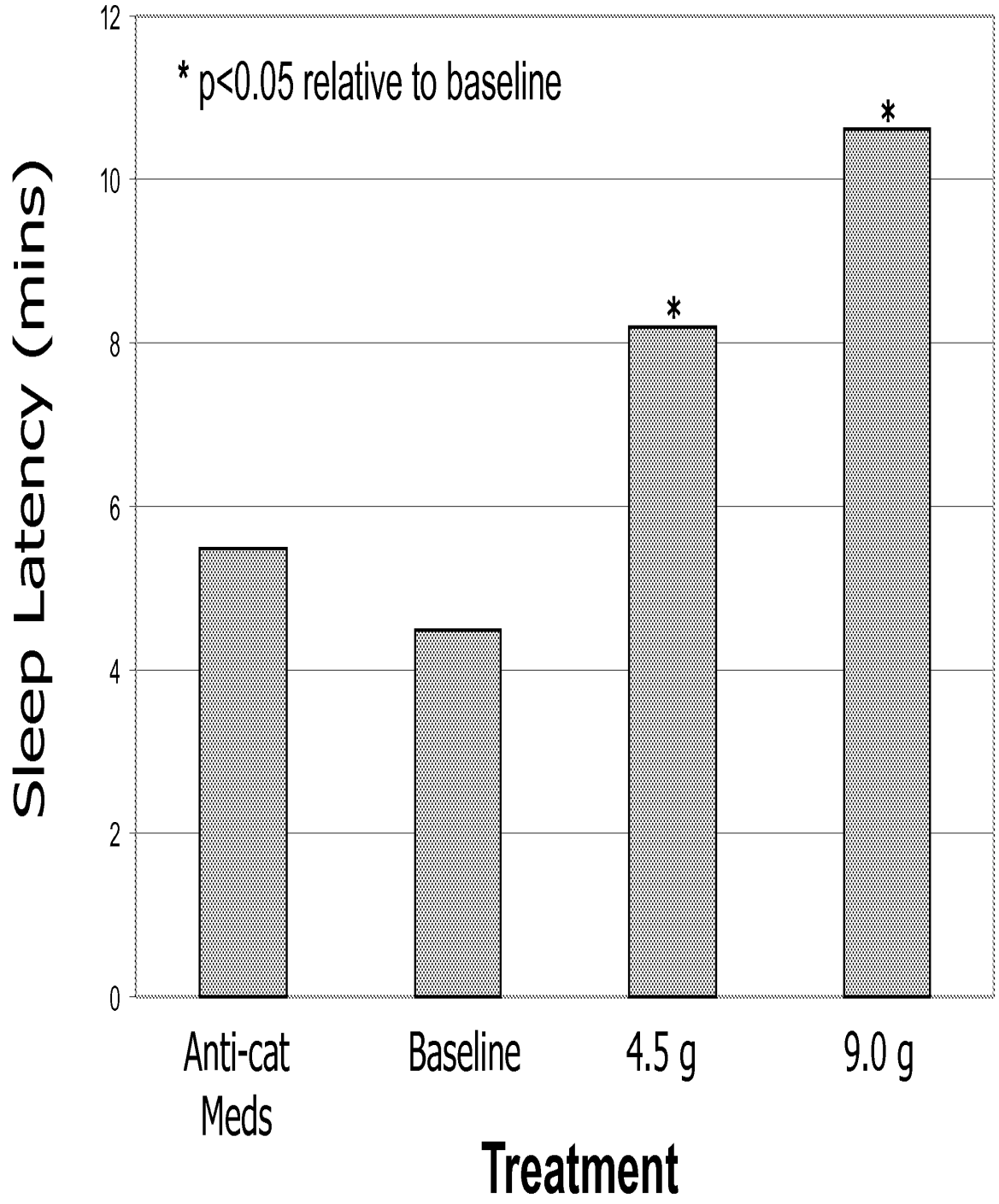
Xyrem

Delta Power



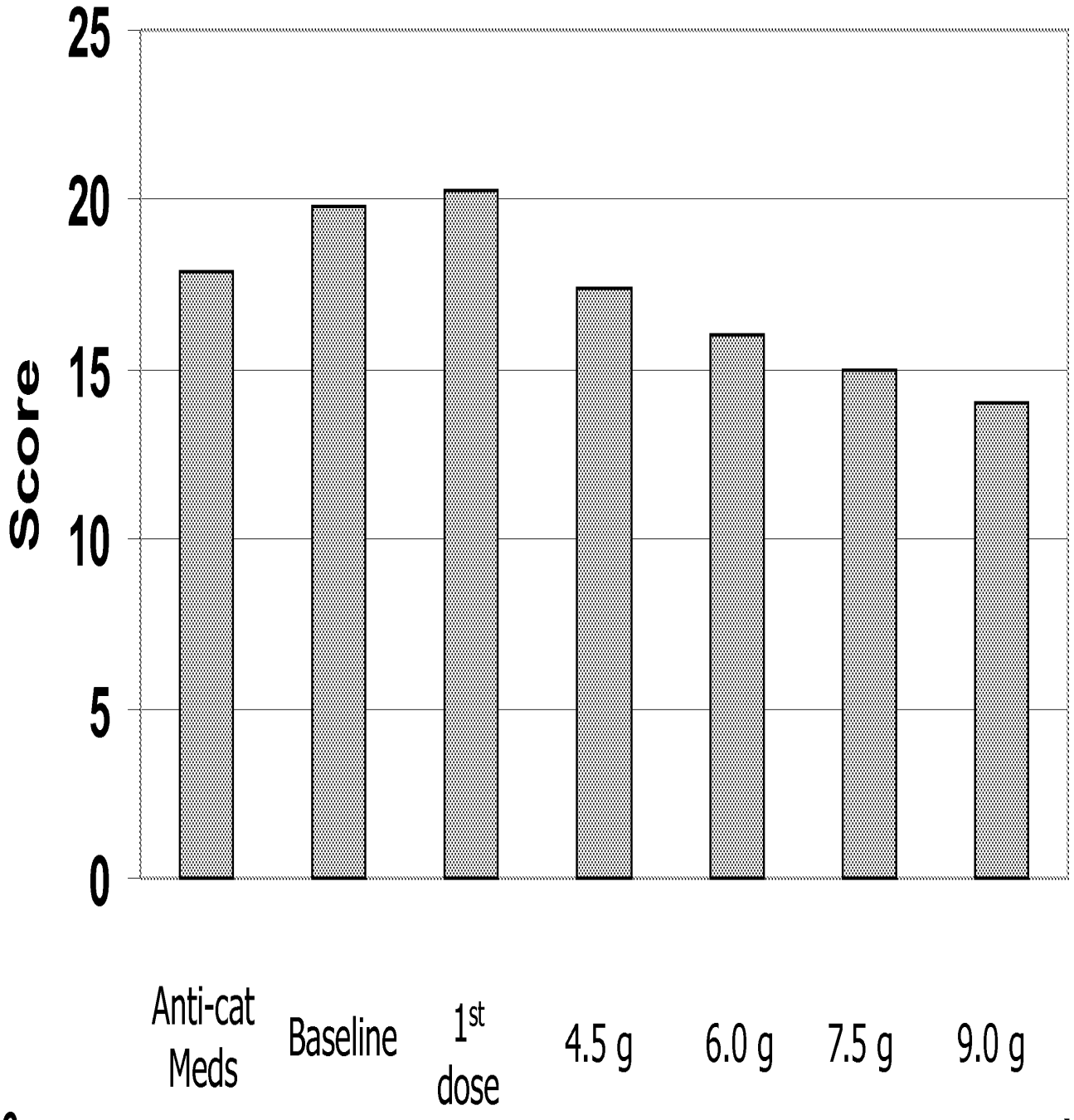
Xyrem

MWT Sleep Latency (Daytime)



Xyrem

Epworth Sleepiness Score (Daytime)



Xyrem

Correlation Between Daytime and Nocturnal Effects

Variable	Variable	Coefficient	P-Value
Delta Power	**Epworth**	**-0.23**	**0.0086**
Delta Power	MWT	0.18	0.0914
Stage 3&4 Sleep	Epworth	-0.17	0.0599
Stage 3&4 Sleep	MWT	0.21	0.0550

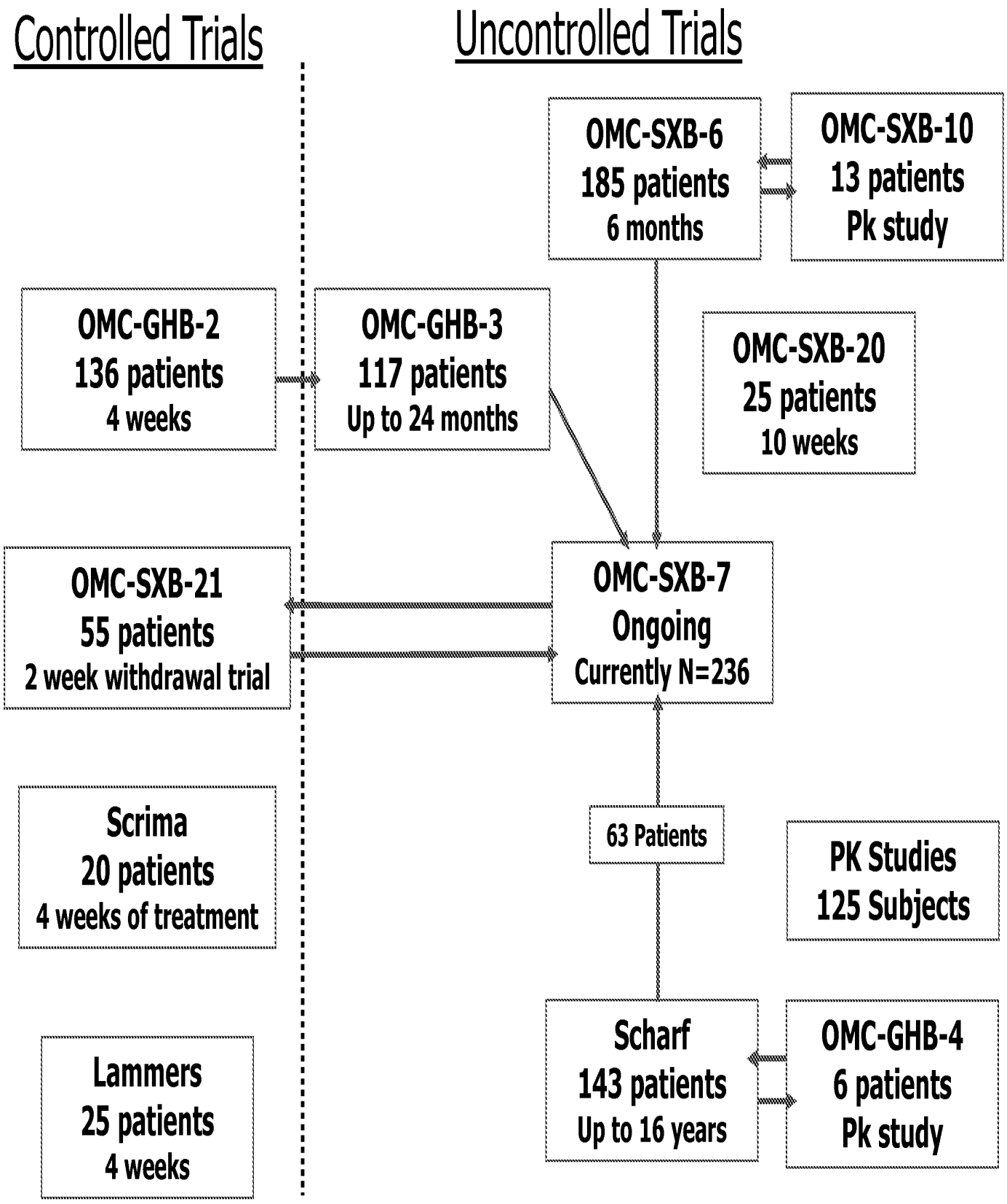
OMC-SXB-20
Overall Conclusions

- PSG parameters modulated as a function of Xyrem treatment
  - Xyrem increases measures of restorative sleep
    - Stages 3 & 4
    - Delta Power
- Daytime sleepiness decreased
  - MWT and Epworth
- Correlation between daytime and nocturnal effects
  - Possible novel neurological mechanism

Safety Summary Overview

William Houghton, M.D.

Chief Operating Officer & Medical Officer,
Orphan Medical, Inc.



Xyrem

Sodium Oxybate Exposure
All Trials Including Scharf

Any Exposure	479 patients
PK	125 subjects
Total	604
≥6 months	360 patients
≥12 months	286 patients
Patient-years	1328

Sodium Oxybate Exposure
Updated ISS Excluding Scharf

Any Exposure	399 patients
PK	125 subjects
Total	524
≥6 months	296 patients
≥12 months	223 patients
Patient-years	330

Updated ISS Database
Summary of Patient Exposure by Dose

	Sodium Oxybate Dosage (g/d)					
	Total	**3.0**	**4.5**	**6.0**	**7.5**	**9.0**
≥ 6 months	296	9	50	115	59	62
≥ 12 months	223	5	27	60	26	34
≥ 24 months	48	2	4	13	9	13

Updated ISS Database Treated Patient Disposition

Patient Disposition	Sodium oxybate
Patients Treated	399
Completed Treatment	46 (12%)
Ongoing Treatment	210 (52%)
Discontinued Treatment	143 (36%)
Adverse event	52 (13%)
Patient request	34 (9%)
Patient non-compliance	19 (5%)
Other	18 (5%)
Lost to follow-up	11 (3%)
Lack of efficacy	5 (2%)
Protocol deviation/violation	4 (<1%)
Death	2 (<1%)

NOTE: 3 placebo patients did not proceed to active treatment trials

Updated ISS Database
Summary of Adverse Events

	Total	Placebo	Sodium Oxybate
Total Patients	n=402	n=54	n=399
At least 1 AE	82%	70%	82%
Severe AE	20%	6%	20%
D/C due to AE	13%	2%	13%
Serious AE	7%	0%	7%
Deaths	<1% (2)	0%	<1% (2)

Updated ISS Database
Dose Distribution of Adverse Events

Xyrem Dose (g/d)	3	4.5	6	7.5	9
Total Patients:	97	269	290	133	129
At least 1 AE	60%	51%	62%	54%	78%
Severe AE	3%	9%	12%	5%	16%
D/C due to AE	5%	6%	5%	3%	14%
Serious AE	0%	2%	4%	2%	8%
Deaths	0%	0%	1%	0%	0%

Updated ISS Database
Most Frequent Adverse Events (n=399)

COSTART Preferred Term	All Adverse Events
Headache	28%
Nausea	23%
Dizziness	19%
Pain	18%
Somnolence	14%
Pharyngitis	12%
Sleep disorder	11%
Accidental injury	10%
Flu syndrome	10%
Infection	10%
Viral infection	10%
Asthenia	9%
Vomiting	8%
Nervousness	8%
Confusion	7%
Urinary Incontinence	7%

Placebo-Controlled Clinical Trials Most Frequent Adverse Events

Adverse Event COSTART Term	Placebo (n=79)	Sodium Oxybate (n=147)
Dizziness	3%	23%
Headache	15%	20%
Nausea	5%	16%
Somnolence	9%	12%
Pain (unspecified)	4%	12%
Sleep disorder	3%	9%
Confusion	1%	7%
Infection	1%	7%
Dyspepsia	6%	6%
Vomiting	1%	6%
Urinary incontinence	0%	5%
Nervousness	8%	5%

OMC-SXB-21
Safety Summary

Most Common* Adverse Events
Double-Blind Treatment Period

COSTART Term	Placebo (n=29)	Xyrem (n=26)
Anxiety	2 (7%)	0
Headache	2 (7%)	0
Rash	1 (3%)	1 (3%)

*AEs with ≥ 2 occurrences

OMC-SXB-21
Possible Withdrawal Associated AEs

COSTART Term	Placebo (n=29)	Xyrem (n=26)
Anxiety	2 (7%)	0
Dizziness	1 (3%)	0
Insomnia	1 (3%)	0
Sleep Disorder*	1 (3%)	0
Somnolence	1 (3%)	0

* Verbatim Term: Increased awakenings

Scharf Trial

- Conducted under an Investigator IND without external monitoring prior to Orphan Medical IND
- Represents 16 years of clinical experience (rather than drug development research) without regulatory disciplines
- Patients were located all over the country
- Data source primarily from diary recordings without medical review and interpretation
- Lack of patient compliance contributed to significant discontinuation
- Dosing accountability and dose titration is less clearly defined
- Less defined entry criteria

Adverse Events

- Scharf open-label clinical study
  - Dosing exposure
  - Patient disposition
  - AE incidence (16 years)
  - AE incidence (1st 6 months)

Scharf Trial (16 years)
Patient Disposition

Total Patients	143 (100%)
Ongoing	71 (50%)
Transferred to OMC-SXB-7	63 (44%)
Continued in Scharf Trial	8 (6%)
Early Withdrawal	71 (50%)
Patient Non-Compliance	24 (17%)
Adverse Event	23 (16%)
Cost	13 (9%)
Patient Request	5 (4%)
Lack of Efficacy	4 (3%)
Protocol Deviation	1 (<1%)
Other	1 (<1%)
Screen Failure	1 (<1%)

Scharf Trial (16 years)
AE Incidence

Adverse Event	Incidence (%)
Viral infection	57%
Headache	52%
Pain	48%
Accidental Injury	42%
Nausea	41%
Flu syndrome	39%
Pharyngitis	38%
Rhinitis	36%
Increased cough	34%
Sleep disorder (sleepwalking)	32%
Urinary incontinence	23%

Comparison of Updated ISS Database to Scharf Trial (First 6 months) Most Frequent Adverse Event Incidence

COSTART Preferred Term	Updated ISS (n=399)	Scharf Trial (n=143)
Headache	28%	33%
Nausea	23%	23%
Dizziness	19%	18%
Pain (unspecified)	18%	26%
Somnolence	14%	0%
Pharyngitis	12%	14%
Sleep disorder	11%	9%
Accidental injury	10%	10%
Flu syndrome	10%	11%
Infection	10%	1%
Viral infection	10%	29%
Rhinitis	9%	14%
Sinusitis	8%	11%
Malaise	2%	10%

Adverse Events of Special Interest

- Incontinence / convulsions
- Confusion
- Neuropsychiatric events
- Sleepwalking

Incontinence

Incontinence

- FDA Issue:
  - Are the adverse events of incontinence in clinical trials with sodium oxybate associated with seizures?

Incontinence
Method

- Analysis included:
  - Questionnaire to all affected investigators
  - Examination of safety databases for temporal association with CNS symptoms
  - Prospective overnight EEG in 6 patients with prior history of incontinence
  - Literature review
  - Review by independent experts

Urinary Incontinence

Incontinence Events			Temporal Association With CNS Symptoms	
Clinical Trial	Number of Patients	Number of Events	Number of Patients	Number of Events
OMC-GHB-2 N=136	8 (6%)	15	2 (1.5%)	2
OMC-GHB-3 N=118	13 (11%)	51	2 (1.7%)	2
Scharf N=143	33 (23%)	140	7 (5%)	12

Fecal Incontinence

Fecal Incontinence Events			Temporal association with CNS symptoms	
Clinical Trial	Number of Patients	Number of Events	Number of Patients	Number of Events
OMC-GHB-2 N=136	1 (<1 %)	1	0	0
OMC-GHB-3 N=118	1 (<1%)	Intermittent	0	0
Scharf N=143	1 (<1 %)	1	1 (<1%)	1
OMC-SXB-11 N=34	1 (3%)	1	1 (3 %)	1

Incontinence Conclusion

- There is limited support for a relationship between incontinence and seizures from clinical trials, prospective EEG studies, or the literature

Convulsions

- Updated Integrated Clinical Trials
  - 14 patients with events coded to “convulsion”
    - 13 of 14 patient events recorded as “cataplexy”
    - 1 complex case (“fugue state”)
- Scharf Trial
  - 9 patients with events coded to “convulsion”
    - 5 of 9 patient events recorded as “cataplexy”
    - 2 patient events attributable to pre-existing history
    - 2 other patients with seizure events associated with polypharmacy

“Confusion”

Summary of Adverse Events COSTART Coded as "Confusion"

- Updated ISS
- 402 patients
  - 30 (7%) patients
  - 48 adverse events
  - 3 (<1%) patients discontinued
  - Possible dose relationship
- Scharf Open-Label
- 143 patients
  - 10 (7%) patients
  - 15 adverse events
  - No discontinuations
  - No dose relationship

Updated ISS
Verbatim Terms for "Confusion"

Verbatim	Number of Patients	Number of Events
Confusion, acute confusion, Confusion on awakening	15	25
Disoriented, disoriented upon awakening, disorientation	14	16
Confusion, disorientation	1	1
Feeling 'drunk' after taking drug	3	3
Dazed feeling	1	1
Couldn't comprehend	1	1
Woozy feeling	1	1

- --2 AEs of "confusion" prior to treatment
- --48 events in total

Updated ISS
Action Taken for AE of Confusion

- No change in dosage in 37 events
- Adjustment in dosage in 4 events
- Temporary discontinuation in 4 events
- Permanent discontinuation of 3 patients

Controlled Trial: OMC-GHB-2 Confusion as AE

Preferred Term	Placebo (N=34)	3g (N=34)	6g (N=33)	9g (N=35)	p-value
Any adverse event	24 (70.6%)	25 (73.5%)	25 (75.8%)	26 (74.3%)	0.986
Confusion	1 (2.9%)	3 (8.8%)	1 (3.0%)	5 (14.3%)	0.2779

- Highest incidence at 9g
- 6/10 developed during 1st week (4 at 9g)
- 7/10 were age >50
- High incidence may reflect fixed dosage without titration

Confusion -- Conclusions

- Information recorded was symptoms only
- Lack of contemporaneous, formal mental status examinations for patients with "confusion"
- This reported "confusion" and other associated symptoms (e.g. unsteadiness) are not unexpected with sedating medications
- Higher incidence may result without dose titration

Neuropsychiatric Events

Summary of Neuropsychiatric Adverse Events

- Updated ISS
- 402 patients
  - 52 (13%) patients
  - 57 adverse events
  - 12 (3%) patients discontinued
- Scharf Open-Label
- 143 patients
  - 41 (29%) patients
  - 84 adverse events
  - 2 (1%) patients discontinued

Updated ISS
Summary of Neuropsychiatric Events

COSTART Term	Number of Patients
Total	**(57 Events in 52 Patients)**
Depression	27
Hallucinations	9
Stupor	6
Suicide Attempt	4
Paranoid Reaction	4
Coma	2
Psychosis	2
Manic Depressive Reaction	1
Personality Disorder	1

Scharf Open-Label Trial
Summary of Neuropsychiatric Events

COSTART Term	Number of Patients	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

Conclusions
Neuropsychiatry and Confusion

- Most patients with major events had a pre-existing psychiatric disorder
- Many events do not qualify as neuropsychiatric symptoms
- Assignment of causality is difficult
  - Narcolepsy – depression, psychosis
  - Stimulant medications
  - Pre-study screening deficiencies

Sleep Disorders

Sleepwalking (Somnambulism)

Sleepwalking
Summary of Events

- Integrated Trials
  - 28/402 (7%) patients reported events
- Scharf Trial
  - 45/143 (31.5%) patients reported events
  - Reported primarily in diaries

Sleepwalking Differential Diagnoses

- Arousal disorders
  - NREM parasomnias
  - REM parasomnias
- Partial complex seizures
- Prolonged absence seizures
- Others
  - Oxybate-induced confusional state
  - Automatic behavior in narcoleptics

Sleepwalking in Controlled Trials

	Number of Patients			
	Placebo		Sodium Oxybate	
Trial	Total	Sleepwalking	Total	Sleepwalking
OMC-GHB-2	34	0	102	2
OMC-SXB-21	29	0	26	0
Scrima	20	1	20	0
Lammers	25	0	25	0
Total	108	1 (0.9%)	173	2 (1.2%)

Sleepwalking -- Conclusions

- Incidence in integrated safety database trials (7%) is similar to the range reported in the literature (4-10%) [Mahowald 1998]
- Diary recording without medical classification possibly represents an increased reporting as sleepwalking events in the Scharf trial
- Slight increase in incidence over the general population may be representative of:
  - Xyrem effects – increase in slow wave sleep
  - REM behavior disorder, common in narcoleptics

Summary of Safety

- Exposure to date: 604

  (524 excluding Scharf)
- Dose: 3-9 g/day
- Common adverse events
  - Headache, unspecified pain, nausea, dizziness
- Less common adverse events
  - Vomiting, confusion, restlessness, agitation, sleepwalking, and enuresis

Summary of Safety

- All events have been reversible
- No significant changes in lab values or vital signs identified
- No evidence of organ toxicity
- No consumption by other family members
- No Xyrem diversion

Safety Conclusion

Xyrem is generally well-tolerated

Integrated Summary of Benefits and Risks

William Houghton, M.D.

Chief Operating Officer & Medical Officer,
Orphan Medical, Inc.

Benefit-Risk Assessment
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.

Narcolepsy - Overview

- Rare disease with an incidence of approximately 0.05%
- No currently approved treatment for cataplexy
- FDA priority review
- Off-label use of TCAs, SSRIs inadequate
- Stimulants used to treat daytime sleepiness
  - Do not treat cataplexy

Benefits of Xyrem

- Established by:
  - Patient diary recordings
  - Investigator rating of overall clinical improvement
  - Objective measures of change in sleep architecture and daytime response

Clinical Benefits of Xyrem

- Short and long-term control of cataplexy
- Subjective and objective improvements in daytime sleepiness
- Beneficial changes in sleep architecture
- Overall benefit of therapy indicated by investigator and patient evaluations

Safety of Xyrem

- Generally well tolerated
- Most common symptoms include:
  - Nausea, dizziness, headaches, pain and confusion
- Less common, but important are enuresis and sleepwalking
- Some dose relationship is suggested for nausea, confusion, enuresis
- No deaths associated with the drug in clinical trials

Somnambulism

- Possible association

Confusion

- May be associated with therapeutic doses

Enuresis

- There is a definite association with the drug that may have a dose-relationship
  - No reliable association with seizure

Convulsions

- There is no reliable link in seizure causality with Xyrem
  - 2 patients with known history
  - 2 patients with confounding factors (concomitant alcohol, benzodiazepine withdrawal)

Laboratory Measures

- Changes seen were small, not clinically significant and comparable across treatment groups
- No evidence of organ toxicity at therapeutic doses

Tolerance

- No evidence of kinetic or dynamic tolerance
- No drug-drug interactions observed

Withdrawal Phenomenon

- Serious syndrome in abuse population, relating to escalated dose and frequency
- No evidence in patients in clinical trials

Abuse Issues

- Well-recognized public health issue
- No evidence in patients with narcolepsy, treated with Xyrem
- Company commitment
  - Support of federal and state controls
  - Restricted distribution system
  - Patient and physician education

Conclusions

- We have established statistically and clinically significant evidence for the reduction in cataplexy, and 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 with long-term exposure
- The medical benefits clearly outweigh the risks

Abuse Liability and Overdosage

Robert Balster, Ph.D.

Medical College of Virginia

Abuse Liability of Xyrem

- The current abuse of GHB-like substances probably reflects their ready availability more than their pharmacology.
- If approved, Xyrem will not contribute to the public health problem of abuse of GHB-like substances.

GHB and GHB-like Substances

- Gamma hydroxybutyrate (GHB)(SCH III)
- Precursors
  - Gamma butyrolactone (GBL)
  - 1,4-butanediol (1,4-BD)
- Others
  - Tetrahydrofuran (THF)
  - Gamma hydroxyvalerate (GHV)

Abuse of GHB-like Substances Results Primarily From Availability

- Retail sales
- GHB and precursors were readily available through internet sources
- Precursors have wide commercial use
- Any of these precursors can easily be converted to GHB by anyone
- These precursors themselves are now widely abused

Scientific laboratory studies of GHB suggest low inherent abuse potential.

Scientific Data on the Abuse Potential of GHB

- *Unique Pharmacology*
- *Drug Discrimination* - lack of equivalence to abused depressants
- *Self-Administration* - weak reinforcing effects
- *Physical Dependence* - more difficult to produce than with abused depressants

Conclusions From Abuse Potential Studies

- GHB has abuse potential generally consistent with Schedule IV drugs
- Similar conclusion reached by others
  - WHO recommended Schedule IV
  - UN Commission places GHB in Schedule IV under the Psychotropic Convention

Potential Sources of Abuse of Xyrem

- Abuse or misuse among patients
- Diversion for illicit use

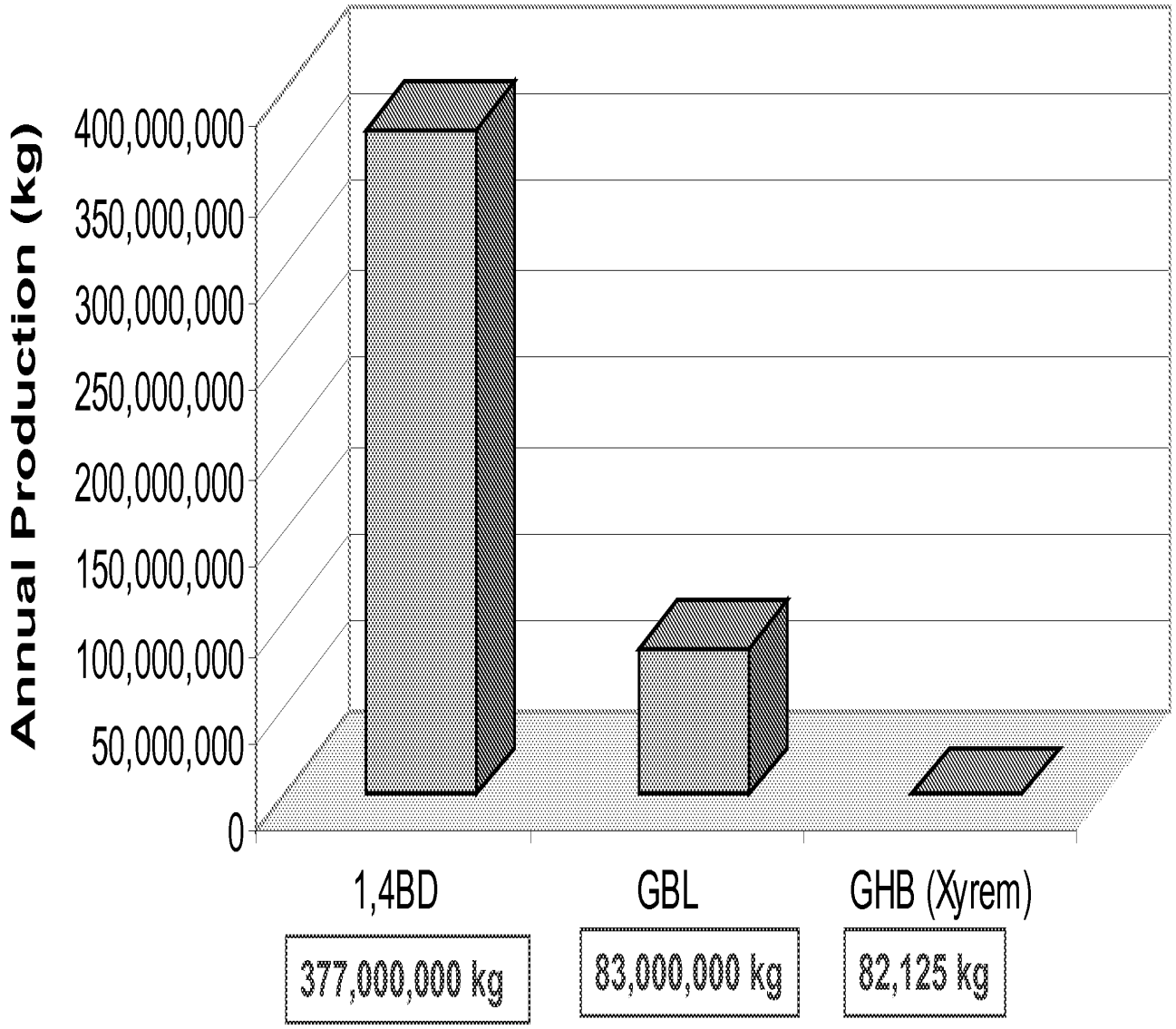
Abuse Among Patients is Unlikely

- In general, substances given as therapeutic treatment rarely are abused by patients
- No reports of abuse in Xyrem trials
- Narcolepsy patients already being treated with medications with abuse potential
- Short duration of action requires multiple daily administrations to maintain elevated levels in the body necessary for physical dependence

Illicit Diversion of Xyrem Unlikely

- No evidence of diversion of Xyrem
- Patient Success Program for distribution should prevent diversion
- Xyrem would be an insignificant source of GHB-like substances to the general public

GHB, GBL and 1,4- Butanediol
Comparison of Production Quantities



Xyrem

Abuse Liability Summary

- Epidemic of abuse of GHB-like substances has resulted primarily from ready availability
- Scientific studies of GHB show modest abuse potential
- Xyrem abuse unlikely in patients
- Contribution of Xyrem to public health problem of GHB-like substance abuse will be insignificant.

Risk Management Through Responsible Distribution and Appropriate Education

Xyrem Success Program

Patti Engel, R.N., BSN

Vice President of Marketing & Sales,
Orphan Medical, Inc.

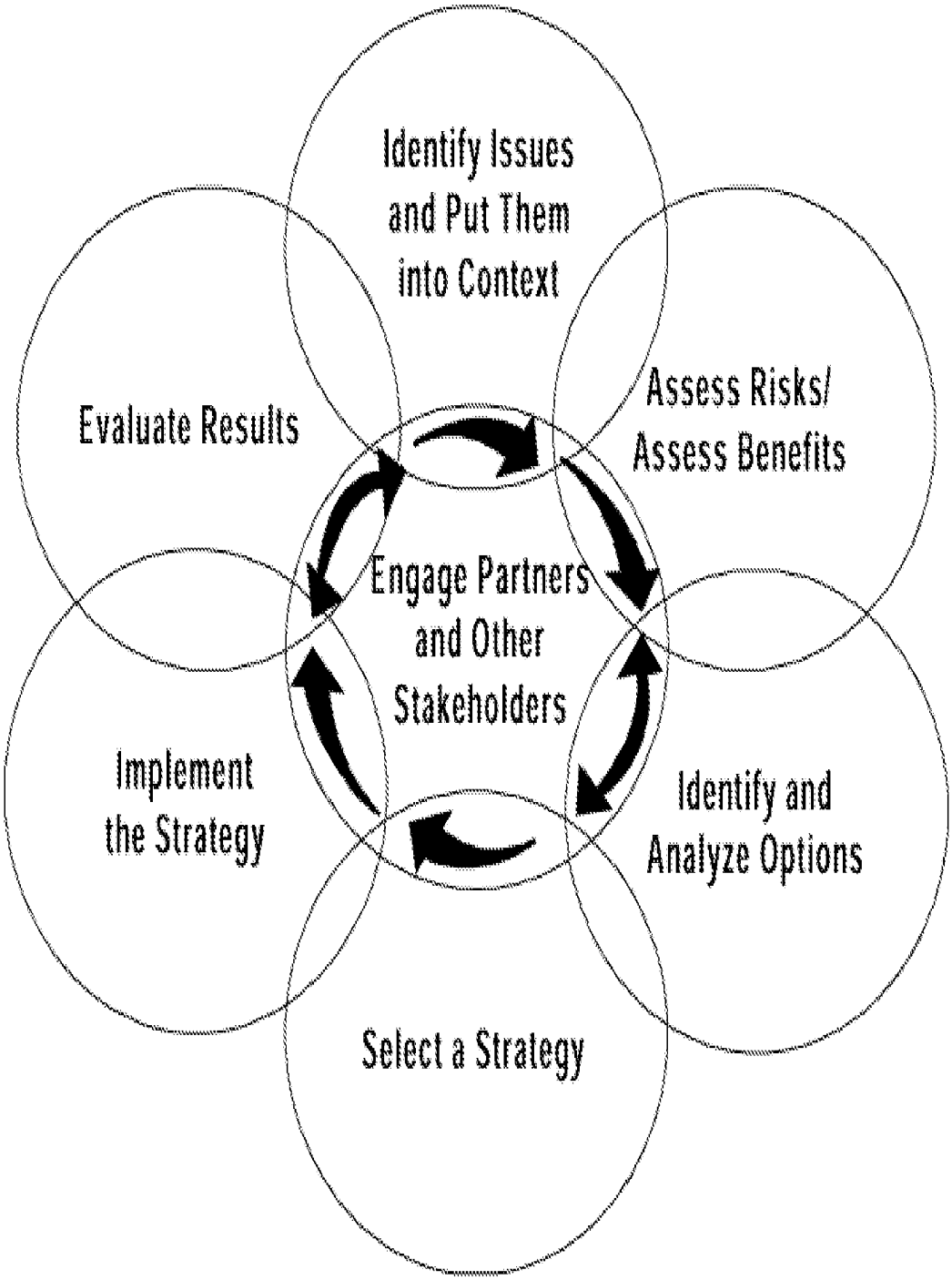
Xyrem Success Program

- A comprehensive system designed to ensure responsible distribution and use of Xyrem
- Goals:
  - Allow access to Xyrem for patients who need it
  - Make Xyrem inaccessible to those who would use it inappropriately

Xyrem Success Program

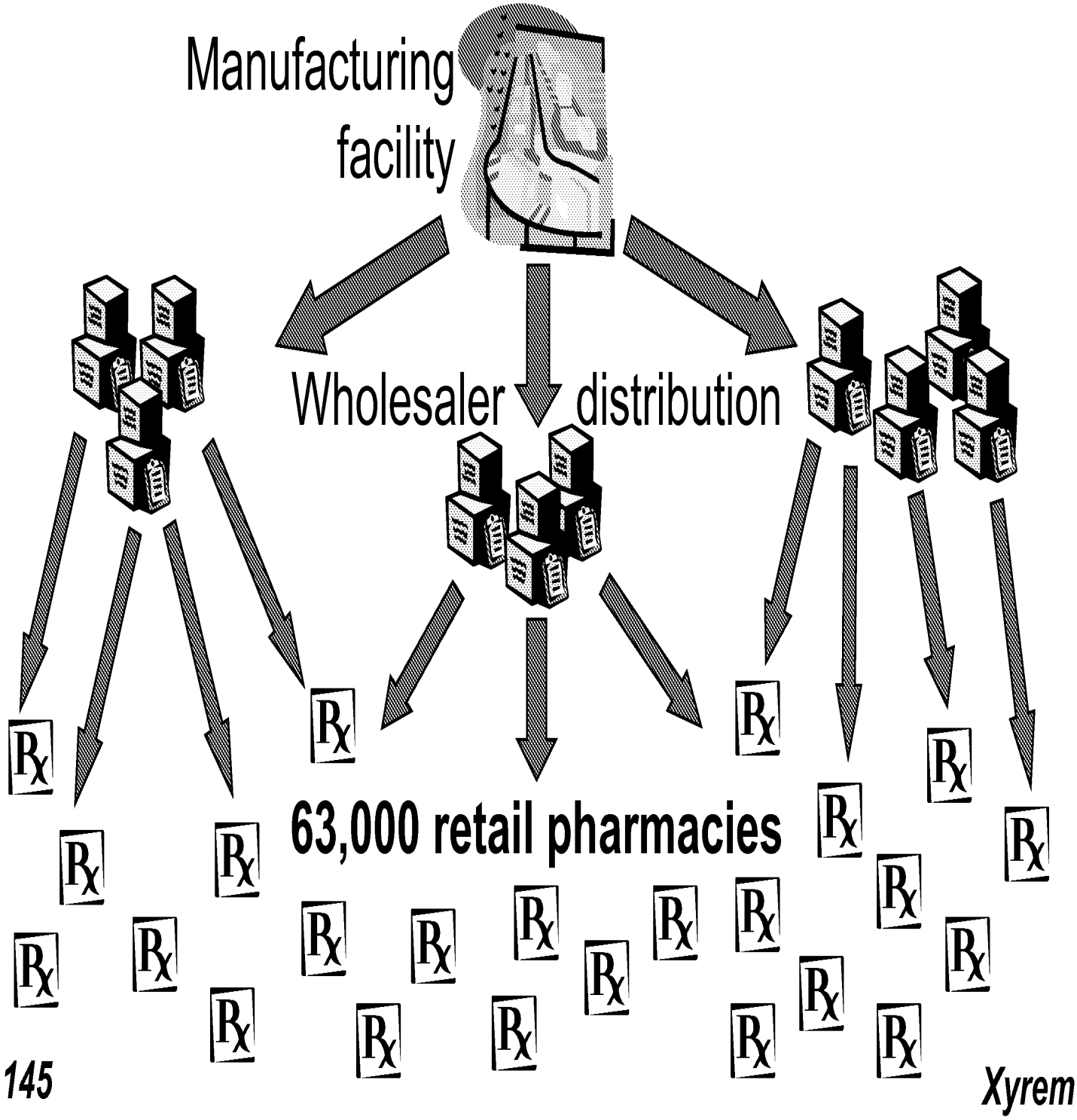
- Initiated by Orphan Medical and developed after extensive consultation with:
  - Narcolepsy patients
  - Patient/Family support groups
  - Physicians who treat narcolepsy
  - Emergency medicine physicians
  - Poison control center directors
  - Pharmaceutical distribution experts
  - Toxicologists
  - Forensics experts
  - Drug diversion investigators
  - Field law enforcement
  - State controlled substance authorities
  - Drug abuse trend experts

Risk Management Through Risk Confrontation



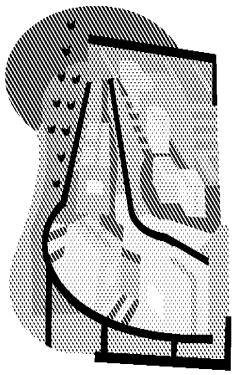
Xyrem

Standard Pharmaceutical Distribution



Xyrem

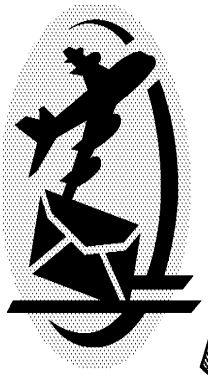
Xyrem Closed Distribution System



Single Manufacturing Facility

Single Specialty Pharmacy

Overnight courier



Patient

Xyrem's Distribution

- One Specialty Pharmacy
  - Xyrem distributed from a single location
    - Controls
    - Records

Physician Promotion and Education

- Xyrem promotional and educational efforts will focus on potential physician prescribers
- Key specialties include:
  - Neurology
  - Pulmonary diseases
  - Psychiatry
  - Internal medicine
  - Sleep medicine (includes several primary specialties)

Physician Promotion and Education

- Approximately 35 sales representatives will call on physicians and their clinical staffs
  - Communicate clinical benefits of Xyrem
  - Present Xyrem Physician Success Program[SM]
    - Physician signature required
- No physician sampling

Physician Success Program Materials

- Multi-faceted education program
  - Distribution process
  - Xyrem dosing and administration
  - Home storage and secure handling
  - “Doctor be wary”
- Unique prescription form
- Contact information at Specialty Pharmacy

Prescription Process

- Physician decides to prescribe Xyrem
- Physician faxes a special Rx to Specialty Pharmacy
- Specialty Pharmacy assigns patient to dedicated pharmacy team

Physician Verification

- Specialty Pharmacy verifies physician is "eligible" to prescribe Xyrem:
  - DEA's NTIS database
    - MD licensure
    - Current CIII prescribing privileges
  - State medical board

Patient Verification

- Specialty Pharmacy calls prescribing physician's office
  - Verify the Rx

Pre-Shipment Patient Counseling

- Specialty Pharmacy contacts patient:
  - Determine patient/designee location and availability for receipt of Rx shipment
  - Explain contents of shipment

Rapid Trac® System

- Detailed, real-time tracking
- Delivered ONLY by authorized signature
- If patient/designee unavailable, package returned to Specialty Pharmacy after one re-delivery attempt
- If lost, investigation begins regarding shipment's whereabouts

Patient Success Program Materials

- Multi-faceted education program
  - Distribution process
  - Xyrem dosing and administration
  - Home storage and secure handling
  - Criminal and civil penalties for illicit use
- Contact information at Specialty Pharmacy
- Reimbursement information

Post-receipt Contact

- Once received, Specialty Pharmacist contacts patient within 24 hours to:
  - Confirm receipt of package
  - Discuss with patient:
    - Penalties for illicit use
    - Xyrem dosing and administration
    - Home storage and secure handling
  - Discuss child resistant packaging

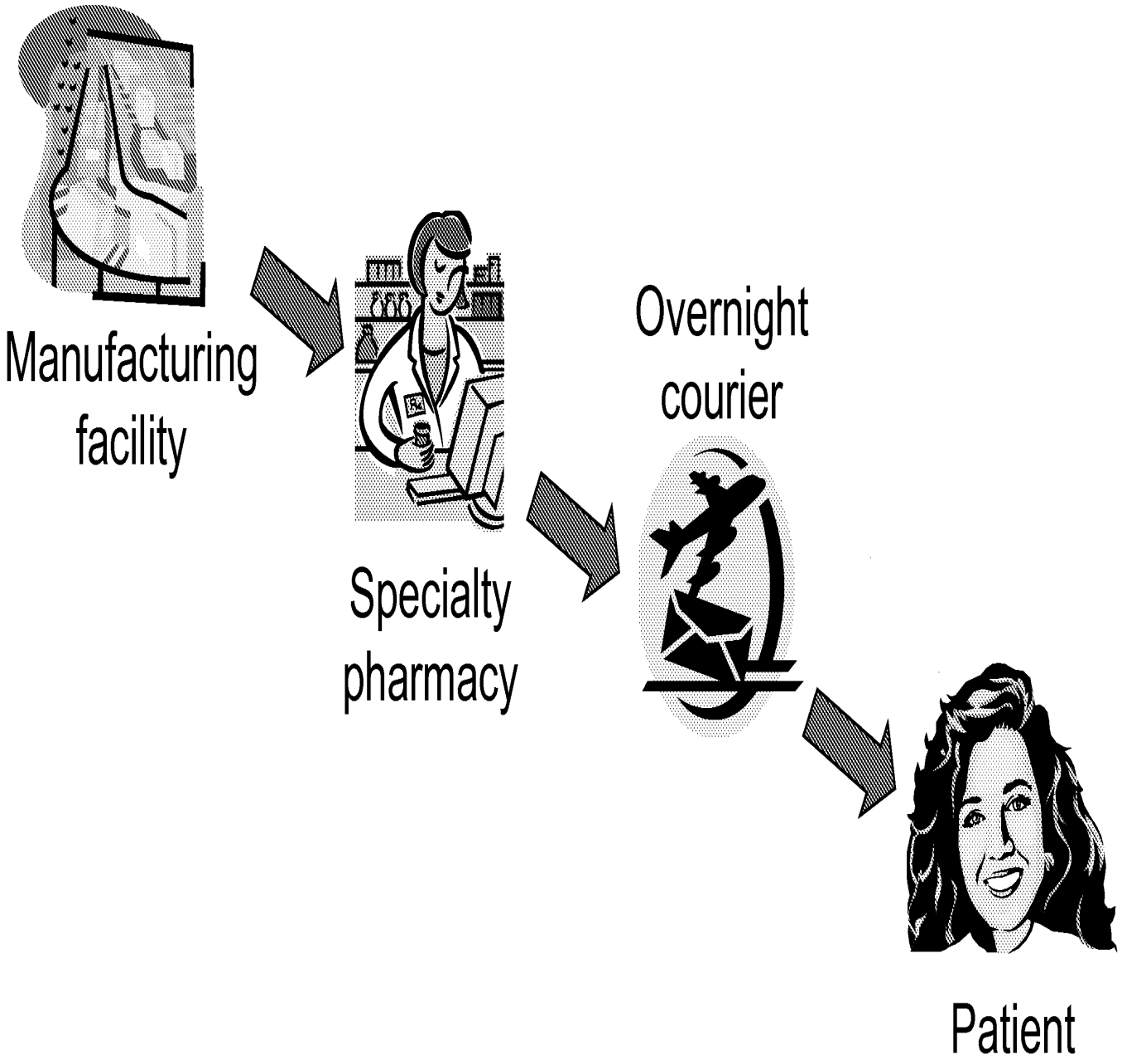
Benefits of Central Data Repository

- Identification of:
  - Duplicate prescriptions
  - Over-prescribing
  - Over-use by patients
- Information *prior* to filling Rx
- Appropriate pharmacist intervention

Xyrem Success Program

- A comprehensive program that ensures the responsible distribution of Xyrem, resulting in:
  - Availability of Xyrem to patients who need it
  - Inaccessibility to those who would use it illicitly

Xyrem Closed Distribution System



Back-up Slides Displayed at Peripheral and Central Nervous System Drugs Advisory Committee Meeting

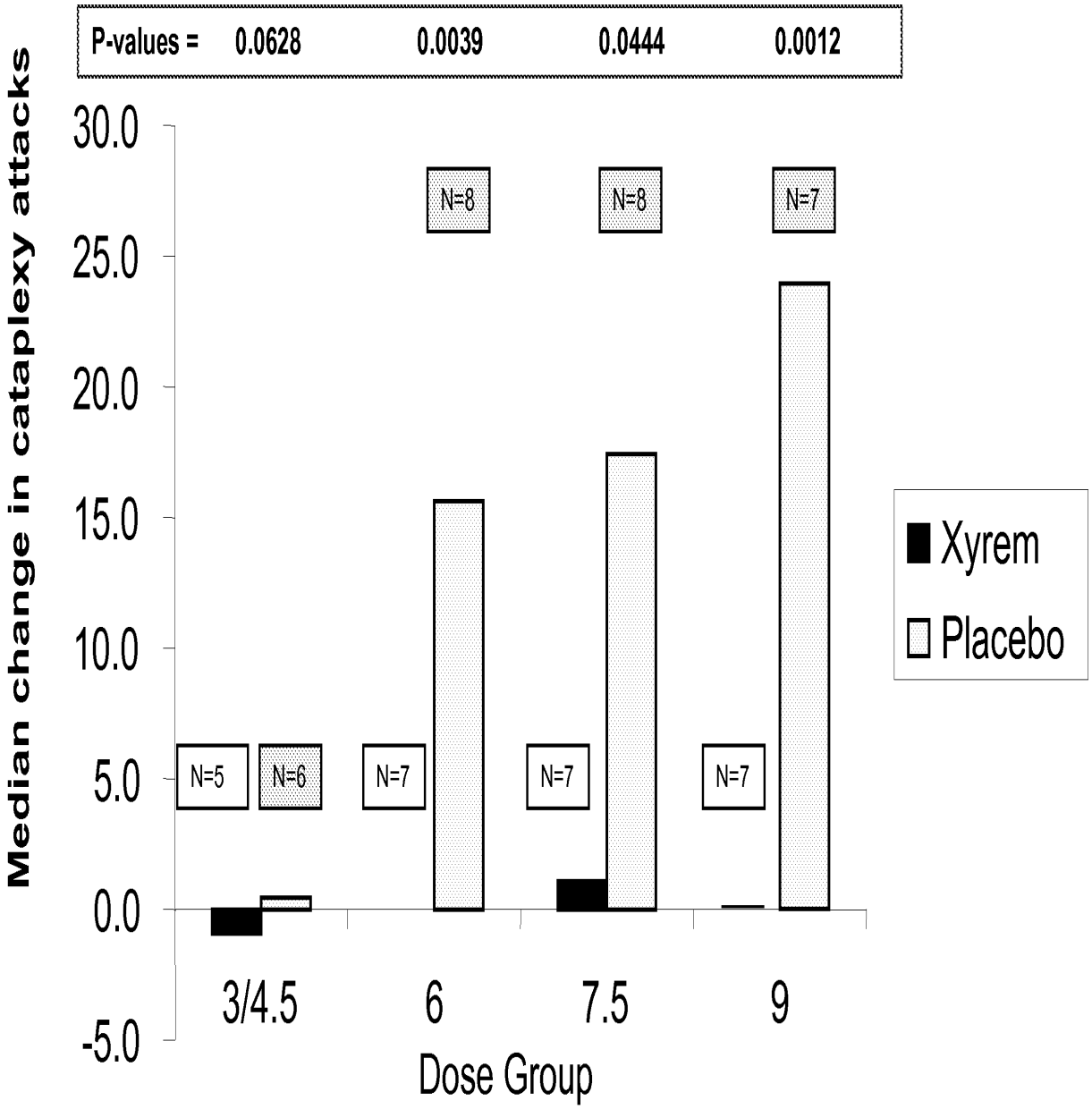
June 6, 2001

Xyrem®
(Sodium Oxybate) oral solution

- Formulation
  - Sodium oxybate 500 mg/mL
  - Malic acid 1.3 mg/mL
  - pH 7.5 in purified water USP
- Package Components
  - Child resistant cap
  - Press In Bottle Adapter (PIBA)
  - Syringe for measuring each dose
  - Child resistant dosing cups (2)

OMC-SXB-21

Median Change In Cataplexy Attacks by Dose



Xyrem

Updated ISS Database
Summary of Patient Exposure by Dose

	Sodium Oxybate Dosage (g/d)					
	Total	**3.0**	**4.5**	**6.0**	**7.5**	**9.0**
≥ 6 months	296	9	50	115	59	62
≥ 12 months	223	5	27	60	26	34
≥ 24 months	48	2	4	13	9	13

Updated ISS Database with Scharf
Summary of Patient Exposure by Dose

	Sodium Oxybate Dosage (g/d)					
	Total	**3.0**	**4.5**	**6.0**	**7.5**	**9.0**
≥ 6 months	360	25	87	171	83	70
≥ 12 months	286	12	55	114	50	42
≥ 24 months	150	6	26	66	34	23

Updated Integrated Summary of Safety Summary of "Confusion" Events

- Demographics:
  - Gender: 9 males; 21 females
  - Age: 25.7 – 73.8 years (67% ≥ 50 years)
  - Dose at Onset:
    - 3.0g – 4 events
    - 4.5g – 10 events
    - 6.0g – 12 events
    - 7.5g – 8 events
    - 9.0g – 13 events
    - Placebo – 1 event

Xyrem® (sodium oxybate) oral solution

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

June 6, 2001

Orphan Medical Inc.

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
2:13–cv–07884–ES–JAD	12/27/2013	NEWARK, NJ

PLAINTIFF	DEFENDANT
JAZZ PHARMACEUTICALS, INC.	PAR PHARMACEUTICAL, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 6,472,431 B2	OCT. 29, 2002	Assignee: Orphan Medical , Inc.
2		
3		
4		
5		

In the above––entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
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In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Dianne C. Richards	12/27/2013

Copy 1––Upon initiation of action, mail this copy to Director Copy 3––Upon termination of action, mail this copy to Director
Copy 2––Upon filing document adding patent(s), mail this copy to Director Copy 4––Case file copy

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC.,
Plaintiff

V.

SUMMONS IN A CIVIL CASE

PAR PHARMACEUTICAL, INC.,
Defendant

CASE NUMBER: **2:13–CV–07884–ES–JAD**

TO: *(Name and address of Defendant):*

A lawsuit has been filed against you.

Within 21 days after service of this summons on you (not counting the day you received it) –– or 60 days if you are the United States or a United States Agency, or an office or employee of the United States described in Fed. R. civ. P. 12 (a)(2) or (3) –– you must serve on the plaintiff an answer to the attached complaint or a motion under rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff`s attorney, whose name and address are:

If you fail to respond, judgment by default will be entered against you for the relief demanded in the complaint. You also must file your answer or motion with the court.

WILLIAM T. WALSH
CLERK

Dianne C. Richards
(By) DEPUTY CLERK

ISSUED ON 2013–12–31 10:10:25.0, Clerk
USDC NJD

RETURN OF SERVICE

Service of the Summons and complaint was made by me(1)	DATE
NAME OF SERVER *(PRINT)*	TITLE

Check one box below to indicate appropriate method of service

☐ Served personally upon the defendant. Place where served: _____

_____

☐ Left copies thereof at the defendant's dwelling house or usual place of abode with a person of suitable age and discretion then residing therein.

☐ Name of person with whom the summons and complaint were left:_____

☐ Returned unexecuted:_____

_____

_____

☐ Other (specify) :_____

_____

_____

STATEMENT OF SERVICE FEES

TRAVEL	SERVICES	TOTAL

DECLARATION OF SERVER

I declare under penalty of perjury under the laws of the United States of America that the foregoing information contained in the Return of Service and Statement of Service Fees is true and correct.

Executed on _____ _____

Date *Signature of Server*

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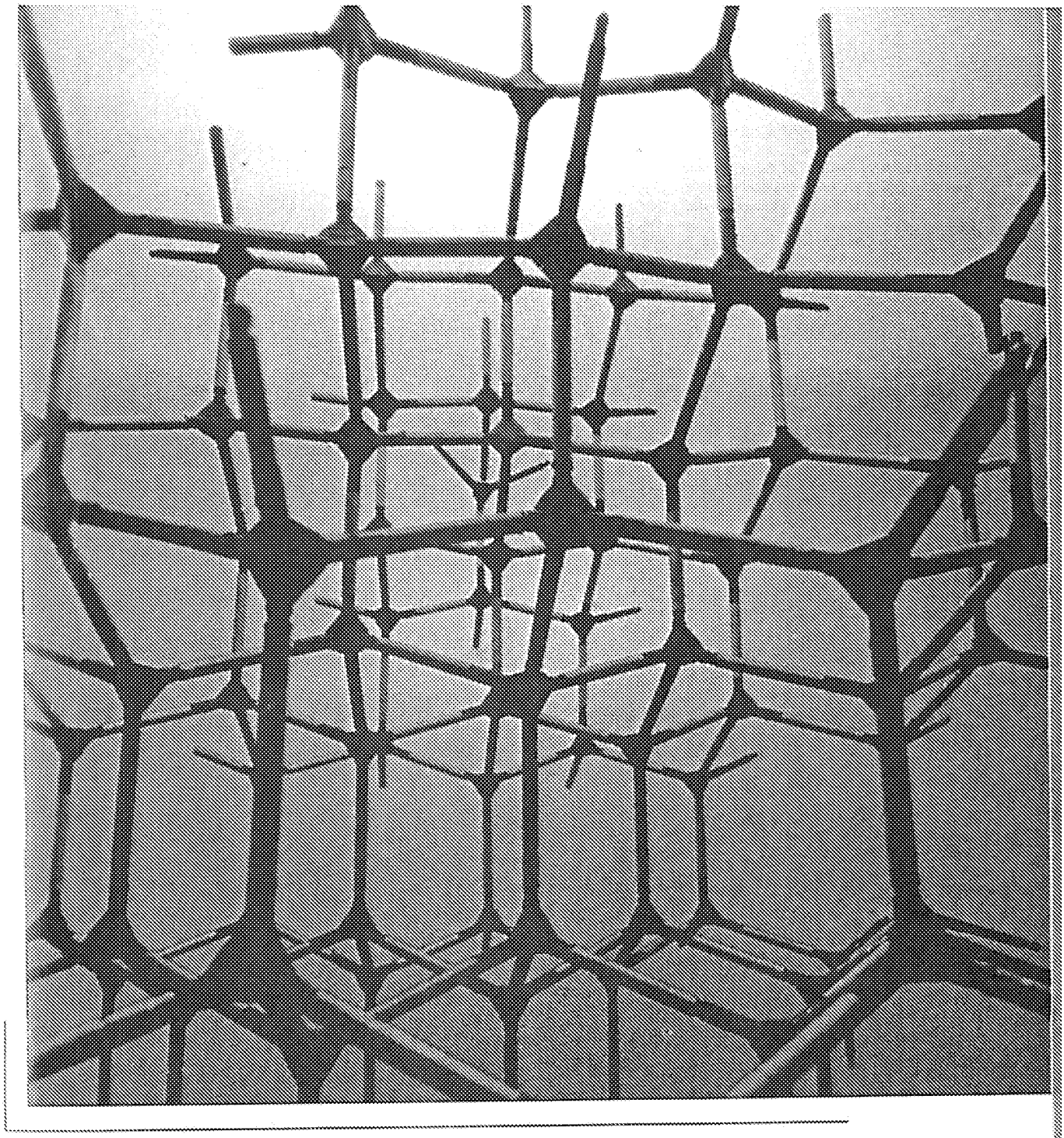
Address of Server



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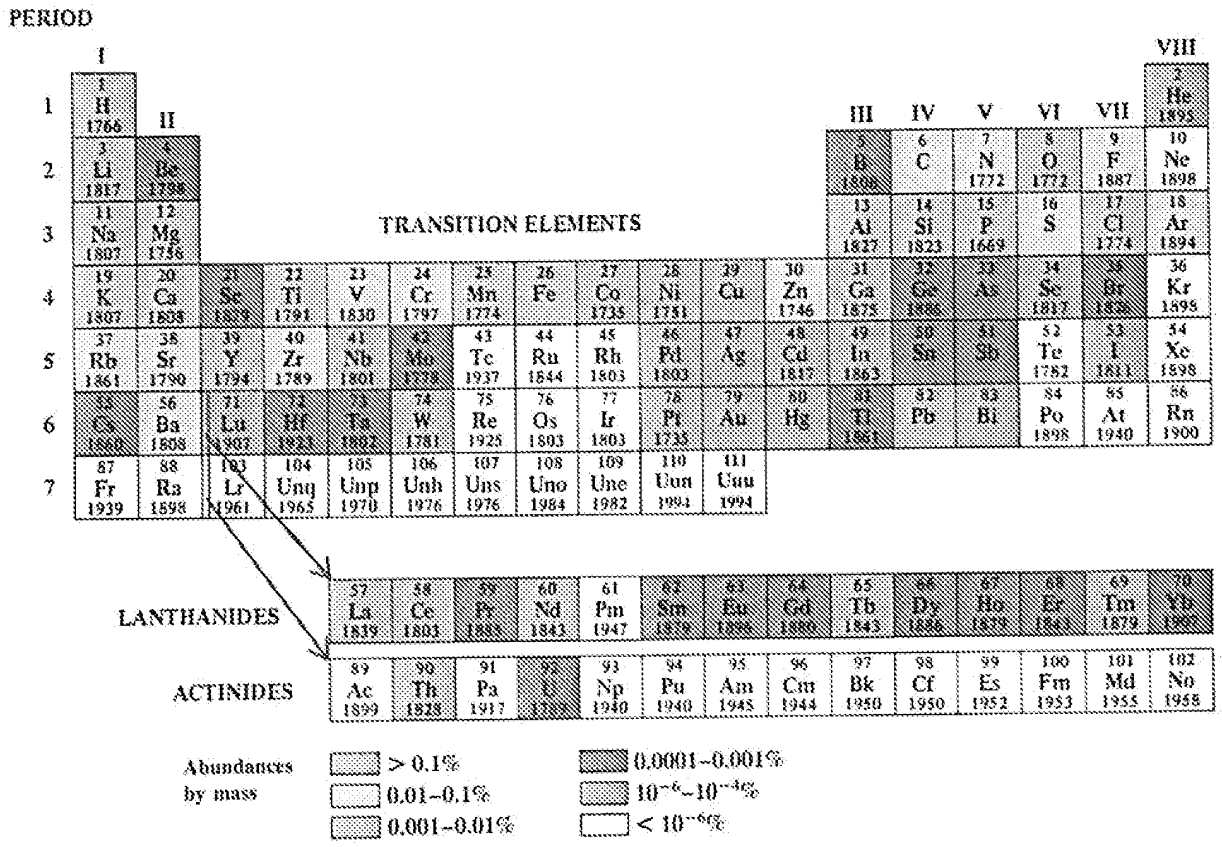


Figure 2-7

The modern periodic table of the elements. Below each symbol is the element's year of discovery; elements with no dates have been known since ancient times. Above each symbol is the atomic number. The color coding indicates the relative abundance by mass of the elements in the world (the atmosphere, oceans and freshwater bodies, and the earth's crust to a depth of 40 km). Oxygen alone comprises almost 50% of this mass, and silicon comprises more than 25%.

division between metallic and nonmetallic elements (see inside the front cover of this book). One of the major accomplishments of modern chemistry is its ability to account for these systematic variations (and many individual exceptions as well) both qualitatively and quantitatively.

2-2 IONS AND IONIC COMPOUNDS

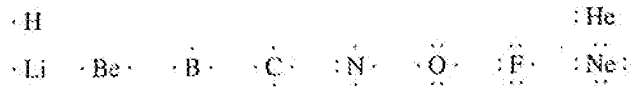
The periodic table is a useful way to describe systematically the properties of the elements, and we shall return to it frequently. Chapter 13 will show how the structure of the periodic table arises from the application of quantum mechanics to the electronic structures of atoms. Here we confine our discussion to a simple and helpful model called the **Lewis electron-dot model.** It was proposed by the Ameri-

can chemist G. N. Lewis in 1916, well before modern quantum mechanics was fully developed. It works equally well for ions and ionic compounds and for the compounds we shall shortly identify as covalent.

The Lewis model begins by recognizing that not all the electrons in an atom participate in chemical bonding. Electrons appear to occupy a set of **shells** surrounding the nucleus, and those in inner shells (called **core electrons**) are not significantly involved in the formation of bonds between atoms. The outermost, partially filled shell (called the **valence shell**) contains the electrons that need to be included in most descriptions of chemical bonding, the **valence electrons.** A filled shell possesses great chemical stability. Progress through the elements in order of increasing atomic number reveals a filled shell whenever a noble-gas element such as helium, neon, or argon is reached. The additional electron in atoms of the first element past a noble-gas element (that is, the outermost electron in an alkali-metal atom) is the first occupant of a new shell, so an alkali-metal atom has one valence electron. With the exception of helium, the number of valence electrons in a neutral atom of a main-group element (those in Groups I through VIII) is equal to the element's group number in the periodic table.

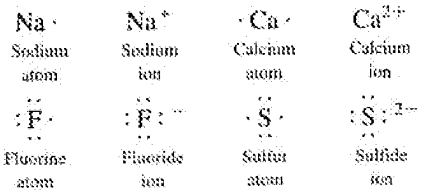
The main-group elements that follow a series of transition-metal elements require some special attention. Atoms of bromine, for example, have 17 more electrons than atoms of argon, the preceding noble gas. We still say that bromine has 7 valence electrons (like chlorine), not 17. The reason is that in the fourth, fifth, and sixth periods the ten electrons added in the course of the transition-metal series (although they are very important for the bonding of those elements) have become *core* electrons by the time the end of the transition-metal series is reached. The bonding properties of an element such as bromine resemble those of the lighter elements in its group.

The Lewis model represents valence electrons with dots; core electrons are not shown. The first four dots are displayed singly around the four sides of the symbol of the element. If there are more than four valence electrons, their dots are paired with those already present. The result is a **Lewis dot symbol** for that atom. The Lewis notation for the elements of the first two periods is



The Formation of Ionic Compounds

A positively charged **ion** (called a **cation**) forms when an atom loses one or more electrons, and a negatively charged ion (called an **anion**) forms when an atom adds electrons. The creation of ions is indicated by removing dots from or adding them to the Lewis dot symbol and also by writing the net electric charge of the ion as a right superscript. For example:



Special stability results when an atom, by either losing or gaining electrons, forms an ion whose outermost shell has the same number of electrons as the outermost shell of a noble-gas atom. Except for hydrogen and helium, whose valence shells are completed with two electrons, atoms of the first few periods of the periodic table have a maximum of eight electrons in their valence shells. We say that a chlorine ion ($:\ddot{\underset{\cdot\cdot}{Cl}}:^-$) or an argon atom ($:\ddot{\underset{\cdot\cdot}{Ar}}:$) has a completed **octet** in its valence shell.

The tendency of atoms to achieve valence octets describes much chemical reactivity. Atoms of elements in Groups I and II achieve an octet by losing electrons to form cations; atoms of elements in Groups VI and VII do so by gaining electrons to form anions. Reactions of the metallic elements on the left side of the periodic table with the nonmetallic elements on the right side always transfer just enough electrons to form ions with completed octets. The following equations, in which e^- stands for an electron, use Lewis symbols to show the formation first of a cation and an anion and then of an **ionic compound.**

$$Na\cdot \longrightarrow Na^+ + e^- \qquad \text{Loss of a valence electron}$$

$$e^- + :\ddot{\underset{\cdot\cdot}{Cl}}\cdot \longrightarrow :\ddot{\underset{\cdot\cdot}{Cl}}:^- \qquad \text{Gain of a valence electron}$$

$$Na^+ + :\ddot{\underset{\cdot\cdot}{Cl}}:^- \longrightarrow Na^+ :\ddot{\underset{\cdot\cdot}{Cl}}:^- \qquad \text{Combination to form the compound NaCl}$$

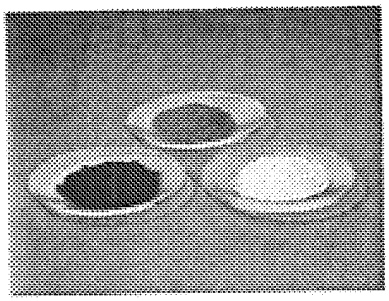
Another example is the formation of $CaBr_2$:

$$\cdot Ca\cdot + 2:\ddot{\underset{\cdot\cdot}{Br}}\cdot \longrightarrow Ca^{2+} + 2:\ddot{\underset{\cdot\cdot}{Br}}:^- \longrightarrow Ca^{2+}(Br^-)_2$$

Neutral atoms not having octets — Positive ion with octet — Negative ions with octets — Ionic compound

The model predicts a 1:1 compound between Na and Cl and a 1:2 compound between Ca and Br, in agreement with experiment.

Ionic compounds, except those with OH^- as the anion, are often called **salts** by analogy with NaCl, common table salt. They are solids at room conditions and generally have high melting and boiling points (for example, NaCl melts at 801°C and boils at 1413°C). Solid ionic compounds usually conduct electricity poorly, but their melts (the molten liquids) conduct well.



Three compounds of lead and oxygen. Lead dioxide (PbO_2, *left*) contains Pb^{4+} ions; litharge (PbO, *right*) contains Pb^{2+} ions; minium (Pb_3O_4, *top*) contains both Pb^{2+} and Pb^{4+} ions. (Leon Lewandowski)

Names and Formulas of Ionic Compounds

The combination of cations with anions results in ionic compounds. Each one's name consists of the name of the cation followed by that of the anion. Ions can be either monatomic or polyatomic; the latter are also referred to as molecular ions.

A monatomic cation bears the name of the parent element. We have already encountered such examples as the sodium ion (Na^+) and the calcium ion (Ca^{2+}); ions of the other elements in Groups I and II are named in the same way. The transition metals and the metallic elements of Groups III, IV, and V differ from the Group I and II metals in that they often form several stable ions in compounds and in solution. Although calcium compounds never contain Ca^{3+} ions (always Ca^{2+}), the element iron forms both the Fe^{2+} and Fe^{3+} ions, and thallium forms both the Tl^+ and Tl^{3+} ions. When a metal forms ions of more than one charge, we distinguish them by placing a Roman numeral in parentheses after the name of the metal:

Cu^+	copper(I) ion	Fe^{2+}	iron(II) ion	Sn^{2+}	tin(II) ion
Cu^{2+}	copper(II) ion	Fe^{3+}	iron(III) ion	Sn^{4+}	tin(IV) ion

An earlier method for distinguishing between such pairs of ions used the suffixes *-ous* and *-ic* added to the root of the (usually Latin) name of the metal to indicate the ions of lower and higher charge, respectively. Thus, Fe^{2+} was called the ferrous ion and Fe^{3+} the ferric ion. This method, although still sometimes used, is not recommended for systematic nomenclature and will not appear again in this book.

A few polyatomic cations are of importance in inorganic chemistry. These include the ammonium ion, NH_4^+ (obtained by adding H^+ to ammonia); the hydronium ion, H_3O^+ (obtained by adding H^+ to water); and the particularly interesting molecular ion formed by mercury: Hg_2^{2+}, the mercury(I) ion. This species must be carefully distinguished from Hg^{2+}, the mercury(II) ion. The Roman numeral I in parentheses means in this case that the average charge on each of the two mercury atoms is +1. Compounds with the empirical formulas HgCl and HgBr correspond to Hg_2Cl_2 and Hg_2Br_2.

A monatomic anion is named by adding the suffix *-ide* to the first portion of the name of the element. Thus, chlor*ine* becomes the chlor*ide* ion, and oxy*gen* becomes the ox*ide* ion. The other monatomic anions of Groups V, VI, and VII are named similarly. Many polyatomic anions exist, and the naming of these species is more complex. The names of the oxoanions (each contains oxygen in combination with a second element) are derived by adding the ending *-ate* to the stem of the name of that second element. Some elements form two oxoanions. The *-ate* ending is then used for the oxoanion with the larger number of oxygen atoms (e.g., NO_3^-, nitr*ate*), and the ending *-ite* is added for the name of the anion with the smaller number (e.g., NO_2^-, nitr*ite*). For elements such as chlorine, which form more than two oxoanions, we use the additional prefixes *per-* (largest number of oxygen atoms) and *hypo-* (smallest number of oxygen atoms). An oxoanion containing hydrogen as a third element includes that word in its name. The HCO_3^- oxoanion, for example, is called the hydrogen carbonate ion in preference to its common (nonsystematic) name, "bicarbonate ion," and HSO_4^-, often called "bisulfate ion," is better designated as the hydrogen sulfate ion. Table 2-2 lists some of the most important anions. It is

Table 2-2 Formulas and Names of Some Common Anions

F^-	fluoride	CO_3^{2-}	carbonate
Cl^-	chloride	HCO_3^-	hydrogen carbonate
Br^-	bromide	NO_2^-	nitrite
I^-	iodide	NO_3^-	nitrate
H^-	hydride	SiO_4^{4-}	silicate
O^{2-}	oxide	PO_4^{3-}	phosphate
S^{2-}	sulfide	HPO_4^{2-}	hydrogen phosphate
O_2^{2-}	peroxide	$H_2PO_4^-$	dihydrogen phosphate
O_2^-	superoxide	SO_3^{2-}	sulfite
OH^-	hydroxide	SO_4^{2-}	sulfate
CN^-	cyanide	HSO_4^-	hydrogen sulfate
CNO^-	cyanate	ClO^-	hypochlorite
SCN^-	thiocyanate	ClO_2^-	chlorite
MnO_4^-	permanganate	ClO_3^-	chlorate
CrO_4^{2-}	chromate	ClO_4^-	perchlorate
$Cr_2O_7^{2-}$	dichromate		

important to be able to recognize and name the ions from that table, bearing in mind that the electric charge is an essential part of the formula.

The composition of an ionic compound is determined by overall charge neutrality: the total positive charge on the cations must exactly balance the total negative charge on the anions. The following names and formulas of ionic compounds illustrate this point.

Tin(II) bromide	One 2+ cation, two 1− anions	$SnBr_2$
Potassium permanganate	One 1+ cation, one 1− anion	$KMnO_4$
Ammonium sulfate	Two 1+ cations, one 2− anion	$(NH_4)_2SO_4$
Iron(II) dihydrogen phosphate	One 2+ cation, two 1− anions	$Fe(H_2PO_4)_2$

Example 2-1

Give the chemical formulas of (a) calcium cyanide and (b) copper(II) phosphate.

Solution

(a) Calcium cyanide is composed of Ca^{2+} and CN^- ions. For the overall charge to be 0, there must be two CN^- ions for each Ca^{2+} ion. Thus, the chemical formula of calcium cyanide is $Ca(CN)_2$.
(b) The ions present in this compound are Cu^{2+} and PO_4^{3-}. To ensure charge neutrality, there must be three Cu^{2+} ions (total charge +6) and two PO_4^{3-} ions (total charge −6) per formula unit. Thus, the chemical formula of copper(II) phosphate is $Cu_3(PO_4)_2$.

Related Problems: 11, 12

2-3 COVALENT COMPOUNDS AND THEIR LEWIS STRUCTURES

Elements in Groups III through V of the periodic table (especially in the first two periods) have a lesser tendency to form ions than those at the left and right sides of the table. Consider the simplest stable compound of carbon and hydrogen: methane (CH_4). Unlike ionic compounds, this substance is a gas at room temperature, not a solid. Cooling methane to low temperatures condenses it to a solid in which the CH_4 molecules retain their identities. Methane dissolves in water to a slight extent, but it does not ionize. Thus, it is not useful to think of methane as an ionic substance made up of C^{4-} and H^+ ions (or C^{4+} and H^- ions). It is a nonionic compound.

The Lewis electron-dot model can describe the bonding in molecules of nonionic substances as well as in ionic compounds. Electrons are not transferred from one atom to another in a nonionic compound, but are *shared* between atoms to form **covalent bonds.** Hydrogen and chlorine combine, for example, to form the **covalent compound** hydrogen chloride. This can be indicated with a **Lewis structure** for the molecule of the product, in which the valence electrons from each atom are redistributed so that one electron from the hydrogen atom and one from the chlorine atom are now shared by the two atoms. The two dots representing this electron pair are placed between the symbols for the two elements:

$$H\cdot + \cdot\ddot{\underset{\cdot\cdot}{Cl}}: \longrightarrow H:\ddot{\underset{\cdot\cdot}{Cl}}:$$

PEDIATRIC SUBCOMMITTEE OF THE

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

June 6, 2001

Slides

Consideration of (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.

Orphan Medical Presentations ppt html

Disclaimer

The statements contained in this document are those of the product's sponsor, not FDA, and FDA does not necessarily agree with the sponsor's statements. FDA has not made a final determination about the safety or effectiveness of the product described in this document.

NDA 21196 Xyrem for Narcolepsy, Orphan Medica, Inc., Comments About Sleepwalking, Ranjit Mani, MD pdf htm

Effect of GHB on Measures of Daytime Sleepiness in Narcolepsy, Ranjit Mani, MD pdf htm

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GHB Abuse in the United States, Carol Falkowski ppt htm

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Public Statement of Deborah Zvosec, PhD, Hennepin County Medical Center pdf

Zvosec, Deborah L. PhD, Stephen W. Smith, MD. et al, "Adverse Evens, Including Death, Associate with the Use of 1,4-butanediol," *N Engl J Med,* Vol. 344, No. 2, January 11, 2001, pp 87-94.*

Statement of Trinka Porrata pdf

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Medical Officer, Orphan Medical, Inc.

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William Houghton, M.D.Chief Operating Officer & Medical Officer, Orphan Medical, Inc.

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Xyrem Pharmacokinetics: Summary

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William Houghton, M.D Chief Operating Officer & Medical Officer, Orphan Medical, Inc.

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William Houghton, M.D.Chief Operating Officer & Medical Officer, Orphan Medical, Inc.

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Patti Engel, R.N., BSNVice President of Marketing & Sales,Orphan Medical, Inc.

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Xyrem Success Program

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Physician Promotion and Education

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NDA 21196
Xyrem® for Narcolepsy
Orphan Medical, Inc.

Comments About Sleepwalking

Background

In this NDA and especially in the Scharf Study, the term "sleepwalking" has been used as a verbatim (investigator) term for a common adverse event. The COSTART preferred term under which this entity has been coded is "sleep disorder."

The sponsor has not discussed this adverse event, either in the original NDA submission or in this Amendment. Given the frequency and potential/actual consequences of this adverse event (see below) I have chosen to discuss it further briefly

In most instances of "sleepwalking" in this NDA, a detailed description of patient behavior during that adverse event is not available.

The medical term "sleepwalking" refers to a non-REM parasomnia classified as an arousal disorder. During episodes patients exhibit complex behaviors including automatic and semi-purposeful motor activities: sitting up in bed, walking, climbing stairs, opening and closing windows and even more complex tasks, such as preparing food, may be features. Acts that are destructive or harmful may be seen, such as throwing objects, and climbing out through a window. During and immediately following episodes patients are confused; they have amnesia for the episodes. It is not at all clear that the term "sleepwalking" has a similar connotation when used in this NDA, or that it refers to a single clinical entity. In the majority of instances of sleepwalking in the Scharf study, this term appears to be derived from daily logs maintained by patients

There does not appear to be an association between narcolepsy and typical sleepwalking as defined in the paragraph above. However about 50% of narcoleptic patients have periods of automatic behavior that are described as memory lapses or blackouts; patients have amnesia for their activities during these episodes. Semi-purposeful activity is possible during such episodes which may manifest with phenomena such as walking into objects, getting lost while driving, and writing unintelligibly. Such episodes are believed to be due to micro-sleeps that intrude into wakefulness, and are most frequent in the mornings. Again there is no information supplied with the NDA that would strongly suggest

that any of the “sleepwalking” episodes correspond to automatic behavior occurring as part of narcolepsy.

Incidence Of “Sleepwalking” In Xyrem® NDA

Controlled Clinical Trial OMC-GHB-2

The incidence of adverse events coded under the COSTART preferred term “sleep disorder” is as follows among the 4 treatment groups

Dose Group	Total Number Randomized	Number of Patients with “Sleep Disorder” (COSTART)	% of Patients with “Sleep Disorder” (COSTART)
Placebo	34	1	2.9
3 g/day	34	2	5.9
6 g/day	33	4	12.1
9 g/day	35	5	14.3

The sponsor has attempted to characterize the term “sleep disorder” further in the following table which I have copied from the OMC-GHB-2 clinical trial report

		GHB		
Description	**Placebo**	**3g**	**6g**	**9g**
Prolonged sleep paralysis	1	1	2	5
Sleep walking	0	0	0	2
Poor sleep maintenance/ frequent arousal	0	1	2	1
Microsleep	0	0	1	0

Integrated Clinical Trials (of which OMC-GHB-2 is a component)

“Sleep disorder” (COSTART) occurred in 46/402 (11.4%) of patients participating in these trials. There was no dose-response seen and the sponsor has not characterized this adverse event further except in the case of those participating in OMC-GHB-2. Thus it is unclear how many patients recorded as having a “sleep disorder” (COSTART) might have been considered to have “sleepwalking”

Scharf Trial

Based on my review of all the Case Report Forms for this study, 45/143 (31.5%) of patients were listed as having one or more episodes of “sleepwalking.” A single patient (# 01-042, initials MJM) is described as having 346 episodes, and many patients had multiple episodes.

The patients listed as having “sleepwalking” constitute the entire cohort of those coded under the COSTART preferred term “sleep disorder” in this study

Characterization Of "Sleepwalking" Episodes

As already indicated the sponsor has not provided more detailed descriptions of patient behavior during these episodes except in a very small number of instances.

I have not attempted to characterize the "sleepwalking" episodes in regard to patient demographics, duration, severity and seriousness of episodes, GHB dose at onset, concomitant medications and illnesses, outcome and other parameters. I currently lack both the time and resources to perform such an analysis. The sponsor should, however, be required to perform such an analysis prior to approval. Such episodes, regardless of their etiology, have had serious consequences as outlined below.

Consequences Of "Sleepwalking" In Xyrem® NDA

Narratives are provided below for patients who were reported to have events of serious or potentially serious consequence during episodes of "sleepwalking." These consequences include taking an overdose of GHB as well as other actions. Several of these narratives are elsewhere in this review but are reproduced here for convenience. All instances occurred in the Scharf study.

Patient 01-215 (Initials AEB)

This 46 year old woman with narcolepsy, who sustained a skull fracture 5 years prior to study entry, took GHB in a variable dose of 4.5 to 10.5 g/day in 2 or 3 divided doses despite being prescribed 7.5 g/day (this is not consistent with what has been entered in the medication logs in the Case Report Form. About 4 months after entering the study she reported symptoms of nausea, a tipsy feeling, blurred vision, and a swollen face and hands. These symptoms persisted for 14 days, no action was taken, and her doses subsequently were variable and as high as 10.5 g/day. She continued in the study for a further 4 years when she was discontinued on account of non-compliance which involved not submitting daily sleep log diaries and modifying dosing schedules without prior consultation with Dr Scharf.

A number of unexplained fits of laughter (termed "hysterical" in one instance, and "uncontrollable" at other times), and **episodes of "sleepwalking" (during one of which she tried to drink nail polish remover)**. Episodes of headache, nausea, dizziness, blurred vision, enuresis, "fogginess", "stumbling around-unsure of self on feet after gamma", "drugged effect, vision blurred, unsteady on feet", "drunken stupor; rage", other similar events, and sleeplessness, were also noted during the study.

A telephone contact with the patient 12 ½ years after she discontinued from the study indicated that her neurological adverse events, with the exception of blurred vision, had resolved once GHB was discontinued.

Patient 01-017 (Initials WF)

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.

Patient 01-267 (Initials RMM)

This 65 year old woman had a history of obesity, sleep apnea on treatment, and narcolepsy. She began taking GHB in a dose of 4.5 g daily.

About 4 ½ years after study entry she was reported to have taken an overdose of GHB, consuming a third nightly dose instead of merely two doses. The patient's daughter reported that the patient was shortly afterward incontinent of urine, awoke and (for unclear reasons) was covered with spaghetti sauce. She also appeared dazed and confused. Her diaries are unavailable for that period and it is therefore unclear what her regular dose of GHB was at the time. She was taken to an emergency room but had recovered by that time. She was reported to have continued GHB after that episode but ceased returning any daily diaries at all beginning about 5 ¼ years after study entry and was therefore recorded as having left the study on account of non-compliance. Repeated letters to the patient from the study center were reportedly unanswered. Further information about this patient is unavailable.

During her participation in the study she was also recorded to have multiple episodes of sleepwalking and multiple additional episodes of urinary incontinence, not apparently occurring contemporaneously. She was also seen at an emergency room for an episode of somnolence which was felt to be related to her sleep apnea. She reported swollen ankles and wrists, and pain, numbness and tingling in her feet.

(It is not clear from the above or from the Case Report Form whether the overdose occurred during an episode that would have been considered to represent "sleepwalking")

Patient 01-206 (Initials DRS)

This 62 year old woman had a history of narcolepsy, hypertension and heavy smoking. She began taking GHB in a dose of 3 g/day.

While participating in the trial she had 7 episodes of sleep walking. 2 episodes which occurred, separated by a 2-day interval, 7 ½ months after she entered the study, led to her discontinuing GHB. During each of these episodes she was found by her husband with a burning cigar or cigarette in her hand, apparently not aware of having been smoking. On one of these occasions she was found

in a room other than their bedroom asleep with a cigar in her hand. On the second occasion the cigarette was found to be burning her nightgown; her husband threatened at that point to leave her unless she stopped taking GHB. The patient's entries in her daily sleep log indicate that she was unaware of her actions during these episodes and had no personal recollection of them subsequently .

Reviewer's Comments

- In the absence of adequate clinical descriptions in most instances it is unclear what the adverse event investigator term "sleepwalking" represents, or whether it refers to single or multiple entities.
- Regardless of what the term "sleepwalking" means in the context of this NDA, it is clear that such episodes are common; almost one-third of patients participating in the long-term Scharf safety study did have one or more such occurrences, and a single patient is recorded as having as many as 346 episodes. The incidence of this adverse event in the entire Integrated Clinical Trials grouping is unknown (except for a single study, OMC-GHB-2)
- The few clinical descriptions of this adverse event that are available in this NDA suggest that during "sleepwalking" episodes patients may be confused and may act in a manner that could be prejudicial to their own safety and that of others.
- The sponsor has not, so far, attempted to analyze this adverse event as an entity
- The fairly high incidence and potential consequences of such episodes make it essential that the sponsor should be asked to better characterize the instances of sleepwalking in this NDA prior to the drug being approved for marketing.
- In this reviewer's opinion (and on a largely speculative basis) it is possible that the term "sleepwalking" as used in this entity could be describing one or more of the following entities
    - An acute confusional state induced by GHB
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NDA 21196
Xyrem® for Narcolepsy
Orphan Medical, Inc.

Comments About Sleepwalking

Background

In this NDA and especially in the Scharf Study, the term "sleepwalking" has been used as a verbatim (investigator) term for a common adverse event. The COSTART preferred term under which this entity has been coded is "sleep disorder."

The sponsor has not discussed this adverse event, either in the original NDA submission or in this Amendment. Given the frequency and potential/actual consequences of this adverse event (see below) I have chosen to discuss it further briefly

In most instances of "sleepwalking" in this NDA, a detailed description of patient behavior during that adverse event is not available.

The medical term "sleepwalking" refers to a non-REM parasomnia classified as an arousal disorder. During episodes patients exhibit complex behaviors including automatic and semi-purposeful motor activities: sitting up in bed, walking, climbing stairs, opening and closing windows and even more complex tasks, such as preparing food, may be features. Acts that are destructive or harmful may be seen, such as throwing objects, and climbing out through a window. During and immediately following episodes patients are confused; they have amnesia for the episodes. It is not at all clear that the term "sleepwalking" has a similar connotation when used in this NDA, or that it refers to a single clinical entity. In the majority of instances of sleepwalking in the Scharf study, this term appears to be derived from daily logs maintained by patients

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FDA Presentation To PCNS
June 6, 2001
Ranjit Mani, M.D.

EFFECT OF GHB ON MEASURES OF DAYTIME SLEEPINESS IN NARCOLEPSY

MEASURES OF DAYTIME SLEEPINESS IN GHB TRIALS

OMC-GHB-2

- Epworth Sleepiness Scale (Secondary)
- Frequency Of Sleep Attacks (Secondary)
- Duration Of Sleep Attacks (Secondary)

Scrima Study

- Sleepiness Index Of Multiple Sleep Latency Test (Primary)
- Frequency Of Sleep Attacks (Secondary)

Lammers Study

- Frequency Of Sleep Attacks (Secondary)
- Duration Of Sleep Attacks (Secondary)

OMC-SXB-21

None

Total Number Of Secondary Efficacy Measures In GHB Trials

OMC-GHB-2:	10
Scrima:	17
Lammers:	7
OMC-SXB-21:	0

OMC-GHB-2: Analysis Of Measures Of Daytime Sleepiness

Parameters	Treatment	Change in medians from baseline to endpoint	P-value for overall comparison *	P-value GHB group vs placebo
Excessive Daytime Sleepiness (Epworth Scale)	Placebo	-2.0	0.0006	
	3 g	-1.0		0.1137
	6 g	-3.5		0.1860
	9 g	-5.0		0.0001
Frequency of Daytime Sleep Attacks	Placebo	-0.26	0.0101	
	3 g	-0.20		0.1022
	6 g	-0.48		0.0497
	9 g	-0.48		0.0122
Duration of Daytime Sleep Attacks	Placebo	-3.10	0.0282	
	3 g	-5.00		0.9995
	6 g	-9.75		0.4413
	9 g	-7.95		0.0689

* based on ANCOVA

SCRIMA STUDY: ANALYSIS OF MEASURES OF DAYTIME SLEEPINESS

Sleepiness Index Of Multiple Sleep Latency Test

Treatment Group	GHB N = 20	Placebo N = 20
Mean Baseline Sleepiness Index	88.5	
Mean Overall Sleepiness Index During Treatment	87.2	90.3
Mean Overall Change From Baseline During Treatment	-1.3	1.8
GHB-Placebo Difference For Overall Treatment Effect	-3.1	
P-value for overall GHB-placebo difference	0.085	

SCRIMA STUDY: ANALYSIS OF MEASURES OF DAYTIME SLEEPINESS

Frequency Of Daytime Sleep Attacks (Attacks/Day)

Treatment Group	GHB N = 20	Placebo N = 20
Mean Baseline Frequency Of Sleep Attacks	2.8	
Mean Overall Frequency Of Sleep Attacks During Treatment	1.9	2.1
Mean Overall Change From Baseline During Treatment	-0.9	-0.7
GHB-Placebo Difference For Overall Treatment Effect	-0.2	
P-value for overall GHB-placebo difference	0.530	

LAMMERS STUDY: ANALYSIS OF MEASURES OF DAYTIME SLEEPINESS

Measure	**Treatment Group**	**Median/Mean of Daily Score ***			**p-value for Change from Baseline to Endpoint (GHB vs placebo)**
		Baseline	Endpoint	Baseline-Endpoint Change	
Severity of Daytime Sleepiness (n =24)	Placebo	1.60	1.59	-0.01	0.034
	GHB	1.60	1.28	-0.32	(Wilcoxon)
Frequency Of Daytime Sleep Attacks (n =24)	Placebo	1.83	2.14	0.31	0.0008
	GHB	2.17	1.36	-0.81	(ANCOVA*)

*Not a protocol-specified analysis

PROBLEMS WITH PROPOSED CLAIM FOR EXCESSIVE DAYTIME SLEEPINESS

- Most measures for excessive daytime sleepiness were secondary
- Only measure that was primary was “negative”
- Majority of measures “negative” (after adjustment of Type I error for multiple comparisons)
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GHB - the CEWG perspective

December 1990

Miami "Florida Poison Information Center reports 7 cases of adverse effects"

June 1991

Miami "at least 7 cases of adverse effects . . ."

June 1993

New York City - "GHB has recently become available in nightclubs"
Mixed with amphetamine; mixture called "Max"

December 1993

Miami – resurfaced as drug of abuse in nightclubs, among body builders

New York City – "still available in nightclubs"

June 1994

Miami - 5 accidental overdoses. The drug has resurfaced since it was banned over 3 years ago. It is marketed in nightclubs and among body builders.

December 1994

Miami - "at least 7 overdoses in 1994"

June 1995

Boston – reports from Rhode Island of a cocktail mixture of GHB and amphetamine

June 1996

Texas "has become a problem in the Dallas/Ft. Worth area"

Miami -increased reports abuse in club settings

New Orleans "GHB becoming widely available and abused"

December 1996

Atlanta- "remains available and has become popular"

Detroit - Used in nightclubs for effects similar to flunitrazepam

Miami- made in homemade labs and associated with sexual assault and robbery

New York City "GHB is more conspicuous" GHB & ketamine & alcohol = "Special K-lude"

Phoenix "increased at raves and nightclubs"

Texas "GHB use is spreading across the state" "scoop" ED mentions

June 1997

Atlanta - GHB used in gyms and fitness centers

Baltimore - raves are a source of GHB

Boston – GHB synthesized by college students, implicated in poisonings with alcohol

Detroit - several seizures of GHB

Honolulu –DEA reports in Honolulu nightlife scene

Miami - GHB emerged as homemade club drug responsible for increasing number of medical emergencies. State law makes GHB Schedule 2.

New York City – GHB used by club patrons

Phoenix - GHB used at raves, nightclubs, gay clubs as a pleasure enhancer

San Francisco – Internet recipe for GHB being used. Marked increase in ED mentions

Texas – GHB becoming more commonly used in Texas

December 1997

Atlanta- used among adolescents and young adults in the urban club scene

Baltimore- GHB available

Boston- availability increased recently in connection with clubs and raves

Honolulu- GHB available in small amounts in Oahu's nightclub scene

Miami – "GHB is the fastest growing new problem in the depressant category, replacing flunitrazepam. GHB clandestine labs in Jacksonville area.

Newark- recipes on Internet and ads for precursors proliferate

New York City – GHB especially visible in nightclubs

San Francisco- "GHB has made a strong debut on the local club and party scene" Used by men and women, gay and straight, as a disinhibiting party drug

Texas -28 overdoses of GHB in 1997

June 1998

Atlanta- GHB at gay circuit parties and at nightclubs

Baltimore- available

Boston- GHB still legal and not controlled in MA, 2 clan labs

Detroit – 3 law enforcement seizures

Miami- "dramatic increase in GHB medical emergencies especially for those under age 20. A GHB analog appears

New Orleans- GHB shipped overnight in to LA and New Orleans from Texas

Phoenix- GHB as date rape drug, cooked on stove top labs

San Diego – GHB in media accounts

San Francisco- Club drugs not seen much except for GHB

Texas- GHB overdoses increasingly reported/110 poison center calls regarding GHB

December 1998

Atlanta – GHB available, popular

Boston- GHB now controlled, implicated in rapes, poisonings, and deaths
"slight overdose can cause drowsiness or unconsciousness"

Denver- daily users tend to be in teens or twenties. During parties GHB is often given away

Detroit – GHB schedule I in Michigan effective July 1998

Miami - "GHB and its analogs are widely abused, increasingly by adolescents"
4 deaths in Broward County, FL (Ft. Lauderdale)

Minneapolis- GHB surfaced as new drug of abuse among adolescents and
appeared in city crime labs

Seattle - several reports of drug rape with GHB and homicide
One ED case every other week "This trend bears watching."

Texas- "GHB overdoses, some with life threatening symptoms continue to be reported. 71 Poison Center calls in first half of 1998.

SPECIAL REPORT: ***GHB Overdoses and Deaths in South Florida***
Joe Spillane, Pharm. D., ABAT and
Madeline Camejo. Pharm.D.

June 1999

CEWG Meeting Summary:

"GHB continues to spread across the country, with recipes proliferating on the Internet. It has been increasingly involved in poisonings, overdoses, date rapes and fatalities in at least 14 CEWG areas, up from 8 last year. GHB is a rave drug used mostly by adolescents and young adults in: Baltimore, Atlanta, Baltimore, Boston, Chicago, Denver, Detroit, Los Angeles, Miami, Minneapolis, Newark, New Orleans, San Diego, San Francisco, Seattle, Arizona, and Texas. GBL and 1,4 BD metabolize in to GHB in the body and produce GHB-like symptoms."

December 1999

- **Atlanta**: "Reports of overdoses from a combination of GHB and alcohol among gay men suggest that the drug continues to be available and popular in certain settings. "

  Baltimore: GHB/GBL was responsible for 10 overdoses in the first 3 months of 1999.

  Boston: "Heavy GHB use has been reported in some Boston clubs, some-times associated with overdoses requiring ED treatment. "

  Newark - a GHB precursor (GBL) was suspected of sending 18 people to hospitals, and 2 GBL-related overdoses were reported among Princeton students.

  Minneapolis - one to five GHB-related overdoses are treated per month. Minnesota legislature designated GHB and its salts, compounds, derivatives or preparations as Schedule III controlled substances, effective August 1, 1999

  San Francisco - "The most often mentioned 'club drug' lately, at least among gay men, has been GHB as well as its precursor, gamma-butyrolactone (GBL) or 'Blue Nitro. '"

  Seattle - ED staff continue to report anecdotal accounts of three to four incidents per month of incapacitation, induced intoxication, rape and other criminal behaviors.

  South Florida: "Eleven of the 26 ED patients with GHB toxicity in the first half of 1999 were completely comatose, 3 experienced respiratory failure requiring endotracheal intubation, and 9 were combative at some point during their visit. "

Meeting Summary/Advance Report:

"On March 13, 2000, gamma hydroxybutyrate (GHB) was placed in Schedule I of the Controlled Substances Act. GHB is easily produced by combining gamma butyrolactone (GBL) with either potassium hydroxide or sodium hydroxide in a container. Kits for making the drug are sold over the Internet. Because the drug is easily synthesized and manufactured, local operators serve as distributors. GHB is usually sold by the capful at a cost of $5 to $10 per cap.

Overdose of GHB can occur rapidly and may produce dizziness, drowsiness, nausea, and visual disturbances. Higher dosages can lead to unconsciousness, seizures, severe respiratory depression, and coma. Overdoses typically require emergency room treatment and, for coma and respiratory depression, intensive care. In 1999, the Food and Drug Administration received 122 reports of GHB abuse from health professionals. The DEA documented 60 GHB-related deaths as of January 2000; almost 60 percent of the deaths occurred among young people age 20 to 29.

GBL, the precursor chemical for the manufacture of GHB, has been marketed as a health supplement and became a List 1 chemical on February 18, 2000. Kits for manufacturing GBL are sold on the Internet. GBL also is synthesized in the body to produce GHB so that some partygoers drink small quantities of GBL "straight." This often causes violent regurgitation of the fluid or other severe reactions.

Atlanta - GHB is increasingly available

Boston The Massachusetts Poison Control Center reported receiving more calls involving GHB and its precursor GBL than was the case for other club drugs. GHB/GBL accounted for 32 percent of illicit drug-related calls.

Chicago GHB is sold as a liquid in amounts ranging from drops from a dropper (at raves or parties) to capfuls.

Detroit The Detroit Poison Control Center reported 100 cases of GHB/ GBL in 1999, with 22 of these being life-threatening. Six cases involved GHB.

Los Angeles GHB use continues to increase in Los Angeles.

Minneapolis - Two GHB toxicity deaths occurred in 1999. A growing but small number of people who sought treatment reported GHB/GBL as the primary substance of abuse, physical dependence, tolerance, and withdrawal

Newark GHB is routinely used at rave parties and around college campuses. GBL was recently linked to 18 hospitalizations.

St. Louis GHB use increased in the St. Louis area. Five GHB-related deaths were reported in Missouri. GHB is sold in clubs for $5 a capful or $40 an ounce.

San Francisco GHB is available but that it is not as commonly used as MDMA.

Texas GHB, GBL, and similar precursor drugs remain a serious problem. Increasing cases were reported by poison control centers in 1999.

23 GHB-related deaths reported in five CEWG areas: 2 in Minneapolis/St. Paul (in 1999); 9 in Broward County (between 1996 and the first half of 2000); 3 in Miami-Dade County (since July 1999); 3 in Texas (in 1999); one in Washington State; and 5 in Missouri.

Atlanta - "GHB is easily accessible at raves and is commonly used by both teenagers and young adults. The DEA continues to report that its use is associated with sexual assault."

Boston - "In press reports, GHB, often called 'liquid ecstasy' or 'liquid X,' is sometimes confused with ecstasy. Although both are so-called club drugs and are often used in the same settings, their effects are quite distinct, with GHB presenting higher risk for both overdose and dependence."

Chicago - "Compared with other club drugs, overdose experiences are more frequent with GHB, especially when used in combination with alcohol. GHB is not tracked in most quantitative indicators, but use is perceived to be low in comparison to that of ecstasy."

Detroit – reports of GHB and GBL abuse have been numerous and continuing in 1999 and 2000.

Los Angeles – GHB continues to be a major club drug

Minneapolis – a St. Paul hospital ED reports treating 5 GHB-related cases per week since September

Missouri- Two near-deaths reported in St. Charles, Missouri, where GHB was used for drug rape.

Newark – It is increasingly reported that GHB and ketamine are used at rave parties around college campuses. "Unfortunately no reporting system tracks the use of such substances in the state."

Phoenix – GHB and GBL are readily available.

South Florida – "when GBL products were banned, new brand names for 1,4 butanediol products appeared almost weekly, and overdose and addiction are reported frequently. In virtually every GHB-related case, the reason for the ED visit was decreased responsiveness/coma usually lasting less than 3 hours."

Texas – "GHB and its precursors remain a dangerous problem, with poison control center cases increasing in 1999.

Washington DC – GHB used by individuals who attend music and dance clubs. "Some club owners do not want to deal with the problems that people suffer from when taking GHB (especially with alcohol) on their premises. They are now removing GHB users and dealers from their clubs.""

compiled by Carol Falkowski, June 2001

GHB Abuse in the United States

6/13/01

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WRITTEN TESTIMONY
OF
SHARON A. FITZGERALD

FOR THE

JUNE 6, 2001 NEUROPHARMACOLOGY ADVISORY COMMITTEE MEETING

Prior to my involvement in the Xyrem study, beginning in late 1995, the quality of my life was being destroyed by narcolepsy.

Almost everyone knows that narcoleptics fall asleep at odd times. Unfortunately, daytime sleepiness is just one of a complex of narcolepsy symptoms, all of which are either eliminated or improved by using Xyrem. Not all narcoleptics have all of the symptoms. I have experienced all of the following.

DAYTIME SLEEPINESS:

Since the age of 25 (1969), falling asleep at unpredictable times has made it difficult for me to work. As an employee, I learned to hide in the restroom to take 10-15 minute naps when the uncontrollable urge to sleep came over me. No matter when I went to bed at night, no matter how many vitamins I took, I could not stay awake all day at work, and I couldn't plan to make the sleep attacks occur at 10:00 o'clock and 2:00 o'clock for scheduled breaks.

This is a symptom narcoleptics attempt to hide from everyone else. It is almost impossible. Narcoleptics fall asleep in meetings. Jobs that allow for escape for a hidden nap at unpredictable times are rare. Not everyone has an office with a door that closes. Employers notice sleeping employees, and, even with today's protective laws, sleepers lose their jobs.

After the death of my husband in 1976, as my narcolepsy was still relatively mild and undiagnosed, I completed my undergraduate degree and then began law school. Increasingly severe symptoms made completing law school slow and difficult. While taking notes during lectures I would begin to dream. Several times I actually wrote a few words about my dreams before dropping my pen. I began to fear for my sanity. Who was writing these things about helicopters and my mother in the middle of my notes on civil procedure? I sought medical help. After four months of testing my doctor inquired, "Do you ever feel muscle weakness when you laugh or get emotional?" I asked, "Doesn't everybody?" and Eureka! I had a diagnosis: Narcolepsy. The good news was, I wasn't crazy. The bad news: At the time, my doctors knew of no treatment.

I am not easily deterred. I graduated. Not with my class. Not among the top 25%, as had been my goal, but I did, finally, graduate. However, I was afraid to take the job offered, clerking for a District Court Judge, because I feared that I would fall asleep in court, sitting up in front for all to see. In Boulder, Colorado, I established a reputation as a compassionate and effective advocate in family and juvenile law. However, I was unable to serve enough clients as a part-time sole practitioner and mediator, during my wakeful hours, to make a sufficient living to support my children and myself. I paid a charitably small rent to live with generous friends. I had to ask that my student loans be deferred.

For a parent, daytime sleepiness is very troublesome, in fact, dangerous. I was a single parent, a circumstance faced by many narcoleptics whose marriages suffer from this condition. I was lucky. My kids survived. I have fallen asleep in a pediatrician's waiting room; at a production of Hansel and Gretel in which my son played Hansel; while reading stories to my kids; at parks while they played on the swings; and while helping with their homework. They got very good at watching for our stop so they could awaken me to get off the bus.

Things got a bit better for me in 1992 when my physician recommended I try Ritalin for daytime wakefulness. However, Ritalin and other wakefulness medications contribute to my high blood pressure, and have other problematic side effects. Xyrem makes it possible to get good, effective nighttime sleep, so I can take significantly less of the wakefulness drugs. I've taken Xyrem for most of the past 6 years, with no side effects.

HYPNOGOGIC HALLUCINATIONS AND NIGHTTIME WAKEFULNESS:

While everyone else is sleeping, an untreated narcoleptic alternates between vivid, often frightening dreams, and hours of worried wakefulness.

Falling asleep at night, and sometimes awakening, can be a horrific experience. You believe you are awake. You know where you are sitting or lying, and your awareness of your surroundings is clear and accurate. But you experience hallucinations. For me, often it was hearing the sounds of an intruder entering my home from behind me. I was paralyzed, and unable to turn around to confront my attacker to defend my children and myself. In a real-life experience, an actual intruder had tried to sexually assault me, so these hallucinations were terrifying.

A 16-year old narcoleptic I met at a sleep clinic told me about his horrifying dreams of space aliens and other monsters. His experiences and mine were parallel, in that sometimes we were so aware that we were dreaming that we would attempt to will ourselves into wakefulness, and actually dream that we were awake, doing ordinary

morning things like going to the bathroom or eating breakfast, only to have our attacker jump out at us from the shower stall or the cereal box. Trust me, it was no compliment if either of us said, "I'll see you in my dreams!"

Before Xyrem, I had hypnogogic experiences virtually every night, on my way to sleep. When I lived alone, I dreaded going to bed, knowing that it would happen, and knowing that no matter how I prepared myself, when I was in that experience, I would believe that it was real. When I remarried, I learned to fear for my husband's safety. He would hear me making fearful noises in my dreams, and would awaken me and try to comfort me into more restful sleep. He stopped trying to help in this way after I attacked him and bit him severely, as I thought he was my attacker.

After finally getting to sleep, for the rest of the night I would alternate between dreams and hours of wakefulness, during which I worried about the inevitably sleepy tomorrow. Before diagnosis, the dreams became very vivid and intricate. They repetitively concerned similar themes, developing into stories over time. It was as if I had one life during the day, and another at night. I began to feel unable to distinguish between dreamed events and realty. This contributed to the fear of insanity that drove me to seek medical help.

Prior to Xyrem, anti-depressants helped with the serial dreams, but did nothing for the hypnogogic hallucinations, and I experienced troublesome side effects. On Xyrem, the nightmares are gone. What dreams I have are normal, and rarely recalled, like a normal person. I get good, restful sleep, and no side effects.

AUTOMATIC BEHAVIOR:

When sleepy during the day, instead of falling asleep, some narcoleptics will continue doing an activity while not fully conscious. Before I was informed of it's clinical name, I named it "going to stupid."

For me, the experience was annoying and embarrassing, but did not cause serious problems. While working on the computer, I have "gone to stupid," finding myself unable to do simple functions, like saving a document, and have had to re-do some work as a result. I learned to recognize the condition and simply stopped and took a nap, losing time instead of ruining or losing a document. I was lucky.

I've heard stories of other, much more dangerous events, such as a woman who brought a pot of oil, rather than water, to a boil, which resulted in severe burns and property damage.

Since I've been on my present medication regimen, including Xyrem, I haven't experienced any events of "going to stupid."

CATAPLEXY:

Early symptoms were just momentary muscle weakness when I laughed. My face felt strange, and my knees felt wobbly. By the time I found Xyrem, my cataplexy was severe. When my granddaughter, Alexis, was a toddler, she kissed my cat while the two of them were sitting in my window seat. I found it so adorable that I collapsed totally to the floor. All muscles go limp. You can't protect yourself from hitting your head on the coffee table on the way down. You just fall.

Walking in the hall at work, then as a mediator for the Colorado Department of Labor and Employment, my supervisor told a joke. Instead of laughing, without warning, I fell to the floor. Employers worry about liability. A couple of cataplexy attacks at work, especially when you work for the Division of Workers' Compensation, are pretty likely to lead to unemployment. I had an unbelievably supportive supervisor, and fortunately, I was only a week away from starting Xyrem when this occurred.

Based on stories my grandmother told, I think my grandfather had undiagnosed narcolepsy and cataplexy. He was not so fortunate as I. He spent a lot of time alone in his room at unpredictable times, demanding silence from his family. When he was about 45, he had become so concerned about the possibility of falling off a roof, in his business as a general contractor, that he tried to change careers. It was shortly after the Great Depression. A potential employer promised to hire him if he purchased a particular kind of truck. He spent all his savings on the truck. When the job fell through, my grandfather decided that his insurance policy would be more helpful to his wife and three daughters than he was, and he ended his life.

I had the good fortune of knowing what cataplexy is before mine became severe. Before I found Xyrem, I did what I could to anticipate problems. As an example, I asked friends to stick close by on Law School Graduation Day, so they could support me if the sheer joy of it put me on the ground. I got pretty wobbly, and my friends kept me upright. I've never been seriously injured by a fall, suffering only some severe bruising. Fortunately, before Xyrem, I never had an emotional experience on the stairs, which at my home present a clear and present danger of a potentially fatal fall.

Many others have not been so fortunate. I've heard stories. The most startling was about a narcoleptic who was not able to escape a house fire because his fear caused cataplectic collapse. When you collapse, the muscles used for speech also fail, so you cannot cry out for help. Cataplexy, at best is hugely embarrassing. At worst, it is extremely dangerous.

Various anti-depressants I've tried had only partial success in controlling my cataplexy, caused distressing side effects, and the pharmacist's warnings threatened worse ones. Going off anti-

depressants resulted in an extreme rebound of cataplexy, far worse than any cataplexy I experienced before trying them.

In contrast, since I began using Xyrem, my cataplexy has been nearly totally eliminated. Only on rare occasions have I had a slight facial relaxation or a tiny knee wobble in response to a very emotional situation. These were so insignificant that no one else noticed them at all. I've experienced no side effects from Xyrem. Additionally, when I had to abruptly stop using Xyrem for a short time, my cataplexy returned slowly, over a three-week period. Other than the return of all the other symptoms of narcolepsy, I had no additional negative symptoms from terminating my Xyrem regimen. Thankfully, the time that Xyrem was unavailable to me was brief.

WHAT A DIFFERENCE XYREM MAKES!

Since going on Xyrem in the fall of 1995, I have been able to function as an essentially normal person in spite of my diagnosis of "Severe Narcolepsy with Cataplexy."

I have had some career success. I am now a full time Administrative Law Judge with the Colorado Department of Labor and Employment. I can work an 8 to 10 hour day, reliably stay awake to hear all my cases, share a funny anecdote with an attorney, and decide emotional issues involving people who are severely disabled by industrial injuries, without collapsing.

Because of my employment, I am presently current on my student loan payments. If I am able to continue to meet the demands of my job, they will be paid off within the next 18 months.

I am a responsible and happy member of a great family that I thoroughly enjoy. I am able to be a full partner to my husband, to whom I've been happily married for precisely seven years as of June 6, 2001, rather than a nighttime endangerment or a financial burden.

I enjoy helping out with my three grandchildren, rather than falling down when they do something cute or have a problem. Three years ago I was able to assist at the birth of Justin, Alexis' little brother, with no cataplexy. I was thrilled to carry him from the delivery room to his first physical examination. Last fall, we traveled to California to get to know my son's firstborn, little Griffin. Later that week, when he became quite ill, I was fully competent to drive him and his frantic parents to the emergency room, and comfort them during his examination and treatment. I was also able to rejoice over his swift and complete recovery. And when I was granted the distinction of being the first to see the empty place after Alexis lost her first tooth, I picked her up, hugged her, and shed a tear of joy, all in an upright position!

I was privileged to be the primary family caregiver for my mother when she suffered a year of dementia. I was with her to provide comfort as she succumbed to pneumonia. I stood up and spoke of the beauty of her life at her funeral.

Without Xyrem, Cataplexy would have robbed me of all of those experiences.

Without Xyrem, I could be unemployable.

Without Xyrem, it would not be safe for me to hold my grandchildren.

Without Xyrem, I would have to try to avoid emotion. Please think about that. Thinking about it makes me very emotional.

The things that make life worthwhile are facing challenges that make us angry, or sad, or frightened, and overcoming them; and celebrating the joy of our successes and our blessings. Xyrem returns the value in life to narcoleptics who have cataplexy. Without Xyrem, my life would be worse than empty.

Please understand. I am a very fortunate narcoleptic. God blessed me with sufficient intelligence to graduate from law school while half asleep, and enough inborn tenacity and stubbornness to never take "You can't!" as the final answer. I live in Denver. My mother's doctor, unlike most physicians in the area even today, heard about the study of the substance we now call "Xyrem," being done in a nearby suburb. That happenstance has allowed me to reclaim a productive life. Thousands of narcoleptics in this country are not nearly so lucky. They desperately need for Xyrem to be available, by prescription, in their towns, in order to complete high school, hold jobs, build successful marriages, and raise children safely.

Xyrem gives back to narcoleptics the bottom-line American Dream, the opportunity to pursue happiness, without falling down when the going gets tough, or when the goal of happiness is attained. As a member of the Narcolepsy Network, and of Orphan Medical's Xyrem Patient Counsel, I am testifying, not only for myself, but also as an ambassador for all those other narcoleptics, and for our children and grandchildren, who may inherit this condition from us. Please find a way to balance the concerns of all persons interested in this drug. Please allow the approval and distribution of Xyrem for treatment of narcolepsy to go forward, now.

Thank you for taking the time to consider our side of this story.

Sharon A. Fitzgerald,
11824 West Belmont Drive
Littleton, CO 80127-6244

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. . . out of the darkness, into the light . . .®

May 16, 2001

Sandra Titus
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-21)
5600 Fishers Lane
Rockville, MD 20857

Dear Ms. Titus:

I will be appearing at the June 6, 2001 FDA Advisory Committee meeting for sodium oxybate, a treatment for narcolepsy and cataplexy. Attached is a written history of the drug for use by committee members. I will confine my oral comments to the lessons we have learned from restricted distribution systems for Clozaril and Thalidomide.

I look forward to seeing you on June 6.

Very truly yours,

Abbey S. Meyers
President

ASM:aa

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Testimony by
Abbey S. Meyers, President
National Organization for Rare Disorders (NORD)

Regarding
Xyrem (sodium oxybate), Orphan Medical Inc.

Before the
FDA Peripheral & Central Nervous System Drugs Advisory Committee

June 6, 2001

A TWENTY YEAR SAGA

Sodium Oxybate was one of the original therapeutic compounds that led to enactment of the *Orphan Drug Act of 1983*. Its value in treating the most devastating symptoms of Narcolepsy, known as Cataplexy, has been known since the late 1970s. Even after the law was enacted, no company was willing to develop the drug for the commercial market because they believed it would not be profitable enough.

During the 1980s, the FDA's Office for Orphan Products Development funded a research grant to an academic scientist for a small clinical trial of sodium oxybate. After several years, he published the study, which raised the expectations of the narcolepsy community. Still no company was interested. We turned to the generic drug industry, and a generic manufacturer agreed to adopt the drug. He spent about five years stabilizing the compound but did not launch a new clinical trial. Finally that company was merged with another, so FDA again sought a new sponsor. Orphan Medical stepped in where no other company was willing to tread.

About that time, the drug began to appear in health food stores with bogus muscle building claims. But the one thing sodium oxybate does very well is put people to sleep. When young people started arriving at emergency rooms, doctors realized they were in a deep sleep, and they started raising warnings. FDA eventually ordered the supplement off the market when it became associated with the "date rape" drugs. DEA wanted to make it illegal for all uses, without regard to it's valid medical use for narcolepsy. We pointed out that none of the illegal use of the drug was associated with the pharmaceutical formulation, and instructions for making sodium oxybate are on the Internet. Therefore, the FDA and DEA cannot stop use of the compound unless they take the instructions off the Internet.

Now after more than 20 years, the studies are done and Orphan Medical has submitted an NDA for approval of sodium oxybate for narcolepsy and cataplexy. People with the most severe form of narcolepsy need this orphan drug desperately. The question is safety of a distribution process that will assure it gets into the hands of patients who need it, and not to the young people who will use it for the wrong purpose.

Keep in mind that people with narcolepsy currently struggle with an inequitable distribution system for amphetamines. If they need Ritalin or Dexedrine, they usually have to tell their pharmacist days in advance because most pharmacies do not want to stock those drugs. They cannot order amphetamines through the mail, and in many states they are forced to see their doctor more than medically necessary in order to get new prescriptions. It is not easy to have a disease that is treated with medicines that have potential for abuse.

I submit that safe distribution systems can be implemented, notwithstanding the Internet. Unless law enforcement and Congress are willing to take the information off the World Wide Web, those who misuse sodium oxybate will be able to continue manufacturing it in their kitchen sink. We already have good models for controlled distribution of prescription drugs, and these are the models that this committee should consider.

The best model is probably thalidomide, a drug that matches no other in the history of medicine in terms of horror, but is nevertheless an approved orphan drug on the American market today. Doctors who prescribe it, and pharmacies that dispense it, register with the manufacturer so that every pill can be monitored and traced in the distribution system. Another important drug is Clozaril for schizophrenia. That drug also is carefully distributed through registered pharmacies, and patients have to prove that they received a satisfactory blood test before their next weekly prescription is dispensed. Our primary concern about these systems is that manufacturers should not be privy to patients' names and addresses. An independent party should guard personally identifiable information.

Both Thalidomide and Clozaril have been approved by the FDA and successfully marketed in the United States even though their distribution is tightly controlled. For serious diseases that do not respond to other therapies, it is incumbent on FDA to find safe ways to get the treatments to the patients who need them. Narcolepsy with cataplexy is a very serious disease, as dangerous as epilepsy because patients lose consciousness suddenly and uncontrollably. We know the most important rule of medicine is, "First, do no harm". To deny this drug to people with cataplexy will do harm to them. We ask you to allow this drug to get to market with a carefully controlled distribution system so we can put this nightmarish saga of sodium oxybate behind us and let these patients get back to living productive lives.

Thank you.

NARCOLEPSY NETWORK
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Cincinnati, Ohio 45242

Tel: (513) 891-3522 **Fax: (513) 891-3836** **E-mail: narnet@aol.com**

February 28, 2001

Peripheral and Central Nervous System Drugs Advisory Committee
c/o Sandra L. Titus
Center for Drug Evaluation and Research (HFD–21)
US Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
e-mail: tituss@cder.fda.gov

Subject: New Drug Application 21-196
Xyrem (Sodium Oxybate)

Dear Committee Members and Ms. Titus:

Thank you for this opportunity to address your study of safety, efficacy, and risk management issues regarding Xyrem (a.k.a. GHB). I will briefly inform you of both my long personal use of GHB, and my very serious concerns as Executive Director of Narcolepsy Network. My hope and purpose are that you will allow the estimated 25,000 Americans who suffer from the disabling cataplexy symptom of narcolepsy the same positive and even life-saving benefits I have received from this product.

First, my personal experience with GHB as a narcolepsy patient. I am 57 years old, married, with two adult children, and am an attorney in private practice (family and criminal law). **I may be the first American to have used GHB for narcolepsy, and the longest continuing user of this drug, now approaching 19 years.** My narcolepsy/cataplexy symptoms first appeared in my mid-30's, and by age 39 included severe and recurring cataplexy, together with excessive daytime sleepiness and sudden recurring sleep attacks. My cataplexy was causing numerous daily episodes of complete body collapse, such that I could no longer even walk from my home or office without serious risk of harm to myself

and others. Feeling any emotion (humor, anger, and even mere surprise or enthusiasm) would cause me to suddenly collapse like a puppet without strings. I would usually fall backwards, with my head whipping down last on concrete, metal, table corners, stairs – whatever was there. I have often been "rescued" by emergency crews, police, lifeguards, strangers and friends. Some falls resulted in hospital visits for injuries, fortunately none permanent. But there are others whose falls have been fatal. Moreover, I would fall suddenly into REM sleep, even in mid-sentence. Disability was staring me in the face.

Then, in August 1982 my treating doctor sent me to Sunnybrook Medical Center in Toronto, Canada to begin prescriptive use of GHB under the research studies being conducted by Dr. Mortimer Mamelak. After three weeks, I returned home and continued using GHB, as monitored by my local physician under an approved FDA individual investigational new drug application. My significant cataplexy and sudden sleep attacks disappeared almost overnight. I was immediately able to return to my full-time law practice. Since then, I have continued using GHB under the FDA clinical investigative procedures conducted first by my local physician, and in recent years by Orphan Medical. **During these 19 years, I have never changed the dose, have never experienced tolerance, and have noted no side effects. Simply stated, the drug is as safe and effective now as it was at the start.** (Frankly, it is difficult to imagine a pharmaceutical product offering such quick, complete, safe and enduring benefits.)

Secondly, my privileged service as Executive Director of Narcolepsy Network in recent years is motivated by the effective medical treatment I received, and a desire that others with narcolepsy might be as fortunate. Narcolepsy Network is a national nonprofit organization whose mission is to educate the public, healthcare professionals, and government representatives regarding this disabling neurological disease, and to facilitate more prompt, informed and effective treatment for persons with narcolepsy. We work closely with the National Center for Sleep Disorder Research at the National Institute of Health,

the American Academy of Sleep Medicine, the National Sleep Foundation, sleep disorder centers as well as Orphan Medical and other pharmaceutical companies developing orphan products for narcolepsy. We have sought to inform federal and state government officials, whenever appropriate, of the dramatic medical benefits provided by GHB to patients participating in the clinical trials. A fortunate result has been the present bifurcated scheduling of GHB on the federal level and in many states. I have often stated to congressional committees and legislative representatives over recent years that the greatest tragedy in the development of treatments for narcolepsy has been the unavailability of GHB, in prescriptive form, to other patients like myself with narcolepsy and cataplexy. Now I respectfully ask this committee to assist in eliminating such an unnecessary situation.

Finally, we are very mindful of and cannot ignore the injuries, deaths, and other "victimizations" which many young Americans have suffered from unlawful and/or uncontrolled consumption of GHB or its related chemical compounds. Narcolepsy Network and myself have cooperated extensively with law enforcement agencies, medical professionals, and community drug agencies. Our continuing purpose is to minimize unlawful use of GHB, and to design safeguards to reduce access and availability. These concerns deserve your and our utmost attention.

However, equally deserving of your highest consideration is the promise and potential of medically controlled GHB to allow persons with narcolepsy with severely disrupted lives and frequent disability to again rejoin their jobs, communities and families.

Thank you for your professional consideration.

Respectfully,

Robert L. Cloud
Executive Director
Narcolepsy Network, Inc.

Titus, Sandra L

From: ciindy [redacted]
Sent: Monday, June 04, 2001 8:12 AM
To: Titus, Sandra L
Subject: fda hearing statement

----- at
My name is Cindy Pekarick, and I would like to describe how ghb analogs killed my daughter.

In ***October of 1998***, my daughter Nicole, a college student, waitiress, and gym enthusiast met a new boyfriend who

introduced her to a product called "Renewtrient. In ***November*** she researched the product via 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 competely recovered and ready for another workout. In ***December*** I found out she was taking this

supplement, didn't believe all 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.

By ***April***, she returned home. She became behind in all her bills. She was bruised on her legs

and arms. She stopped attending classes, and kept losing her keys, wallet, and her pager. In May I discovered she had

essentially "dropped out of school".

By June, I could see mild changes in Nicole's behavior. She began taking "power naps" as she called them. She

would sleep for 3 hours in the middle of the day and get up at 4 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 wierd, then she goes to sleep.

When she wakes up she never remembers anything that she did. She started taking it once in a while so she

could go to sleep right away when she got home from work, 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 analogs all along, since November. I began my

quest for information regarding Renewtrient, Revivarent, and Invigorate, which my younger daughter claimed Nicole took.

In ***August***, Nicole was found having a seizure in a public bathroom. She had urinated and defacated on herself while

pulling at her clothes and flailing her arms. She was rushed to the hospital where we arrived to see her unconscious,

intubated, with her arms, legs, and waist strapped to the bed. They claimed her seizure was violent, and she barely had a

pulse when they found her. It was at this time that 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. We told them

what we thought she had taken, but they didn't have a test for it. I begged the doctors to transfer her to a treatment center

for chemical dependency, but they couldn't do it without the patient's permission. She was clueless as to why she was

hospitalized. She had no recall of anything that happened to her. In fact,she wanted to know where her clothes were. She was

discharged, but began psychological counseling a few days later.

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 this "g" had a hold on her was

a step in healing. I assured her we would find a treatment center as soon as possible and that everything would be ok.

On Monday morning, on our way to the treatment center, Nicole refused to go. She claimed the "g" wasn't addictive,

that she did research and she was just having reactions to it. She said she was now in control of her life and future. She

remained in counseling and by the end of September, Nicole had applied, transferred, and was accepted at the university.

She was so excited, that she stopped at my school on her way home to tell me that she would start classes in

January. Things seemed OK on the surface, but she was hiding tremors, hallucinations, and insomnia. She went days without

sleeping, but never told me.

On October 3, 1999 around 2 PM, 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 PM, but she would never hear it. She was in her final sleep. My firstborn child

was found in bed, blue about 6 PM. We found a bottle of Jolt in the trunk of her car. The autopsy revealed she had gbl and

ghb in her system at the time of death. No other chemicals were found.

Nicole was an honor student while captain of two varsity teams and she belonged to a ballet company.She graduated

3rd in her high school class, and was both a Bloustein and a Garden State Scholar. For her undergraduate studies she

majored in biology, with the plan to major in engineering for her masters degree. Her ultimate goal was to become a bio-

medical 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, intelligent, beautiful, funny, witty, and charming

young lady. Her only fault was that she was naive.

Statement by Eric C. Strain, M.D. on Behalf of the College on Problems of Drug Dependence

Food and Drug Administration

Peripheral and Central Nervous System Drug Advisory Committee

June 6, 2001

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 and I am a professor in the Department of Psychiatry and Behavioral Sciences at Johns Hopkins University School of Medicine. I am a Board Certified Psychiatrist with added Board Qualification 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 travel to today's meeting, and I have no relationship with Orphan or other pharmaceutical companies that make narcolepsy products.

There are two points 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 Drug Abuse Advisory Committee 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, 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 the Peripheral and Central Nervous System Drug Advisory Committee for allowing me to make these comments today. The hope of the College is that these comments will spur tangible demonstration of the 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.

Public Statement, Food And Drug Advisory Committee Meeting on the approval of Xyrem (gamma hydroxybutyrate)

My name is Dr. Deborah Zvosec. My research is in the area of gamma hydroxybutyrate (GHB) abuse, toxicity, addiction and withdrawal. Dr. Stephen Smith and I, with others, published a case series in Morbidity and Mortality Weekly Report in February 1999, describing adverse events due to ingestion of "dietary supplements" containing gamma butyrolactone (GBL). 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; toxicity episodes included 2 deaths that occurred with no co-intoxicants and no evidence of aspiration or asphyxiation or adulterants. Among the many health risks of GHB that I could describe to you today, I will focus on GHB addiction. In the course of our work, my name and Dr. Smith's name were listed on the Project GHB help site. We have received calls from over 40 addicted patients from 25 states and have treated an additional 5 cases of inpatient withdrawal at Hennepin County Medical Center in Minneapolis.

The majority of these addicted individuals began using GHB to treat insomnia, anxiety, depression, chemical dependence, or for bodybuilding purposes, as recommended by product marketers, web sites, and fringe pro-GHB physicians such as Dr. Ward Dean, author of "GHB, The Natural Mood Enhancer." Our patients began with small doses, often only at night, and discovered that it made them feel very good. They increased dosing frequency and, as tolerance developed, they needed more GHB in order to feel good; within months, they were taking GHB every 1-3 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; they lost their jobs; they acquired tremendous debt to support their habit; and they became comatose while driving and crashed their cars, frequently on multiple occasions, and often causing injury and sometimes death. They called us in absolute desperation. We helped with locating and consulting with a physician on their inpatient detoxification. Detoxification 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 detoxification and some also experienced muscle twitching and tremors. Of the over 40 patients we have worked with, only a handful have remained GHB-free, frequently despite chemical dependency treatment. Many have detoxified numerous times but continue to relapse, sometimes within hours of release from treatment. Unfortunately, many never lost faith in GHB and continued to be convinced that they could get back on G and use this wonder drug responsibly. They continue to argue its health benefits.

One of our patients was a 50-year-old businessman who used GHB for 5 years, initiating use to enhance bodybuilding and increasing to around the clock dosing within 2-3 months. His life was entirely controlled by the need to have GHB with him at all times. He had 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 of GHB users. It was only on the morning of his admission for withdrawal that she learned the truth. After 6 days of detoxification with diazepam, he was through the worst of the hallucinations and appeared to be on the road to recovery. A psychiatrist treated him with sleeping medications and antidepressants, but within 3 days, he began using GHB again to control profound anxiety attacks and depression.

It has been the same story over and over. Few who have ventured deep enough into GHB have been able to emerge again, and when they do, neither they nor their families emerge unscathed.

GHB is perhaps the most addictive drug ever abused. Experienced drug users describe a euphoria that surpasses that of any other drug. Availability by 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 Xyrem prescriptions for fake sleep disorders, and for insomnia, fibromyalgia, depression, anxiety, 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, which is determined by cost, perceived quality, ease of procurement, and legal status.

Clinical literature reports an addicted user who spent up to $200 per day for GHB (over $70,000 per year). Our patients have reported ingestion of up to a bottle of supplement/solvent product every 1-2 days, at $60-100 per bottle ($11,000-$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 cheap 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 to such users. We know that users are watching for the release of Xyrem. Recreational drug sites post links to narcolepsy sites and publications about Xyrem; hotyellow98.com, for example, instructed "click here to find out when GHB will be released under the trade name of Xyrem."

There is no systematic federal, state, or local data on the demographics, epidemiology, use patterns, or costs of GHB abuse or addiction. Adverse events are vastly underreported because: 1) we have no field test to detect GHB; 2) we have no routine hospital toxicology screening test for GHB; 3) most clinicians and toxicologists do not know to look for GHB and it is easily masked by or confused with other intoxications; and 4) we have no systematic reporting mechanism accessible to all practitioners. Furthermore, we have no data on chronic or long-term effects of frequent use and addiction. No federal or state funds have been spent on research, education, or prevention of GHB-related health risks in the general public. There are no treatment protocols that have been scientifically validated for either acute GHB toxicity or severe withdrawal, both of which are highly variable and extremely unpredictable.

The nature and course of the Xyrem approval process troubles me deeply. In contradiction to past procedures, the determination of Schedule III status for medically-used GHB occurred prior to discussion of scientific proof of safety and efficacy. Release of Xyrem for off-label prescription, at this time, to a distribution system that uses voluntary self-monitoring with no mandatory governmental oversight or regulation is madness. I urge you to maintain Xyrem/GHB under research status so that narcolepsy patients may receive their medications until an externally monitored and regulated prescription and distribution system may be established. Potential repercussions of ill-advised or premature action are profound. Precedent has already been broken with this split scheduling. It must be broken again if we hope to avoid learning from more tragic mistakes.

Deborah L. Zvosec, Ph.D.
Research Associate, Department of Emergency Medicine
Hennepin County Medical Center
Investigator, Minneapolis Medical Research Foundation
Minneapolis, Minnesota

FDA PCNS Committee Meeting (June 6, 2001)
Statement by Trinka Porrata
Drug Consultant (Retired Narcotics Officer)

There is no way to crush five years of intensity into five minutes. I have lived and breathed GHB issues since June 1996 when I was first assigned to handle it for LAPD. Four young men collapsed; two literally died and were brought back by paramedics. I was stunned that hardly anyone knew anything about this drug, but one thing was clear------people were dying from GHB and it was being missed due to lack of ability to test for it and lack of knowledge that it even exists.

I'm not a doctor or a chemist. I realize research is important, but I'm sickened when reality is brushed off with "Oh well, that wasn't a clinical study" or "You can't PROVE it was GHB versus an analog." In some cases we can prove it; meanwhile, no federal agency has made any systematic effort to make such identification possible. I live in a real world of suffering people that can't be captured by clinical studies. I see both immediate disasters and long-term aftermath of GHB. I'll try to cover as much as I can because I feel an obligation to victims of GHB worldwide.

I have read the research. I've talked to hundreds of GHB users/dealers plus patients/doctors in the narcolepsy/cataplexy research. I've reviewed or consulted on hundreds of sexual assault cases where GHB has been identified as the weapon or where symptoms point to GHB. I've helped more than 300 GHB addicts, each of whom can name dozens more just like them and many with 3-5 impaired driving incidents in just a few months. They are in virtually every state of this country and several foreign countries. They aren't whom you would expect; they are businessmen, bodybuilders, airline employees, athletes, exotic dancers, bodybuilders, computer wizards and more bodybuilders. Most of them believed they were taking a safe workout or sleep aid, but then it took over their bodies and souls. I have worked closely with several dedicated doctors during the 17 months we have operated the GHB addiction helpline via www.projectghb.org (aka www.ashesonthesea.com/ghb). We have learned so much about GHB from these previously unrecognized and still typically undertreated addiction cases. I have seen the pain of the families/friends of GHB death victims, the horror of overdoses. My addicts have lost relationships, jobs, fortunes, suffered ongoing disabling injuries. Some lost their lives to GHB, whether by overdose, traffic accident or suicide. The suicidal depression associated with GHB withdrawal is stunning. I have GHB addiction/withdrawal related suicides and/or currently suicidal people from New Zealand to Sweden. I have some "MIAs" who probably did end their lives. Grieving parents have told me their stories; my office wall bears the pictures they have sent me. It has been a heartbreaking five years, mixed with the privilege of learning more and teaching others to recognize the rape, OD and death cases or getting rape victims into treatment or convincing youngsters not to try GHB. It has also been very lonely at times when agencies who should care don't.

DEA has reviewed and documented 71 deaths related to GHB, but stopped counting once the drug was controlled. No one at FDA has ever expressed interest in actively identifying these cases. My database includes about 200 GHB-related deaths now. Robert McCormick of the FDA's orphan drug unit told me emphatically that he did not care how many people had died or were addicted to GHB, as he intended to approve it anyway. Something is wrong with this picture. This is truly the most horrid drug I have encountered in 25 years as a police officer. Much new info has come to light during the past two years, none of it good. Around the world, countries are now just awakening to their problems with GHB, and restrictions on it are tightening. New Zealand tried it as a prescription drug and now realize it was wrong. France is backing away. NIDA is releasing $2 million in research about this drug. This is clearly NOT a time to be pushing it forward on unsuspecting American citizens.

You are here today to approve GHB (disguised as sodium oxybate) for use with narcolepsy/cataplexy. Orphan's investors have been assured (according to their message board posts) that you will approve it (FYI--news reports said that Orphan stock dropped 30 percent when you canceled the previous meeting). But doing so would contribute to the internet-generated belief that real GHB is safe and would simply lead to a rush for the "good stuff." You have not seen my video tapes of the day-to-day struggle of GHB addicts, clearly showing that GHB gives previously healthy people symptoms that can only be described as

narcolepsy/cataplexy. They are destroying themselves with it; wives are terrified of their husbands and often have no idea what is happening to them; many are being locked into psych wards instead of being treated because ERs and doctors don't recognize GHB psychotic episodes and withdrawal syndrome; and they are killing themselves/others behind the wheel. I often hear, "GHB (withdrawal) leaves a hole in your soul." Many are suffering long-term anxiety and depression, Parkinson-like shakes, etc. even 18 months after detoxing. There are no answers for them yet, so how can it be approved, letting it cause similar damage to others?

I am deeply concerned about the "off label use" policy that would enable any doctor to prescribe this drug 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, for example, a condition with vague symptoms for which a drug seeker could easily get a prescription. And, I know that doctors won't realize that Xyrem (sodium oxybate) is GHB. I called an FDA doctor who had written about the dangers of GHB, but another person had taken over GHB issues. The assistant passed the info I gave her to this person, who then called and said that I must be nuts. She had looked on FDA's orphan drug list and didn't find GHB. And, she checked the Orphan website and found that they weren't researching GHB either. She clearly proved my point-----If an FDA employee assigned to know all about GHB can't figure it what sodium oxybate is, the vast majority of doctors around the country would not realize it was GHB! I see no significant talk on the legitimate narcolepsy websites about this impending new drug, but message boards where GHB addicts hang out are buzzing about it. In fact, one of the key figures in illegal GHB internet sales is behind the original posted website www.xyrem.com!

There is very little drug diversion enforcement in the US. Only a handful of agencies devote one iota of time to the diversion of prescription medications to abuse. It is a very small portion of DEA effort. Most state narcotics agencies are too busy with meth, cocaine, heroin, etc., to have anyone assigned to diversion. State pharmacy and medical boards aren't staffed adequately. A doctor, for example, testified before the California Legislature that he was illegally prescribing GHB to his narcolepsy patients (being illegally imported from Europe by a compounding pharmacy) and was untouched because no one had time to follow up. He has a narcolepsy practice and puts out a radical narcolepsy newsletter (which openly attacks the FDA and doesn't identify a publisher), and will undoubtedly be included on Orphan's list of approved doctors. Therefore, Orphan's proposed voluntary (keyword: voluntary) promises of careful controls are frightening. They are designed to put at ease those precious limited resources devoted to drug diversion so that no one will worry about taking time to look at them. And, there are no real penalties associated with failure to abide by their voluntary conditions! The drug can be taken off the market, but how long would that take? The FDA is a huge, cumbersome bureaucracy that has been incredibly slow in dealing with this drug. It took a legislative subcommittee on oversight to demand a scheduling report from FDA in response to DEA's proposal!

Orphan representatives and others have claimed that Xyrem will be too expensive for addicts. But that contradicts the facts. GHB addicts pay up to $100 per day or more for a 2 oz bottle that may be near 100 percent or a 32 oz bottle that may be watered down to even as little as 5 percent. GHB addicts often find themselves with all their credit cards maxed out by their GHB purchases (up to $30,000 in a year). GHB addicts will be diagnosed as narcoleptic/cataplectic because they essentially become that! A number reportedly have done so. I was once personally misdiagnosed as having narcolepsy once when in fact I merely had Epstein Barre virus.

More importantly, once in possession of that prescription and a bottle of Xyrem, the addict will be "home free." There is no "field test kit" for GHB at this time. Thus ALL investigations of GHB cases are difficult. Encountering a prescription (real or counterfeit) and Xyrem bottle, the officer would have absolutely no ability to determine if it contained the prescription product or had been refilled with street GHB or its analogs. NO POSSIBILITY at the street level. It would require elaborate circumstances (establishing a high level of "probable cause" to believe that the bottle contained something other than the legitimate product) to even think of justifying further lab testing. In an impaired driving case, it doesn't matter (in states with thorough DUI laws) since impairment is the issue, not illicit versus licit drugs. In terms of possession cases, few if any agencies will have or be willing to expend the resources to do a detailed analysis (assuming it's even possible to tell the difference). At this moment GHB rape cases go

undetected and/or unprosecuted due to lack of training and testing capabilities. Agencies dread investigating possession cases because of the lack of a test kit. They dread sales cases because of the complexity of analog issues and deceptive practices being used (hiding it as weight belt cleaner, plant food, ink jet cartridge cleaner, etc.). Few agencies are equipped to handle internet sales cases because of the deceptive practices and the difficulty in physically "finding" the internet companies.

To those who claim that "real" GHB is safe and that only the street stuff is dangerous, I say "poppycock." Addicts have used everything from European pharmaceutical grade GHB, carefully manufactured GHB to horribly tainted products, plus varying quality GBL, BD and a third analog. For every one of them who swears that he was "OK" when taking GHB but got in trouble when he took GBL (or BD), there is one who says the opposite. Besides, no matter which one you take, you urinate out GHB. Yes, there have been cases where the medical problems involved high pH (drain cleaner) product or contamination by other toxic solvents; these are rather obvious. The vast majority of incidents are clearly consistent with GHB-related problems. Let's stop ignoring reality.

The unprecedented split scheduling of GHB was an unwise decision, clearly impossible to enforce. Those of us involved in the federal legislation were forced to accept what we knew was an insane compromise or face no scheduling of the drug at all. I know because I flew to Washington, D.C., at my own expense for the privilege of attending a small, by-invitation-only meeting. There were no doctors or scientists, just two Legislators with differing legislation on the issue, a few of their staffers, and a PR representative from Orphan Medical, a representative from the Rare Disease Foundation and me. The agenda was clear. GHB would be Schedule III (second legislation introduced), with Orphan Medical offering their first draft of "voluntary controls," and the previously submitted Schedule I legislation would be killed. Undaunted by what I felt was an intimidation effort, I—and others-- fought like hell for Schedule I behind the scenes anyway and ended up with the split compromise. It was no small political victory just to bring it up to that.

It has been frustrating to watch a drug company dictating to various states how to word their legislation on GHB to meet the drug company's demands and in general calling all the shots. This hasn't been about science or medicine, but about politics. It has indeed been a slick PR operation by a company that clearly has inappropriate political clout (as even commented on by their own investors on their finance message board!) and that has played on the hopes of those with narcolepsy/cataplexy in their drive to make big bucks from a drug of devastation. I have never before seen drug companies openly paying people at forensic conferences to attend their presentations ($175 per person). Inexplicable amounts of money have been spent to "PR" this drug.

Meanwhile, I have lost all respect for one of the current narcolepsy trials doctors, who volunteered his concerns about this drug to me and then, two years later, recanted all of his statements suddenly, after I brought that info into the open. I must assume that his reversal was at the company's request. I have my doubts that narcolepsy/cataplexy trials are as successful and promising as we have been lead to believe. I do feel that those with narcolepsy/cataplexy need a longer-acting, safer "cousin," not GHB; an opinion also expressed by Dr. Mortimer Mamelak on prior occasions.

I can't stand by quietly and let this travesty occur. In my opinion, this would be the biggest mistake ever made by the FDA and the drug would have to be taken off the market in the near future but it won't be soon enough. The now known tragedies and the massive "unknowns" about GHB truly outweigh potential benefits. Please read the "viewers comments" section at www.projectghb.org and vote against approval of this drug at this time.

Testimony of the National Sleep Foundation

Presented to the

Peripheral and Central Nervous System Drugs Advisory Committee

Of the

U.S. Food and Drug Administration

June 6, 2001

By

Richard L. Gelula, MSW
Executive Director
National Sleep Foundation

Disclosure

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Finally, from a financial perspective, the Foundation has operated conservatively and has had budget surpluses for each of the past five years. Support from Orphan Medical did not contribute materially to NSF's maintenance or development. The absence of their contributions would not have differentially affected the Foundation's programs or its functioning.

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The National Sleep Foundation has been an advocate for people with narcolepsy for some time. In 1998, upon recommendation of its Research Committee, then chaired by Thomas Roth, Ph.D., editor of the journal Sleep, the NSF Board approved a comprehensive program titled, "Toward the Cause of Narcolepsy." This program has provided grant funding that supported the breakthrough research at Stanford University, which in 2000 led to the discovery of the canine narcolepsy gene and the subsequent finding that the recently discovered hypocretin peptide is almost or entirely missing in people with narcolepsy. Since 1996, NSF has also invested in another approach to the discovery of the pathophysiology of narcolepsy, the establishment of the National Narcolepsy Registry, a serum DNA and family history registry for narcoleptics and their family members. The National Narcolepsy Registry is housed at and managed by the Montefiore Medical Center in New York City and currently has registered nearly 700 patients and family members. The NNR has been a research resource in seven narcolepsy studies. This initiative was funded by private (non-corporate) donations and by NSF's general operating fund.

Through our Pickwick Post-doctoral Research Fellowship program, NSF is also now funding a two-year study at UCLA on the neurochemical control of muscle tone in sleep and cataplexy.

Additionally, NSF has also provided a significant number of resources to professional and public education about narcolepsy and cataplexy. Given the small number of people directly affected by narcolepsy and the debilitating character of the disease, these contributions to education have been important. We publish brochures about the disease and distribute them at public, patient and medical meetings, through sleep centers across the U.S., upon written request, and we also place them on our Web site, www.sleepfoundation.org. We provide a lot of coverage about narcolepsy in our quarterly news magazine, **sleep***matters*. And over the years, we have devoted a significant number of issues of *Sleep Medicine Alert* to issues related to narcolepsy and cataplexy. Our professional outreach includes attendance and exhibits at such meetings as those held by the Associated Professional Sleep Societies, American College of Physicians/American College of Internal Medicine, American Academy of Neurology, American Psychiatric Association, Academy of Family Practice, and others.

Finally, based on a perspective grounded in patient interests, NSF, under the leadership of its Government Affairs Chair, Dr. William C. Dement, took an active role in advocating against legislation that would have assigned Gamma Hydroxybutyrate (GHB) a Schedule I classification under the Controlled Substances Act, which would have jeopardized further investigation of its therapeutic benefits; and NSF supported the final bill authorizing bifurcated scheduling for this medication. Our advocacy activity was primarily carried out through NSF volunteers and its Advocacy Network, and to a limited degree by NSF's general operating fund.

Summary of NSF's Position on Sodium Oxybate

The National Sleep Foundation calls upon the Peripheral and Central Nervous System Drugs Advisory Committee 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. The National Sleep Foundation does not presume to second-guess the evidence that has been submitted about the safety and efficacy of this drug, but goes on record to say that such considerations should only pertain to affected patients and not other societal considerations: if safe and effective for people with narcolepsy, sodium oxybate should be made readily available to them; any concern for illicit use should be addressed 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, should 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 stabilize patients who usually first experience the dreadful effects of narcolepsy and cataplexy during their developmental years before the completion of education and development of a career.

Background and Key Issues

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 existence for almost all other humans – the alternating cycle of sleep and alertness – into something entirely different, an uncontrolled and 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.

Just imagine what it would be like to have a life where the predictability of alertness cannot be counted on, where you felt such overwhelming sleepiness during the day that you could not stay awake to read texts, listen to lectures, or have the simple pleasure of

going out with a friend or watching a movie, where the experience of extreme emotion, the most human of attributes, such as laughter, anger or surprise, must be guarded against to prevent the loss of control, collapse and embarrassment that comes with a cataplectic attack, where despite all of the sleepiness, you do not even get a good night's sleep and awaken unrefreshed, and where available treatments often are inappropriate and leave you jittery or with other adverse side-effects. And these are only some of the effects of untreated or inadequately treated narcolepsy.

My guess is that if this disease occurred to me or during the development of any person who is here today in a professional capacity, that the AFFLICTION of narcolepsy would have proved to be a sufficient barrier that none of us would have been able to compete at a level necessary to keep up with our unaffected peers or to complete educational and career development at a professional level -- such that, in fact, none of us would be here today.

With this AFFLICTION we are not just talking about "sleepiness," an annoyance, but a condition where no amount of sleep or behavioral intervention provides sustained relief.

And the debilitating characteristics of narcolepsy are compounded by the fact that it is a low prevalence, orphan disease and that its onset most often occurs in the second decade of life when psychological and emotional development is unfinished and when people have not yet completed their education or established a career. It should also be recognized that:

Narcolepsy is not well understood or accepted – this applies to individuals suffering from this affliction as well as their families, schools and universities, employers and including personnel such as teachers, counselors and physicians, as well as peers, classmates and co-workers – in other words, the patient's entire world!

People suffer a double blow because it is thought their sleepiness is volitional and a sign of laziness – a stigma that has a troubling personal effect.

Primary care physicians are not familiar with its signs or symptoms and are unlikely to ask the kinds of questions or order tests that would speed an accurate diagnosis. One report states that it takes narcoleptics 15 years and visits to five different physicians to obtain an accurate diagnosis and in his text on Sleep Medicine, the late neurologist Michael Aldrich states that in his practice, he saw five narcoleptic patients in their 70's who had never been accurately diagnosed with the disease.

People who suffer from narcolepsy usually suffer alone, without support and are confused about their own symptoms. Their numbers are insufficient to ensure the availability of support groups in most locations.

Most people with narcolepsy do NOT have a relative with the disease, thus, even within their family context, the disease is strange and unfamiliar.

Thus, it should come as no surprise that people with narcolepsy suffer from a high rate of depression (Aldrich, 1999; Daniels, E., et.al, 2001) and research has shown that people with narcolepsy have a health-related quality of life rating as bad or worse than persons with Parkinson's disease, epilepsy or suffering from chronic migraine headache (Beusterien, et.al, 1999). Worse is that a rating by health professionals found that they desired greater social distance from narcoleptics than a number of conditions that one might expect a higher ranking such as epileptics and colostomy patients (Cohen & Mudro, 1992).

But the good news is that one study on health-related quality of life found that appropriate medical treatment does improve the HQL for people with narcolepsy (Beusterien, et.al, 1999). At this time, there are no pharmacological treatments indicated for cataplexy and those used off-label such as tricyclic antidepressants have significant quality of life side-effects including suppression of libido.

The National Sleep Foundation believe that narcolepsy exacts an unusual and cruel toll on those who suffer from this AFFLICTION and that this is a patient population greatly in need of medications that would control their symptoms. Such medications would foster more timely and appropriate diagnosis and treatment and would restore a good measure of the confidence and capability otherwise impaired by this cruel disease. I think of my own teenage child and I know that if she developed narcolepsy, I would want her to have access to any medication that might control her symptoms regardless of its effects on other members of society. We ask this panel to do all that it can to help people with narcolepsy and to consider the safety and efficacy of this drug as it applies to patients suffering from this disease.

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Testimony of the National Sleep Foundation

Presented to the

Peripheral and Central Nervous System Drugs Advisory Committee

Of the

U.S. Food and Drug Administration

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###

Memorandum

DATE: May 31, 2001

TO: *Sandra Titus*

FROM: *Matt Speakman*

RE: FDA public advisory committee meeting

CC: [*Patty Engel, Orphan Medical*]

Sandra:

As a narcolepsy patient successfully treated with XYREM, the drug which is to be discussed at the upcoming public advisory meeting, I would like to be alotted no more than 5 minutes to make the following statement.

Six years ago, as I entered my senior year of high school, my grades were slipping, my attitude was negative (to say the least), and my efforts to receive an appointment to the United States Naval Academy were useless.

I had recently been diagnosed with the condition called narcolepsy, a sleep disorder that effects the brain and causes severe daytime sleepiness and cataplexy, a sudden and nearly complete loss of muscular control.

I quickly learned that narcolepsy is a very rare disorder, about which little is known, and for which there are few effective treatments. I spent my remaining year of high school sleeping through class (averaging about 16 to 18 hours of sleep a day), angering my teachers (who suspected drug abuse), and in a generally foul disposition which affected my friendships, relationships, family life, and academic efforts.

I struggled to make it through my first year of college at the University of Kentucky, finding it difficult to awake for classes on time, and to meet friends who would understand the strange behavior patterns that result from "passing out" every few hours.

Determined to find some way to better my condition, my mother searched to find a specialist who dealt with cases such as mine. She found such a specialist in nearby Cincinatti who promised a "wonder drug" and that my life would undoubtedly change for the better.

I was skeptical. I had dealt emotionally with my disorder and had come to a realization that I would live this way for the rest of my life. I had little hope for success in the future, as I wondered what kind of employer would hire such a person.

After my first week of trial medication of GHB, which is now called XYREM, I can not fully explain to you the changes that occurred. Instead of desperately trying to stay awake during the day, I was functioning at nearly 100%. Instead of fighting restlessly at night to maintain a constant sleep, I rested deeply and soundly. The cataplectic attacks (the real monster of narcolepsy) ceased almost completely. Over the past 4 years of using XYREM I have had 4 cataplectic episodes (and only because I failed to take the medication while pulling all-night study sessions). This number is reduced from the 6 to 8 cataplectic episodes a WEEK that I experienced before treatment.

Two weeks ago, I graduated from West Virginia University (cum laude) with a Fine Art degree in graphic design. This week I will send resume's and portfolio all over the country. My ambition and energy (characteristics for which I have always been known) are restored along with my confidence of success in the future. I have built strong friendships and relationships. I have established professional contacts and experience within the field of graphic design.

THE MESSAGE: None of this would be possible without effective treatment for my sleep disorder. My experience with XYREM has been without side effects. YES, without side effects (unless you consider happiness, hope, and confidence to be side effects). I understand and agree with concerns regarding the abuse and misuse of GHB...or any drug for that matter. That is why I ask for a solution to this matter to be resolved as quickly as possible. There are thousands of other narcoleptics who need this treatment, and there are thousands of victims from abuse and misuse of this drug. Please approve the medication for those who need it, regulate it appropriately, and penalize those who abuse it.

Thank you.

-Matt Speakman

724.413.7778

National Association of Drug Diversion Investigators, Inc.
P. O. Box 42015 • Baltimore, MD 21284-2015

Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration

Established in 1987, the National Association of Drug Diversion Investigators (NADDI), 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's principal activities comprise:
(1) Cooperative education and training in the specifics of pharmaceutical drug diversion, investigation and prevention;
(2) The sharing of investigative information and communication with a wide variety of interested parties with regard to the nature, scope and impact of pharmaceutical drug diversion, and;
(3) The development of stronger effective measures to combat the problem.

NADDI supports the safety and efficacy of the new drug application (NDA) 21-196, XYREM® (sodium oxybate), proposed to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness for persons with narcolepsy.

NADDI is aware that in many reported cases, use of GHB has changed from homemade GHB to ingesting of industrial chemicals that convert to GHB in the body. There are no known cases which involve 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.

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 for consideration of this written submission. I would also be willing to provide oral submission of behalf of the organization.

Sincerely,

Charles F. Cichon
President

MICHAEL'S MESSAGE FOUNDATION, INC

My name is Debbie Alumbaugh. 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 or (Gamma Hydroxybutyrate) Toxicity.

Michael was a sophomore at Westwood High School in Ft. Pierce, Fl. He was a black belt in karate, and was also an instructor. He had won several academic awards for reading, music, mathematics and spelling. He was on the honor roll.

On October 1, 1998, Michael came home from school, and asked if he could go to the show with some friends, this was unusual for a school night, as we usually did not allow him out during the school week. We also required Michael to bring home a weekly progress report. That evening, he had brought it home and was doing well making A's & B's. Before he left, a friend came to the house; they went directly to Michael's room. His friend was only in our home for 5 minutes. This is when Michael was given the GHB.

We found out 18 months after Michael died, that when they left our home for the movie, they stopped at the local park to shoot some hoops. Michael had the ball and went for a lay-up and when he came down, he passed out. He lay there unconscious for several minutes. This should have been a red flag to his friends that something was wrong. They giggled and laughed and scooped my son up and put him in the car and onto the movie they went. We understand that Michael didn't see the first five minutes of the movie, he passed out again. When they returned home from the show, Michael's father looked at our son and asked "Are you on something son? Did you take something?" He replied no dad. After continuous questioning, he finally admitted that they had smoked some pot. Brad decided not to lecture Michael this late, he would talk to him tomorrow. Brad never got that chance.

P. O. Box 690453 Vero Beach, Florida 32969
561/464-7612

Michael died that night; in his safest place of all places, alone in his bed.

The next morning Brad went to wake Michael for school. He could hear Michael's alarm blaring. Michael did have intentions of getting up. When he opened the door, he knew our son was dead. He thought his head was going to explode, thought he was going to have a heart attack. Brad's instinct was to close our son's door and run from the house. The scene was horrendous. Our son was on his back, eyes wide open, glassy. His mouth hung open, his tongue so swollen, his father couldn't close his mouth. He had dried vomit running down his chin into a puddle in his collarbone. His hands were in a clawed position, where he had tried to roll himself over but couldn't, because the drug had paralyzed him and taken away his gag reflexes. Because we didn't know why our son had died, there had to be an autopsy. It took twelve weeks for us to learn why our son had died none of his friends would come forward. **GHB** leaves the body very quickly. They took our sons brain; that is where they found this drug. There is no antidote for **GHB** Overdose.

In the last three years, we have lost 174 young people to these designer drugs in Florida alone. That is 173 tragedies just like ours.

After several months, Michael came to his father in a dream. He said "Dad it is wrong to destroy the body the way I did. I need you and Mother to tell my friends, my generation; my story, our tragedy." "You don't have a clue about the drugs they are faced with daily. This put a burden on Michael's father and I until one day we gathered up enough courage and strength to make the first call.

I tell the students what took our sons life, and then tell them a little about Michael. I tell them he was not only a great son, but also a loving son. June 1st, Michael would have celebrated his 18th birthday, and enjoyed the pleasure of graduating on that same day. We missed prom and graduation because of this deadly drug. Since our son's death, our family has not been able to have any celebrations.

We are here to have our voices heard. This is a dangerous and deadly drug. It has taken many lives; not only in death, but in addiction also. Addiction to GHB is as serious as dying from it. What kind of life can there be when you have to have this drug every 2 hours, and without it you go into withdrawal. Detoxification from GHB is very difficult. It cannot be done in 3-5 day period. There must be professional help that knows what to do to save your life. We have devoted our lives to this. We have chosen to take our tragedy and educate our nation. We have turned our grief into

something positive and constructive.

We travel to schools from 6th grade to 12th, and on into college sharing our son's story. Our goal is to take Michael's Message Nationwide; in the hopes of saving another family the heartache and devastation this drug has caused our family. We have shared our message with just over 35,000 students in our first year. Our children are our future. Students inform us after hearing our story that they didn't know, they thought it was safe. That's what the Internet says. They tell us with tears streaming down their faces, that they worry about friends who are taking GHB. We feel that parents and grandparents should hear Michael's Message also. Because it is a relatively new drug, most parents are unaware that it even exists. They must be educated to the signs and symptoms of GHB use and abuse. Education plays a key role, not only informing the kids that it is wrong, but death is a consequence of this activity. Michael's voice must be heard.

I am here today, with the hope that GHB will not be made available legally.

P. O. Box 690453 Vero Beach, Florida 32969
561/464-7612

Attention: Sandra Titus
FDA Center for Drug Evaluation and Research (HFD-1)
Peripheral and Central Nervous System Advisory Committee
5600 Fishers Lane
Rockville MD 20857
NDA 21-196, Xyrem (sodium oxybate, Orphan Medical Inc.)

Presenter: Brian A. Hunter
Young Adults With Narcolepsy – YAWN

Dear Sandra:

I am requesting time to make a formal oral presentation on my views regarding the NDA 21-196 application being held before the Peripheral and Central Nervous System Advisory Committee meeting on June 6, 2001. I will require approximately four (4) minutes to present my views for consideration by the committee concerning risk management issues pertaining to the safety and efficacy of Xyrem (sodium oxybate, Orphan Medical Inc.) I have attached my intended comments for your review.

Young Adults With Narcolepsy, YAWN is an online organization working to support, advocate, and advance public awareness of narcolepsy, on behalf of young adults their families, peers, coworkers, employers, teachers, and others whose lives are affect by this often debilitating sleep disorder. By working at the grassroots level, YAWN is able to make an immediate impact on the lives of our younger generation by coordinating local support groups, involving other non-profit services in providing access to rehabilitative services and social service agencies and by educating teaching professionals from junior high school counselors to University professors.

Thank you for your kind consideration of this request.

Sincerely,

Brian A. Hunter
Director
Young Adults With Narcolepsy – YAWN
3209 Dupont Avenue South
Minneaplis, MN 55408
huntoo38@tc.umn.edu
612-396-9268

I feel it is important to preface my comments today by disclosing that my organization, Young Adults with Narcolepsy (YAWN) has received a $5000 grant from Orphan Medical to underwrite the developmental expenses for our website and have provided a scholarship for my travel and accommodations to attend this meeting.

As founder of YAWN, the first online youth-focused patient support and advocacy organization, and a person with narcolepsy and cataplexy, I believe that 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 a large number of young adults with narcolepsy who have, or would like to have, participated in clinical trials for Xyrem, I am compelled to present my views on risk management issues pertaining to the safety and efficacy of Xyrem (sodium oxybate, Orphan Medical Inc.).

YAWN works to support, advocate, and advance public awareness of narcolepsy on behalf of young adults, their families, employers, teachers, and others whose lives are affected by this often-debilitating sleep disorder. By working at the grassroots level, YAWN is able to make an immediate impact on the lives of these young adults by coordinating local support groups and involving other nonprofit services in providing access to rehabilitative services and social service agencies.

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 social, interpersonal, and educational development of these young adults at a critical point in their development. It has been well documented that the cataplexy and excessive sleepiness of narcolepsy has multiple effects on these individuals and their families. This disease has a significant negative impact on education, interpersonal relationships, gainful employment, motivation, and marital life. I submit that the risk for experiencing the negative impact of untreated cataplexy on the potential of 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% young adults with narcolepsy who suffer with cataplexy. Other therapies including tricyclic antidepressants such as Prozac are only minimally effective in controlling symptoms of cataplexy in this patient population. Xyrem has been shown to be an effective therapy in limiting the cataplexy episodes that result from sudden surges of emotion, including surprise, anger and happiness.

We must recognize the consequences of failing to approve Xyrem to treat the 1:1000 people suffering with narcolepsy, an incidence equal to multiple sclerosis. For example, three months after founding YAWN, I was contacted by the parents of a sixteen-year-old boy living in a small town three hours away from the nearest city. This young man was bright, did well in school, and was active in his community until his twelfth 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 is forced to spend five days a week in a nursing home. What are the costs of providing nursing home care in a public institution for a sixteen-year-old for the next 60-70 years? By not adequately controlling his cataplexy, what are his chances for becoming a contributing member of society?

Unfortunately, this young 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, doesn't have to be the case. In fact, a brighter future has been achieved by the lucky few who have participated in GHB clinical trials. They have become success stories. To these young adults with narcolepsy, GHB 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, by earning their PhDs, by becoming successful artists, entrepreneurs, lawyers, teachers, doctors, politicians, Olympic athletes, or simply by being good parents.

These and the thousands of other talented and capable young adults who have not yet had a chance to fulfill their dreams are the reason I formed YAWN and why I am here testifying before you today. It is my responsibility to protect their right to pursue a happy and productive life by having access to medications that will effectively treat their disease. 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.

Thank you for allowing me to present these remarks to you today. I urge you to approve the NDA 21-196 for Xyrem. There are lives at stake.

Statement Regarding GHB (Xyrem) Approval

Joe Spillane, Pharm.D., ABAT
June 2001

My name is Joe Spillane. I am a pharmacist and a clinical toxicologist. I work as an associate professor at Nova Southeastern University College of Pharmacy and as a clinical coordinator at Broward General Medical Center in Fort Lauderdale, Florida. I also serve on the Broward County Commission on Substance Abuse and coauthor a twice-annual report on substance abuse trends in Broward County, Florida. I am not representing any organization and I have had no affiliation with Orphan Medical. I would like to voice some reservations that I have to the approval and scheduling of gamma hydroxybutyrate GHB (Xyrem) , but I would first like to mention the basis for my concerns.

I'd like to underscore the immense and rapidly growing popularity, highly addictive nature, and lethality of GHB and its precursors.

Overdoses & Drug Rape

In our emergency department alone, which treats approximately 70,000 patients per year, we had 48 GHB or GHB precursor overdoses in 1999. That number rose by approximately 60% to 77 cases in 2000. Most of these patients are brought in by rescue because of decreased level of responsiveness. All require monitoring and many require airway management including intubation and ventilation. Vomiting is particularly common with the abuse of this drug, which can have the potentially fatal consequence of aspiration in an individual with central nervous system depression. Most of our GHB abusers were young people (average age of 26.3yrs old) who were using the drug recreationally often while coingesting alcohol, ecstasy, cocaine, and/or marijuana.

We have had numerous patients say that someone must have given this drug to them without their knowledge, perhaps to facilitate robbery or sexual assault. There have been educational campaigns instructing people not to accept a drink from anyone but the bartender. However, we treated one of the local bartenders for GHB overdose recently who claimed that many of those employed in the local beverage industry are also using GHB and/or its precursors.

Withdrawal

We have treated 5 known cases of GHB or GHB precursor withdrawal in our facility. The sudden cessation of this drug results in physical withdrawal which is prolonged, impressive to observe, and very difficult to treat. Clinical manifestations of withdrawal have included tachycardia, sleeplessness, severe agitation, tremulousness, and hallucinations. Two of these patients experienced two separate withdrawal episodes. I submit that there are probably numerous other withdrawal cases at our institution and throughout the country that go unrecognized and are treated as psychosis.

Withdrawal is extremely difficult to treat and the long-term effects of multiple withdrawal episodes remains unclear.

Deaths

From 1996 through December 31, 2000, there have been nine fatalities in Broward County (a county of 1.6 million people) where GHB was considered one of the proximate causes of death. In most cases the drug was being used recreationally, in combination with alcohol and/or other central nervous system depressants. However, in July of 2000, a 25-yr. old white male was doing "capfuls of GHB all night long". Some friends left him briefly to rent a movie, and found him dead upon their return. On autopsy, his GHB level was very high, his alcohol level was zero, and no other drug was detected.

This is an important case to refute the common misperception that the drug is not lethal unless taken with other CNS depressants such as alcohol, and that the only treatment necessary for GHB toxicity alone is to "sleep it off".

Concerns

It is because of this experience in South Florida that I feel compelled to voice concerns over the scheduling and the proposed distribution system of Xyrem.

First, it is concerning to me that the entire system of distribution is voluntary and that there appears to be very little governmental/regulatory oversight. The proposed distribution system as I understand it, appears to be a fairly closed system where one pharmacy would store the drug and would be responsible for mailing the drug directly to customers. An exception to this would be made if third party payors insisted on the drug being sent to a pharmacy for dispensing. It certainly appears that the system is flexible and accommodating when profit margins might be affected. This is concerning because of the voluntary nature of the system and the understandable commitment of the company to maximize profits for their shareholders.

I also have concerns with the voluntary and proprietary nature of the data on GHB sales and distribution/diversion. Are there any guarantees of the availability of that data to governmental agencies? Again, it appears that all of this hinges upon voluntary action on the part of Orphan and the specialty pharmacy. What happens when the financial interests of the company conflict with the voluntary collection/submission of this information or indeed with the continuation of this closed loop system?

Given the addictive potential of this drug, I wonder what will happen to the patient who can no longer afford the medication or when the patient's insurance no longer covers this medication. What provisions would be made in these instances? What resources are available to treat the withdrawal? How will Orphan participate/contribute to those resources?

I think the potential for accidental pediatric poisoning should be addressed (and possibly already has been). This is a potentially lethal anesthetic/respiratory depressant that may be in a readily accessible container at a patient's bedside while they sleep.

Finally, deep and careful consideration should be given to the future impact of this "bifurcated scheduling" not just for GHB but for future medications. Couldn't any future manufacturer of an addictive/ or potentially abused medication claim that they designed a revolutionary system for distribution? Couldn't they then suggest it be made a schedule III or IV when used for "legitimate medical purposes" and schedule I when diverted? There would certainly be financial incentive on the part of the manufacturer to improve accessibility and cut the costs and potential obstacles of government regulation and oversight by doing so. Any future company could look confidently to the Xyrem decision as an applicable precedent.

Summary

In summary, I wanted to underscore the increasing abuse of GHB and its precursors, its use to facilitate sexual assault and robbery, its highly lethal and addictive properties, and its propensity to precipitate physical withdrawal. I strongly suggest that it would not be prudent to rely on a voluntarily closed system with very little regulation, very little oversight, and no guaranteed access to data to prevent its diversion. Further, the proposed bifurcated scheduling, while economically appealing to the manufacturer, is fraught with potential problems which could lead to increased diversion of GHB and a dangerous precedent for the future. I commend Orphan for their ingenuity and creativity, and for their commitment to bringing this medication to those who could benefit from it. Stricter control, with additional oversight, and verification would certainly enhance the possibility of attaining another one of Orphan's stated goals of reducing abuse and diversion. Thank you for a chance to participate in this important process.

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JS 44 (Rev. 09/11)

CIVIL COVER SHEET

The JS 44 civil coversheet 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 NEXT PAGE OF THIS 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) Attorneys *(Firm Name, Address, Telephone Number, and Email Address)*
Charles M. Lizza, Esq., Saul Ewing LLP, One Riverfront Plaza, Newark, New Jersey 07102-5426, (973) 286-6700, clizza@saul.com

DEFENDANTS
Par Pharmaceutical, Inc.

County of Residence of First Listed Defendant Bergen, NJ
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF 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) (For Diversity Cases Only) and One Box for Defendant)*

	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
- ❒ 362 Personal Injury - Med. Malpractice

PERSONAL INJURY
- ❒ 365 Personal Injury - Product Liability
- ❒ 367 Health Care/ Pharmaceutical 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
- ❒ 440 Other Civil Rights
- ❒ 441 Voting
- ❒ 442 Employment
- ❒ 443 Housing/ Accommodations
- ❒ 445 Amer. w/Disabilities - Employment
- ❒ 446 Amer. w/Disabilities - Other
- ❒ 448 Education

PRISONER PETITIONS
- ❒ 510 Motions to Vacate Sentence

Habeas Corpus:
- ❒ 530 General
- ❒ 535 Death Penalty
- ❒ 540 Mandamus & Other
- ❒ 550 Civil Rights
- ❒ 555 Prison Condition
- ❒ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ❒ 625 Drug Related Seizure of Property 21 USC 881
- ❒ 690 Other

LABOR
- ❒ 710 Fair Labor Standards Act
- ❒ 720 Labor/Mgmt. Relations
- ❒ 740 Railway Labor Act
- ❒ 751 Family and Medical Leave Act
- ❒ 790 Other Labor Litigation
- ❒ 791 Empl. Ret. Inc. Security Act

IMMIGRATION
- ❒ 462 Naturalization Application
- ❒ 463 Habeas Corpus - Alien Detainee (Prisoner Petition)
- ❒ 465 Other Immigration Actions

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
- ❒ 375 False Claims Act
- ❒ 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
- ❒ 850 Securities/Commodities/ Exchange
- ❒ 890 Other Statutory Actions
- ❒ 891 Agricultural Acts
- ❒ 893 Environmental Matters
- ❒ 895 Freedom of Information Act
- ❒ 896 Arbitration
- ❒ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ❒ 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

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 10-6108 & 13-391

DATE 12/27/2013 SIGNATURE OF ATTORNEY OF RECORD

FOR OFFICE USE ONLY

RECEIPT # AMOUNT APPLYING IFP JUDGE MAG. JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC.,	)	
Plaintiff,	)	
v.	)	Civil Action No. 2:13-cv-00391-ES-SCM
	)	(consolidated)
AMNEAL PHARMACEUTICALS, LLC	)	
Defendant.	)	

DEFENDANT AMNEAL PHARMACEUTICALS, LLC'S PRELIMINARY INVALIDITY CONTENTIONS

Pursuant to L. Pat. R. 3.6(d), defendant Amneal Pharmaceuticals, LLC ("Amneal") provides the following preliminary invalidity contentions as to 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"), 8,324,275 ("the '275 patent"), 8,457,988 ("the '988 patent"), and 8,461,203 ("the '203 patent") (collectively "the Patents-in-Suit"). Amneal expressly reserves its right to supplement, modify, or expand its invalidity contentions in accordance with the applicable Federal and Local Rules of Civil Procedure because fact discovery is ongoing, Amneal's invalidity contentions will be the subject of expert testimony, and there has been no claim construction order in this case to date. Amneal specifically reserves the right to supplement these contentions as discovery proceeds in this case, and based on any arguments that Plaintiffs may advance in this case. Amneal also reserves the right to rely on the co-defendants' invalidity contentions and any references cited therein.

Amneal's document production bearing production numbers AMNXYR_000000001-AMNXYR_000002151 and AMNXYR_000002287-AMNXYR_000008016 accompanying these contentions constitutes Amneal's document production pursuant to L. Pat. R. 3.6(d).

I. GENERAL CONSIDERATIONS

Amneal provides these contentions subject to the following objections and reservation of rights:

1. These contentions are based on information reasonably available to Amneal at this time. These contentions are necessarily preliminary and may require subsequent amendment, alteration or supplementation.

2. Amneal's contentions may be in the alternative and do not constitute any concession by Amneal for purposes of invalidity.

3. By submitting these contentions, Amneal does not waive any of its claims or defenses in this case.

4. These contentions should not be taken as an indication of Amneal's position with regard to the proper claim construction of any claim term. Instead, Amneal has made reasonable assumptions, to the extent necessary and appropriate, with respect to the meaning of claim terms for the purpose of these contentions only in the preparation of this statement. To the extent Amneal herein determines that a different meaning is appropriate for any claim term, it will assert that in connection with *Markman* procedures and proceedings, and reserves the right to update these contentions as a result of the *Markman* hearing, or any other subsequent clarification or alteration of the meaning of claim terms, and/or as otherwise authorized or permitted by the Rules of the District of New Jersey and the Federal Rules of Civil Procedure.

5. Amneal 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.

6. Amneal's distribution system has not been finalized. Amneal reserves the right to supplement its non-infringement contentions with respect to the '059 and '988 patents once its distribution program has been finalized.

7. Amneal reserves the right to amend, supplement and/or modify these contentions based on Plaintiff's allegations of infringement and validity.

8. Amneal reserves the right to amend, supplement, and/or modify these contentions based on other arguments Plaintiffs may advance in this case.

9. Amneal reserves the right to amend, supplement and/or modify these contentions based on any defense, claim, assertion, contention and/or claim construction raised by the other Defendant in Plaintiff's action involving the Patents-in-Suit. *See Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, 2:10-cv-06108-ES-SCM (consolidated) (D.N.J. Nov. 22, 2010).

10. 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, work product doctrine, common interest privilege, or joint defense privilege.

11. Provision of these contention statements does not prejudice or limit Amneal's rights to pursue discovery of any other defenses, including, but not limited to, other invalidity or non-infringement defenses.

12. These contentions are not set forth in any particular order and the order of presentation shall not be construed to limit Amneal's right to present all, more or none of these contentions at any hearing or trial in this matter.

13. In the contentions and charts that follow, the contentions and charts for any dependent claim also incorporate the contentions and charts for any claim from which the

dependent claim depends. This includes all prior-art and non-prior-art defenses regarding including but not limited to priority, § 101, anticipation, obviousness, and § 112.

14. Amneal reserves the right to raise any invalidity issue identified at any point in these contentions, whether they be raised in the charts, the narratives for each patent or the description of the prior art or cited in any portion of the prior art references discussed or listed herein or in the attached appendix or within the general knowledge and skill of the person of ordinary skill in the art.

II. PRIOR ART REFERENCES AND OTHER EVIDENCE

A. Listing of Prior Art and Other Evidence

Amneal identifies the following patent and printed publication prior art references, and other evidence, that alone, or when combined, render the claims of the patents invalid for failure to comply with the conditions and requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103, and 112:

1. U.S. Patent No. 6,472,431, issued on October 29, 2002, to Cook *et al.* ("the '431 patent") and its file history (AMNXYR_000006683-AMNXYR_000006719, and AMNXYR_000002391-AMNXYR_000002690)

2. U.S. Patent No. 6,780,889, issued on August 24, 2004, to Cook *et al.* ("the '889 patent") and its file history (AMNXYR_000006720-AMNXYR_000006756, and AMNXYR_000002691-AMNXYR_000002860)

3. U.S. Patent No. 7,262,219, issued on August 28, 2007, to Cook *et al.* ("the '219 patent") and its file history (AMNXYR_000006757-AMNXYR_000006799, and AMNXYR_000002861-AMNXYR_000003116)

4. U.S. Patent No. 7,851,506, issued December 14, 2010, to Cook *et al.* ("the '506 patent") and its file history (AMNXYR_000006879-AMNXYR_000006920, and AMNXYR_000004301-AMNXYR_000004949)

5. U.S. Patent No. 8,263,650, issued September 11, 2012, to Cook *et al.* ("the '650 patent") and its file history (AMNXYR_000006947-AMNXYR_000006986, and AMNXYR_000005148-AMNXYR_000005420)

6. U.S. Patent No. 8,324,275, issued December 4, 2012, to Cook *et al.* ("the '275 patent") and its file history (AMNXYR_000006987-AMNXYR_000007027, and AMNXYR_000005421-AMNXYR_000005770)

7. U.S. Patent No. 8,461,203, issued June 11, 2013, to Cook *et al.* ("the '203 patent") and its file history (AMNXYR_000007052-AMNXYR_000007092, and AMNXYR_000005950-AMNXYR_000006499)

8. Allsopp, M. R. and Zaiwalla, Z., Narcolepsy, *Archives of Disease in Childhood, The Journal of the British Pediatric Association.* 67(3): 302-306 (©1992) ("Allsopp") (AMNXYR_000007179-AMNXYR_000007185)

9. Bédard, Marc-André, *et al.*, Nocturnal γ-Hydroxybutyrate: Effect on Periodic Leg Movements and Sleep Organization of Narcoleptic Patients, *Clinical Neuropharmacology.* 12(1): 29-36 (©1989) ("Bédard") (AMNXYR_000007186-AMNXYR_000007194)

10. Broughton, R. and Mamelak, M., The Treatment of Narcolepsy-Cataplexy with Nocturnal Gamma-Hydroxybutyrate, *Canadian Journal of Neurological Sciences.* 6(1): 1-6 (©1979) ("Broughton") (AMNXYR_000007195-AMNXYR_000007201)

11. Defining Overweight and Obesity, Center for Disease Control and Prevention. (Apr. 09, 2013), http://www.cdc.gov/obesity/adult/defining.html ("CDC") (AMNXYR_000007205-AMNXYR_000007206)

12. Chokroverty, S., Sleep Apnea in Narcolepsy, *Sleep.* 9(1): 250-253 (©1986) ("Chokroverty") (AMNXYR_000007207-AMNXYR_000007212)

13. CRC Handbook of Chemistry and Physics, 71st Edition, p. 8-36 (©1990 by CRC Press, Inc.) ("the 1990 CRC Handbook") (AMNXYR_000007213-AMNXYR_000007215)

14. European Patent Application No. 0235408 A1, published September 9, 1987, to University of Toronto Innovations Foundation ("EP '408") (AMNXYR_000002353-AMNXYR_000002361)

15. European Patent Application No. 0616804 A1, published September 28, 1994, to Laboratorio Farmaceutico C.T. S.r.l. ("EP '804") (AMNXYR_000002362-AMNXYR_000002372)

16. European Patent Application No. 0635265 A1, published January 25, 1995, to Laboratorio Farmaceutico C.T. S.r.l. ("EP '265") (AMNXYR_000002373-AMNXYR_000002390)

17. Ferrara, S. D. *et al.*, Pharmacokinetics of γ-hydroxybutyric acid in alcohol dependent patients after single and repeated oral doses, *British Journal of Clinical*

Pharmacology. 34(3): 231-235 (©1992) ("Ferrara") (AMNXYR_000007216-AMNXYR_000007222)

18. Hoes, M.J.A.J.M. *et al.*, Gamma-hydroxybutyric acid (*) as a hypnotic, *L'Encéphale.* VI: 93-99 (©1980) ("Hoes") (AMNXYR_000007223-AMNXYR_000007230)

19. Laborit, H., "Gamma-Hydroxybutyrate, Succinic Semialdehyde and Sleep," *Progress in Neurobiology.* (©1973 by Pergamon Press Ltd.) ("Laborit") (AMNXYR_000007231-AMNXYR_000007251)

20. Lammers, G.J *et al.* Gammahydroxybutyrate and Narcolepsy: A Double-Blind Placebo-Controlled Study, *Sleep.* 16(3): 216-220 (©1993) ("Lammers") (AMNXYR_000007252-AMNXYR_000007258)

21. Lapierre, J. *et al.*, The Effect of Gamma-Hydroxybutyrate on Nocturnal and Diurnal Sleep of Normal Subjects: Further Considerations on REM Sleep-Triggering Mechanisms, *Sleep.* 13(1): 24-30 (©1990) ("Lapierre") (AMNXYR_000007259-AMNXYR_000007267)

22. Remington's Pharmaceutical Sciences, 19th Edition, 1995, pp. 239, 639, 640, 646, 1410, edited by Gennaro, A.R., Mack Publishing Company. ("Remington's") (AMNXYR_000007747-AMNXYR_000007757)

23. Mamelak, M. *et al.*, The Effects of γ-Hydroxybutyrate on Sleep, *Biological Psychiatry.* 12(2): 273-288 (©1977) ("Mamelak (1977)") (AMNXYR_000007268-AMNXYR_000007285)

24. Mamelak, M., Gammahydroxybutyrate: An Endogenous Regulator of Energy Metabolism, *Neuroscience and Biobehavioral Reviews.* 13(1): 187-198 (©1989) ("Mamelak (1989)") (AMNXYR_000007286-AMNXYR_000007299)

25. Nema, S. *et al.*, Excipients and Their Use in Injectable Products, *PDA Journal of Pharmaceutical Science and Technology.* 51(4): 166-171 (©1997) ("Nema") (AMNXYR_000007314-AMNXYR_000007321)

26. Palatini, P. *et al.*, Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers, *European Journal of Clinical Pharmacology.* 45(4): 353-356 (©1993) ("Palatini") (AMNXYR_000007331-AMNXYR_000007336)

27. Roth, R. H. and Giarman, N., γ-Butyrolactone and y-Hydroxybutyric Acid-I: Distribution and Metabolism, *Biochemical Pharmacology.* 15(8): 1333-1348 (©1966) ("Roth") (AMNXYR_000007758-AMNXYR_000007775)

28. Scharf, M.B. *et al.*, The Effects and Effectiveness of γ-Hydroxybutyrate in Patients with Narcolepsy, *The Journal of Clinical Psychiatry.* 46(6): 222-225 (©1985) ("Scharf") (AMNXYR_000007776-AMNXYR_000007780)

29. Scrima, L. *et al.*, "Gamma-Hydroxybutyrate Effects on Cataplexy and Sleep Attacks in Narcoleptics," *Sleep Research.* 16: 134 (©1987) ("Scrima (1987)") (AMNXYR_000007781-AMNXYR_000007783)

30. Scrima, L. *et al.*, Efficacy of Gamma-Hydroxybutyrate versus Placebo in Treating Narcolepsy-Cataplexy: Double-Blind Subjective Measures, *Biological Psychiatry.* 26(4): 331-343 (©1989) ("Scrima (1989)") (AMNXYR_000007784-AMNXYR_000007798)

31. Scrima, L. *et al.*, The Effects of γ-Hydroxybutyrate on the Sleep of Narcolepsy Patients: A Double-Blind Study, *Sleep.* 13(6): 479-490 (©1990) ("Scrima (1990)") (AMNXYR_000007799-AMNXYR_000007812)

32. Sériès, F. *et al.,* Effects of Enhancing Slow-Wave Sleep by Gamma-Hydroxybutyrate on Obstructive Sleep Apnea, *American Review of Respiratory Disease.* 145(6): 1378-1383 (©1992) ("Sériès") (AMNXYR_000007813-AMNXYR_000007820)

33. Sours, J.A., Narcolepsy and Other Disturbances in the Sleep-Waking Rhythm: A Study of 115 Cases with Review of the Literature, *Journal of Nervous & Mental Disease.* 137: 525 -542 (©1963) ("Sours") (AMNXYR_000007821-AMNXYR_000007838)

34. Chemical Abstract ES30233864 ("CA 338") (AMNXYR_000007202-AMNXYR_000007204)

35. *The United States Pharmacopeia and National Formulary (USP 23-NF 18). Rockville, MD: United State Pharmacopeia Convention; 1995: 2205* ("The 1995 USP") (AMNXYR_000007851-AMNXYR_000007854)

36. U.S. Patent No. 3,051,619, issued on August 28, 1962, to Henri Marie Laborit ("the '619 patent") (AMNXYR_000006624-AMNXYR_000006626)

37. U.S. Patent No. 4,393,236, issued on July 12, 1983, to Joseph Klosa ("the '236 patent") (AMNXYR_000006627-AMNXYR_000006632)

38. U.S. Patent No. 4,983,632, issued on January 8, 1991, to Gian Luigi Gessa, Fabio Fadda, and Chiara Mormile di Campochiaro ("the '632 patent") (AMNXYR_000006633-AMNXYR_000006638)

39. U.S. Patent No. 5,380,937, issued on January 10, 1995, to Gernot Koehler and Anita Koehler ("the '937 patent") (AMNXYR_000006639-AMNXYR_000006642)

40. U.S. Patent No. 5,840,331, issued on November 24, 1998, to Eve Van Cauter and Martin B. Scharf ("the '331 patent") (AMNXYR_000006643-AMNXYR_000006664)

41. Vickers, M.D., "Gammahydroxybutyric Acid," *Newer Intravenous Anesthetics.* 7(1): 75-89 (©1969 by Little, Brown and Company (Inc.)) ("Vickers") (AMNXYR_000007855-AMNXYR_000007870)

42. Wickliffe, B. and Entrekin, D., Relation of pH to Preservation Effectiveness II, *Journal of Pharmaceutical Sciences.* 53(7): 769-773 (©1964) ("Wickliffe") (AMNXYR_000007871-AMNXYR_000007876)

43. International Publication No. 97/16196, published May 9, 1997, to Matrix Pharmaceutical Inc. ("the '196 PCT") (AMNXYR_000007093-AMNXYR_000007116)

44. European Patent Application No. 0386951 A2, published September 12, 1990, to Eli Lilly and Company ("EP '951") (AMNXYR_000002331-AMNXYR_000002344)

45. International Publication No. 97/37688, published on October 16, 1997, to Takeda Chemical Industries, Ltd. ("the '688 PCT") (AMNXYR_000007117-AMNXYR_000007178)

46. U.S. Patent No. 7,668,730, issued February 23, 2010, to Reardan *et al.* ("the '730 patent") and its file history, (AMNXYR_000006800-AMNXYR_000006824 and AMNXYR_000003117-AMNXYR_000003675)

47. U.S. Patent No. 7,765,106, issued July 27, 2010, to Reardan *et al.* ("the '106 patent") and its file history (AMNXYR_000006825-AMNXYR_000006855, and AMNXYR_000003676-AMNXYR_000003991)

48. U.S. Patent No. 7,765,107, issued July 27, 2010, to Reardan *et al.* ("the '107 patent") and its file history (AMNXYR_000006856-AMNXYR_000006878, and AMNXYR_000003992-AMNXYR_000004300)

49. U.S. Patent No. 7,895,059, issued February 22, 2011, to Reardan *et al.* ("the '059 patent") and its file history (AMNXYR_000006921-AMNXYR_000006946, and AMNXYR_000004950-AMNXYR_000005147)

50. U.S. Patent No. 8,457,988, issued June 4, 2013, to Reardan *et al.* ("the '988 patent") and its file history (AMNXYR_000007028-AMNXYR_000007051, and MNXYR 000005771-AMNXYR_000005949)

51. Peripheral and Central Nervous System Drugs Advisory Committee: 06/06/2001 Transcript Regarding Xyrem, Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (June 6, 2001) ("the Advisory Committee Transcript") (AMNXYR_000007365-AMNXYR_000007746)

52. "Diversion Prevention Through Responsible Distribution," *NADDI National Conference*, November 2001 ("the NADDI Presentation") (AMNXYR_000007300-AMNXYR_000007313)

53. Peripheral and Central Nervous System Drugs Advisory Committee: 06/06/2001 Presentation Slides, Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (June 6, 2001) ("the Advisory Committee Slides") (AMNXYR_000007345-AMNXYR_000007364)

54. Peripheral and Central Nervous System Drugs Advisory Committee: 06/06/2001 Final Minutes, Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (June 6, 2001) ("the Advisory Committee Minutes") (AMNXYR_000007337-AMNXYR_000007344)

55. Xyrem Prescription and Distribution Video and Transcript (July 13, 2001) ("Xyrem Video and Transcript") (AMNXYR_000007877 and AMNXYR_000007878-AMNXYR_000007888)

56. U.S. Patent Appl. Pub. No. 2004/0019794 A1, filed July 29, 2002, by Moradi *et al.* ("Moradi") (AMNXYR_000006593-AMNXYR_000006623)

57. U.S. Patent Appl. Pub. No. 2003/0033168 A1, filed April 15, 2002, by Califano *et al.* ("Califano") (AMNXYR_000006517-AMNXYR_000006550)

58. U.S. Patent Appl. Pub. No. 2003/0093295 A1, filed January 31, 2002, by Lilly *et al.* ("Lilly") (AMNXYR_000006579-AMNXYR_000006592)

59. U.S. Patent No. 6,045,501, issued April 4, 2000, to Elsayed *et al.* ("Elsayed") (AMNXYR_000006665-AMNXYR_000006671)

60. U.S. Patent No. 6,315,720, issued November 13, 2001, to Williams *et al.* ("Williams") (AMNXYR_000006672-AMNXYR_000006682)

61. U.S. Patent Appl. Pub. No. 2002/0177232 A1, filed May 22, 2002, by Melker *et al.* ("Melker") (AMNXYR_000006500-AMNXYR_000006516)

62. U.S. Patent Appl. Pub. No. 2003/0074225 A1, filed October 12, 2001, by Borsand *et al.* ("Borsand") (AMNXYR_000006551-AMNXYR_000006578)

63. Ukens, C., "Specialty Pharmacy," *Drug Topics* 144:40-47 (June 5, 2000) ("Ukens") (AMNXYR_000007841-AMNXYR_000007850)

64. "An Interview with Orphan Medical about Xyrem," http://www.talkaboutsleep.com/sleep-disorders/archives/Narcolepsy_xyrem_interview.htm (February 12, 2001) ("Talk About Sleep") (AMNXYR_000007839-AMNXYR_000007840)

65. European Patent Application No. 0527027 A1, published February 10, 1993, to Hunting Engineering Limited ("EP '027") (AMNXYR_000002345-AMNXYR_000002352)

66. Oxtoby, D.W. and Nachtrieb, N.H., Principles of Modern Chemistry, 3rd Edition, 1996, p. 54. (©1996 by Saunders College Publishing) ("Oxtoby") (AMNXYR_000007322-AMNXYR_000007330)

Amneal reserves the right to supplement this identification of prior art as its investigation continues.

B. Summary of Invalidity Positions

- U.S. Patent No. 6,472,431
    - Claims 1-7 are invalid as obvious over the prior art as set forth below.
    - Claims 1-7 are invalid under 35 U.S.C. § 112, ¶1 for lacking written description support and enablement.
    - Claims 1-7 are invalid under 35 U.S.C. § 112, ¶2 for being indefinite.
    - Claims 4 and 7 are invalid under 35 U.S.C. § 112, ¶4 for being improper dependent claims.
    - Claim 4 is invalid under 35 U.S.C. § 112, ¶5 for being an improper multiple dependent claim.
- U.S. Patent No 6,780,889
    - Claim 1 is invalid as obvious over the prior art as set forth below.
    - Claim 1 is invalid under 35 U.S.C. § 112, ¶1 for lacking written description support and enablement.
    - Claim 1 is invalid under 35 U.S.C. § 112, ¶2 for being indefinite.
- U.S. Patent No 7,262,219
    - Claims 1-4 are invalid as obvious over the prior art as set forth below.
    - Claims 1-4 are invalid under 35 U.S.C. § 112, ¶1 for lacking written description support and enablement.
    - Claims 1-4 are invalid under 35 U.S.C. § 112, ¶2 for being indefinite.

- U.S. Patent No 7,851,506
    - Claims 1-3 are invalid as obvious over the prior art as set forth below.
    - Claims 1-3 are invalid under 35 U.S.C. § 112, ¶2 for being indefinite.
- U.S. Patent No. 7,895,059
    - Claim 1-6, 9, and 12-14 are invalid as anticipated by the Advisory Committee Transcript.
    - Claims 1-6, 9, and 12-14 are invalid as anticipated by the NADDI Presentation.
    - Claims 1-16 are invalid as obvious over the prior art as set forth below.
    - Claims 1-16 are invalid under 35 U.S.C. § 101.
    - Claims 1-16 are invalid under 35 U.S.C. § 112, ¶2 for being indefinite.
    - Claims 1-16 are invalid under 35 U.S.C. § 102(f).
- U.S. Patent No 8,263,650
    - Claims 1-18 are invalid as obvious over the prior art as set forth below.
    - Claims 5-10 are invalid under 35 U.S.C. § 112, ¶1 for lacking written description support and enablement.
    - Claims 5-10 are invalid under 35 U.S.C. § 112, ¶2 for being indefinite.
- U.S. Patent No 8,324,275
    - Claims 1-4 are invalid as obvious over the prior art as set forth below.
- U.S. Patent No. 8,457,988
    - Claims 1 and 4-8 are invalid as anticipated by the Advisory Committee Transcript.
    - Claims 1, 4-9, and 12-15 are invalid as anticipated by the NADDI Presentation.
    - Claims 1-15 are invalid as obvious over the prior art as set forth below.
    - Claims 1-15 are invalid under 35 U.S.C. § 101.
    - Claims 1-15 are invalid under 35 U.S.C. § 112, ¶2 for being indefinite.

- Claims 1-15 are invalid under 35 U.S.C. § 102(f).

- U.S. Patent No. 8,461,203
  - Claims 1-18 are invalid as obvious over the prior art as set forth below.
  - Claims 1-18 are invalid under 35 U.S.C. § 112, ¶1 for lacking written description support and enablement.
  - Claims 1-18 are invalid under 35 U.S.C. § 112, ¶2 for being indefinite.
  - Claims 4 and 13 are invalid under 35 U.S.C. § 112, ¶¶2 and 4 for being indefinite and for being improper dependent claims.

III. Written Bases for Invalidity

A. Description of the Prior Art and Other Evidence

1. The '431 patent

The '431 patent is generally directed to "formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial growth." (the '431 patent at Abstract). The claims are directed to methods of "rendering an aqueous medium resistant to microbial growth, comprising adding the gamma-hydroxybutyrate salt…" (*See*, *e.g.*, the '431 patent, claim 1).

2. The '889 patent

The '889 patent is a division of the '431 patent and is generally directed to "formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial growth." (the '889 patent at Abstract). The sole claim is directed to a preservative-free pharmaceutical composition "consisting essentially of an aqueous solution of 500 mg/ml sodium gamma-hydroxybutyrate…" (the '889 patent, claim 1).

3. The '219 patent

The '219 patent is a division of the '889 patent and is generally directed to "formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial growth." (the '219 patent at Abstract). The claims are directed to preservative-free pharmaceutical

compositions "consisting essentially of an aqueous solution of … sodium gamma-hydroxybutyrate…" (*See*, *e.g.*, the '219 patent, claim 1). The claims also require "a pH of about 6-7.5." (*Id.*)

4. The '506 patent

The '506 patent is a division of the '219 patent and is generally directed to "formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial growth." (the '506 patent at Abstract). The claims are directed to methods of treating "a condition responsive to sodium gamma-hydroxybutyrate, comprising orally administering… a first dose of about 4.5 to about 10 grams of sodium gamma-hydroxybutyrate within an hour prior to initial sleep onset and… a second dose… within 2 to 5 hours following initial sleep onset…" (*See*, *e.g.*, the '506 patent, claim 1). The conditions to be treated include narcolepsy and cataplexy. (*See*, *e.g.*, the '506 patent, claims 2 and 3).

5. The '650 patent

The '650 patent is a continuation of the '203 patent and is generally directed to "formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial growth." (the '650 patent at Abstract). The claims include preservative-free pharmaceutical compositions "comprising an aqueous solution of about 500 mg/ml sodium gamma-hydroxybutyrate…" (*See*, *e.g.*, the '650 patent at claim 1). The claims also include methods of treating "cataplexy or daytime sleepiness in a patient having narcolepsy…" (*See*, *e.g.*, the '650 patent at claim 11). The claims further include "a set comprising the pharmaceutical composition… in one or more container means." (*See*, *e.g*, the '650 patent at claim 15).

6. The '275 patent

The '275 patent is a grandchild of the '506 patent and is generally directed to "formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial

growth." (the '275 patent at Abstract). The claims include "a method of treating cataplexy or daytime sleepiness in a patient who has been diagnosed with narcolepsy…" (the '275 patent, claims 1-4). The claims recite dosage levels in terms of grams of sodium gamma-hydroxybutyrate. (*Id.*) Two of the claims further recite specific concentration ranges for each dose. (the '275 patent, claims 3-4).

7. The '203 patent

The '203 patent is a grandchild of the '506 patent and generally directed to "formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial growth." (the '203 patent at Abstract). The claims are directed to methods of "rendering an aqueous medium resistant to microbial growth, the methods comprising admixing a salt of gamma hydroxybutyrate with the aqueous medium…" (*See, e.g.*, the '203 patent, claim 1). The claims further require "adjusting the concentration of the gamma-hydroxybutyrate salt … to a final concentration of from about 310 to about 750 mg/ml…" (*Id.*)

8. Allsopp

Allsopp published in 1992 and discloses that "the narcolepsy syndrome comprises sleep disturbance, cataplexy, sleep paralysis, and hypnagogic hallucinations," and that "the sleep disturbance involves excessive daytime drowsiness with intermittent, irresistible naps, and a disrupted pattern of nocturnal sleep." (Allsopp at p. 302).

9. Bédard

Bédard published in 1989 and discloses that narcolepsy is characterized by cataplexy and excessive daytime sleepiness. (Bédard at 29:1-5). γ-hydroxybutyrate (GHB) is used to suppress cataplectic attacks in narcolepsy patients, by administering GHB at bedtime, with a second treatment usually necessary because of GHB's short half-life. (*Id.* at 30:9-11).

10. Broughton

Broughton published in 1979. It discusses the results of a study in which "sixteen patients with narcolepsy and cataplexy were treated with gamma-hydroxybutyrate (GHB)," and "the subjective quality of night sleep improved in all patients and the number of irresistable [sic] daytime attacks of sleep and cataplexy substantially diminished." (Broughton at summary). Oral doses of GHB are reported to induce sleep. (*Id.* at p. 2). The Broughton study used the sodium salt of gamma-hydroxybutyrate and administered it orally. (*Id.* at p. 2). Diluting the syrup in milk or juice reportedly reduced gastrointestinal upset in some patients, and it retarded the rate of absorption of GHB, so that sleep induction was more gradual and normal. (*Id.* at p. 3). Broughton administered an initial dose of 1.5-2.25 g NaGHB in 10-15 ml within the hour prior to sleep, followed by further 1.0-1.5 g doses during the night with each major reawakening, if at least 2.5 hours had passed since the previous dose. (*Id.* at p. 2).

11. CDC

CDC was last updated on April 27, 2012, and it categorizes a person with body mass index of less than 18.5 as underweight, 18.5 to 24.9 as healthy, 25.0 to 29.9 as overweight, and 30 or higher as obese.

12. Chokroverty

Chokroverty published in 1986 and states that the characteristic clinical picture of narcolepsy syndrome includes cataplexy and uncontrollable sleep attacks during the day. (Chokroverty at p. 250).

13. The 1990 CRC Handbook

The 1990 CRC Handbook published in 1990, and it lists γ-Hydroxybutyric acid with a pK_a of 4.72 in aqueous solution. (The 1990 CRC Handbook at p. 8-36).

14. EP '408

EP '408 published on September 9, 1987. It states that "GHB has been demonstrated in clinical trials to be a safe, oral drug for treatment of narcolepsy." (EP '408 at 2:45-46). GHB is also known as sodium oxybate and is commercially available. (*Id.* at 3:22-23). EP '408 goes on to disclose that ethyl 4-acetoxybutanoate may be compounded and administered in dosage levels similar to those used for GHB. (*Id.* at 2:21-22). The disclosed compound may be taken orally as a solution or emulsion. (*Id.* at 3:26-27).

15. EP '804

EP '804 published on September 28, 1994. It discusses the use of pharmaceutically acceptable salts of gamma-hydroxybutyric acid in preparing pharmaceutical compositions suitable for therapeutic use in the treatment of depression. (EP '804 at abstract). EP '804 discloses the oral administration of a pharmaceutically acceptable salt of gamma-hydroxybutyric acid in the form of single or multi-dose liquid solutions. (*Id.* at 6:32-34). The sodium salt is listed as particularly preferred. (*Id.* at 2:38-39). Examples are given of pharmaceutical formulations containing NaGHB to be used as described in the invention. (*Id.* at 6:37-38 and formulations 1-4). Pharmaceutical compositions of sodium 4-hydroxybutyrate according to the invention may also be buffered. (*Id.* at 6:34). Examples include a single-dose 10-ml bottle containing sodium 4-hydroxybutyrate as the active ingredient in water, and a 14-dose 140-ml bottle containing 4-hydroxybutyrate as the active ingredient in water. (*Id.* at Formulations 1 and 2). Also disclosed is a formulation for intravenous injection that is free of preservatives. (*Id.* at Formulation 3).

16. EP '265

EP '265 published on January 25, 1995, and it discloses that sodium gamma-hydroxybutyrate was previously available as a syrupy solution. (EP '265 at 3:9-23). Aqueous liquid solutions of sodium gamma-hydroxybutyrate are commercially available. (*Id.* at 7:22-23).

Sodium gamma hydroxy butyrate has to be administered more than once a day, due to its rapid absorption and elimination. (*Id.* at 3:14-19). Sodium gamma hydroxy butyrate is absorbed by the gastroenteric apparatus with a maximum peak at about 30-45 minutes after administration and a half-life of 20-25 minutes, and the principle is eliminated within 4-5 hours. (*Id.* at 3:14-17).

17. Ferrara

Ferrara published in 1992 and discloses oral administration of gammahydroxybutyrate to treat the effects of alcohol withdrawal in man. (Ferrara at p. 231). In Ferrara, GHB is administered dissolved in black cherry syrup as obtained from CT, Sanremo, Italy. (*Id.* at p. 232). Ferrara further discloses that GHB has been used in the treatment of sleep disorders. (*Id.* at p. 231).

18. Hoes

Hoes published in 1980 and generally discusses the results of a study of the effects of GHB on insomniacs. (Hoes at p. 94). The study used gamma-hydroxybutyrate dissolved at a concentration of 10 grams per 100 milliliters of chocolate-flavored water. (*Id.*).

19. Laborit

Laborit published in 1973 and states that the coma-inducing action of short-chain fatty acids from C_4 to C_{10} is known. (Laborit at p. 257). GHB-induced sleep has been described as being close to physiological sleep, and Laborit discloses that doses of 50 to 60 mg/kg rapidly induce slow wave sleep followed by REM sleep. (*Id.* at p. 264). Laborit teaches that "molecules

closely related to GHB such as 1,4-butanediol… possess hypnotic properties similar to those of GHB." (*Id.* at p. 258). GHB will reportedly deepen sleep, and it is suggested that the use of GHB to obtain sleep should apply to insomnia. (*Id.* at p. 269).

20. Lammers

Lammers published in 1993, and it discusses a study in which narcolepsy patients treated with GHB exhibited fewer daily cataplexy attacks. (Lammers at summary). Narcolepsy is taught to be clinically characterized by excessive daytime sleepiness, disturbed nocturnal sleep, cataplexy, hypnagogic hallucinations, and sleep paralysis. (*Id.* at p. 216). In the study, gamma-hydroxybutyrate was administered orally as a 10% aqueous solution. (*Id.* at p. 217). Lammers discloses the administration of one 30 mg/kg dose of GHB shortly before nocturnal sleep and a second 30 mg/kg dose 4 hours later. (*Id.* at p. 217).

21. Lapierre

Lapierre published in 1990, and it discloses that GHB is used to treat narcolepsy. (Lapierre at summary). Lapierre teaches that cataplexy is controlled by GHB, which can be administered orally. (*Id.* at pp. 25 and 28).

22. Remington's

Remington's published in 1995. It teaches that hydrochloric acid is a pharmaceutic aid that is used as an acidifying agent. (Remington's at p. 1410).

Remington's also discloses requirements for pharmaceutical stability and some approaches to achieving stability. (*Id.* at pp. 239, 639-640). It teaches means to achieve drug stabilization from photolytic, oxidative, and solvolytic decomposition reactions. (*Id.* at p. 239).

Remington's further defines a pharmaceutical container as a device which holds the drug and is, or may be, in direct contact with the preparation. (*Id.* at p. 646). An immediate container

is defined as that which is in direct contact with the drug at all times. (*Id.*). Light-sensitive drugs for parenteral use are usually sealed in flint ampules and placed in a box. (*Id.*).

23. Mamelak (1977)

Mamelak (1977) published in 1977 and explored the use of sodium gamma-hydroxybutyrate to treat insomnia. (Mamelak (1977) at p. 273). The study used GHB in the form of a banana-flavored syrup, which was obtained from Laboratoire Egic of Paris, France, who market it. (*Id.* at p. 274-275). GHB was administered orally in a dose of 1.0-4.5 g and placebo in a dose of 5 cc banana flavoring in water. (*Id.*). On most nights, a 3-g dose was given. (*Id.* at p. 274). Mamelak (1977) reports that the use of GHB in repeated doses during the night reduced the incidence of daytime attacks of cataplexy and improved daytime functioning, with repeat dosing of GHB two or three times during the night to maintain sleep in cases of severe insomnia. (*Id.* at p. 286).

24. Mamelak (1989)

Mamelak (1989) published in 1989, and it discusses the therapeutic use of GHB to consolidate night sleep in narcoleptics and improve their alertness during the day. (Mamelak (1989) at p. 188). It discloses that oral doses of 20 to 30 mg/kg GHB promote the normal sequence of NREM and REM sleep in normal subjects when given at bedtime. (*Id.*). GHB is rapidly metabolized and the central effects of an intravenous dose of 60-70 mg/kg GHB last about 2 hours. (*Id.*).

25. Nema

Nema published in 1997, and it states that injectable products are required to withstand sterilization processes such as autoclaving. (Nema at p. 166). In addition, Nema states that preservatives may not be allowed in some injectable products, depending on the route of administration. (*Id.*) Chelating agents are also reported to be used in parenteral products to

complex heavy metals, thereby improving the efficacy of antioxidants or preservatives. (*Id.* at p. 167-168).

Nema discloses buffers and chemicals used to adjust the pH of formulations. (*Id.* at p. 168). Nema provides a table of 32 buffers and pH-adjusting agents, including organic (such as acetic acid and citric acid) and inorganic acids. (*Id.* at p. 169).

26. Palatini

Palatini published in 1993, and it discloses that GHB has been used in the treatment of narcolepsy. (Palatini at p. 353). Palatini discusses a study using the oral administration of 12.5, 25, and 50 mg/kg GHB diluted in water, using a cup to administer the GHB. (*Id.* at p. 354). The study used GHB dissolved in a black cherry syrup, available from CT, and the GHB syrup was diluted to 100 ml with water and the cup rinsed with a further 50 ml water. (*Id.*).

27. Roth

Roth published in 1966, and it discloses that, of GHB and the corresponding lactone (gamma-butyrolactone, GBL), GHB is the active form, but GBL has the longer duration of action. (Roth at p. 1333). GBL is reported to be rapidly converted to GHB in the blood and liver. (*Id.* at p. 1342-1343).

28. Scharf

Scharf published in 1985, and it discusses a study in which treatment of narcoleptics with GHB significantly improved the clinical symptoms of cataplexy, sleep paralysis, hypnogogic hallucinations, daily naps, and sleep attacks. (Scharf at abstract). In the Scharf study, 2 doses of 20-25 ml of 150 mg/ml GHB were administered, the first at lights out and the second 4 hours later. (*Id.* at p. 222).

29. Scrima (1987)

Scrima (1987) published in 1987, and it discusses the results of a study that found that GHB decreases sleep attacks and cataplexy in narcoleptics. (Scrima (1987) at p. 134). In the Scrima (1987) study, a dose of 25mg/kg GHB was administered within the hour prior to sleep and again 3 hours later. (*Id.*)

30. Scrima (1989)

Scrima (1989) published in 1989 and generally discusses a study of the effects of GHB treatment on narcolepsy and cataplexy, in which cataplexy was reduced. (Scrima (1989) at Abstract). Subjects were provided pharmacy-prepared bottles of 25 mg/kg GHB mixed with distilled water and syrup of orange, and instructed to ingest one entire bottle immediately before going to bed and the other 3 hours later. (Scrima (1989) at p. 333-334).

31. Scrima (1990)

Scrima (1990) published in 1990 and states that narcolepsy is a chronic disorder characterized by cataplexy and daytime sleepiness, and it discusses the results of a double-blind study indicating that GHB improves sleep depth and continuity compared to placebo. (Scrima (1990) at pp. 479, 480, and 486). Most patients with narcolepsy also have cataplexy and disrupted nocturnal sleep. (*Id.* at p. 479-480). GHB had been reported to induce anesthesia at doses of 60-70 mg/kg and sleep at doses of 40-50 mg/kg. (*Id.* at p. 480). Scrima (1990) notes that oral doses of ~25-35 mg/kg GHB have been reported to induce rapid sleep onset and normal cycling of sleep stages at bedtime. (*Id.*). In the Scrima (1990) study, subjects took 25 mg/kg of GHB within the hour prior to sleep and 25 mg/kg 3 hours later. (*Id.* at p. 482). The GHB was mixed with sterile, distilled water and syrup of orange. (*Id.*). The study's subjects' mean ± SD (range) weights were 85.1 ± 16.4 (57-113) kg for females and 80.4 ± 11.4 (54-90) kg for males, which are equated to mean ± SD (range) body mass index values of 31.8 ± 7.8 (17.6-45.4) for

females and 26.2 ± 2.8 (20.3-29.1) for males. (*Id.*). Scrima (1990) observes that the therapeutic effect of reduction of cataplexy in narcolepsy patients by treatment with GHB appears to be due to the improvement of nocturnal sleep quality. (*Id.* at summary).

32. Sériès

Sériès published in 1992, and it reported that gamma-hydroxybutyrate improved sleep abnormalities in a patient with narcolepsy and central sleep apnea. (Sériès at p. 1378). Sériès reports a study in which subjects were administered 30 mg/kg gamma-hydroxybutyrate as a white powder diluted in orange juice at the beginning of the recording and at the first awakening 3h after the first drug administration. (*Id.* at p. 1379). Each subject received two doses of the drug. (*Id.*). The patients in the Sériès study had a mean ± SEM body mass index of 35.0 ± 1.5 kg/m^2. (*Id.* at summary).

33. Sours

Sours published in 1963, and it states that cataplexy, the second most common and most easily recognized narcolepsy symptom, was characterized by a sudden decrease of muscle tone, limited to particular muscle groups. (Sours at p. 532).

34. CA 338

CA 338 published in 1964, and it discloses that solutions of the alkali metal salts of 4-hydroxybutyric acid are used as anaesthetics. (CA 338 at abstract). The alkali metal salts of GHB, as usually prepared, reportedly have far too high a pH for injection as 20% solutions. (*Id.*). CA 338 discloses the preparation of 4-hydroxybutyric acid salt solutions of pH 7.2-7.7 for injection. (*Id.*). For example, CA 338 details the preparation of sodium 4-hydroxybutyrate solutions of pH 7.2-7.7 for injection, by sequential addition of γ-butyrolactone, water, and sodium hydroxide. (*Id.*).

35. The 1995 USP

The 1995 USP published in 1995, and it lists 13 acidifying agents, including organic and inorganic acids, and nine alkalizing agents among USP and NF Pharmaceutic Ingredients. (The 1995 USP at p. 2205). Included in the list of acidifying agents are malic acid, citric acid, acetic acid, propionic acid, tartaric acid, hydrochloric acid, phosphoric acid, sulfuric acid, and nitric acid. (*Id.*)

36. The '619 Patent

The '619 patent issued on August 28, 1962, and it discloses that sodium 4-hydroxybutyrate is highly soluble in water and, in aqueous solution, has a pH slightly in excess of 7. (The '619 Patent at 1:61-66). The equilibrium between GBL and GHB is taught to lie toward GHB at pH values above 7. (*Id.* at 1:27-37). The '619 patent discloses formulations that are free of preservatives, including one that was administered to a patient to induce anesthesia just prior to undergoing surgery. (*Id.* at examples 1-3).

37. The '236 Patent

The '236 patent issued on July 12, 1983, and it teaches that the calcium and magnesium salts of 4-hydroxybutyric acid can be dispensed as aqueous solutions. (The '236 Patent at 4:39-47). The '236 patent discloses that the sodium salt of 4-hydroxybutyric acid induces anesthesia and sleep, and certain dosage levels generate a sleeping state from which the patient can be awoken. (*Id.* at 1:38-43).

38. The '632 Patent

The '632 patent issued on January 8, 1991, and it discloses the use of gamma-hydroxybutyric acid salts for preparing pharmaceutical compositions useful for the treatment of alcoholism. (The '632 Patent at abstract). Gamma-hydroxybutyric acid derivatives, including its simple salts, have therapeutic uses due "to their narcotic, hypnotic or anticonvulsive effect." (*Id.*

at 3:29-32). The '632 patent lists as a suitable gamma-hydroxybutyric acid salt the sodium salt, and it teaches that the GHB salt content of the compositions can vary from 12.5 to 50% by weight. (*Id.* at 7:32-33 and 7:47-49). The '632 patent teaches oral administration of pharmaceutical compositions, including syrups, of salts of gamma-hydroxybutyric acid. (*Id.* at 7:51-53). For example, the '632 patent discloses a bottle containing 140 ml of solution containing 42.35 g of sodium gamma-hydroxybutyric acid, as well as a bottle containing 20 ml of solution containing 6.05 g of sodium gamma-hydroxybutyric acid. (*Id.* at Examples 1 and 2). The '632 patent also includes an injectable formulation of sodium gamma-hydroxybutyrate free of preservatives. (*Id.* at 8:57-59). The typical dosage for a GHB salt is listed as 0.025 to 0.10 g/kg, with the preferred GHB salt dosage being 0.05 g/kg in a single daily dose. (*Id.* at 7:44-46).

39. The '937 Patent

The '937 patent issued on January 10, 1995. It reports that GHB is available as a pharmaceutical exclusively as the sodium salt and that all experimental and clinical investigations have without exception been performed with the sodium salt, the acid itself, or the corresponding lactone. (The '937 patent at 1:7-15). The '937 patent discloses that GHB has hypnotic effects at 35-90 mg/kg doses and a narcotic effect at dosages greater than 100 mg/kg. (*Id.* at 1:42-43). The '937 patent also states that "the narcosis achieved with GHB broadly resembles physiological sleep." (*Id.* at 1:62-64).

40. The '331 Patent

The '331 patent issued on November 24, 1998, and discloses that gamma-hydroxybutyrate has such clinical effects as increased slow-wave sleep (SWS) and reduction of narcolepsy. (The '331 patent at 6:21-40). SWS is associated with a pulse of growth hormone (GH) that may represent 50-100% of the total daily GH output. (*Id.* at 1:21-25). SWS decreases with age, and the reduction or absence of SWS in the elderly is a major contributor to the overall

decline in GH secretion. (*Id.* at 1:27-38). Reduced GH secretion may be correlated with increased cardiovascular mortality, reduced exercise capacity, and other pathologic states. (*Id.* at 1:42-52).

The '331 patent discloses the use of sodium γ-hydroxybutyrate in pharmaceutical compositions. (*Id.* at 7:1-15). The '331 patent recites that administration may be oral. (*Id.* at 7:63-64). Suitable compositions disclosed include solutions. (*Id.* at 7:44). Typical dosages range between 2.0 and 5.0 grams. (*Id.* at 7:48). The '331 patent teaches administration of one dose within the last hour prior to retiring, or one-half hour or less prior to retiring. (*Id.* at 7:52-61). It may be desirable to administer a second or third dose during the normal sleep period. (*Id.* at 7:61-63).

41. Vickers

Vickers published in 1969 and discloses that gamma-hydroxybutryate has a possible clinical use in night sedation. (Vickers at p. 82). Vickers states that an intravenous or oral dose of 40-50 mg/kg of gammahydroxybutyric acid has been reported, within 5-15 minutes, to induce a sleeping state from which the patient can be awoken. (*Id.* at p. 78). Gamma-hydroxybutyrate is taught to be water soluble in all dilutions, and the pH of the solution is not far from physiological. (*Id.* at pp. 82-87). Gamma-hydroxybutyric acid is marketed for intravenous injection as a solution containing 2.42 g sodium 4-hydroxybutyrate in 10 ml water, with a pH between 8.2 and 8.9. (*Id.* at p. 75). GHB has been tried orally as a night sedative, and that 2 g every 2-4 hours produces sleep. (*Id.* at p. 82-87). Vickers reports the use of 20-30 g per 24 hours without ill effect. (*Id.* at p. 75-76).

42. Wickliffe

Wickliffe published in 1964, and it states that bacterial growth has been shown to be inhibited at pH 2 without the use of additional preservative material and that asepsis also occurs above pH 9. (Wickliffe at p. 770).

43. The '196 PCT

The '196 PCT published on May 9, 1997, and discloses a kit containing vials of lyophilized cisplatin, diluent for cisplatin resuspension, collagen gels, and syringes for mixing and dosing. (The '196 PCT at 8:9-12).

44. EP '951

EP '951 published on September 12, 1990, and discloses a therapeutic kit for the preparation of a parenteral formulation of the antibiotic daptomycin, wherein the kit comprises a container of the antibiotic and a container of buffer to be mixed with the antibiotic. (EP '951 at 14:29-33).

45. The '688 PCT

The '688 PCT published on October 16, 1997, and discloses "a kit for injection which comprises two or more ampoules each comprising a powdery component and a diluent for mixing and dissolving two or more components when administered." (The '688 PCT at 28:26-33).

46. The '730 patent

The '730 patent is generally directed to a "a computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy…." (the '730 patent, claims 1-11). The claimed methods also require "confirming with a patient that educational material has been read prior to shipping the prescription drug [and] checking the exclusive computer database for potential abuse of the prescription drug…." (*See e.g.*, the '730 patent,

claim 1). In addition, the claimed methods require "receiving in a computer processor" the prescription requests, and all but one claim requires "generating with the computer processor periodic reports via the exclusive computer database to evaluate diversion patterns." (*See e.g.*, the '730 patent, claim 1).

47. The '106 patent

The '106 patent is a division of the '730 patent and is generally directed to "a therapeutic method for treating a patient…" (*See e.g.,* the '106 patent, claim 1). All but two of the claims specify that treatment is "with a prescription drug that... also… has the potential to be abused, misused, or diverted…" (*See e.g.*, the '106 patent, claim 1) The remaining two claims specify the patient is narcoleptic and require treatment with sodium oxybate. (*See e.g., Id.* at claim 3). The claimed methods also require "confirming with a patient that educational material has been received and/or read" and checking the exclusive computer database for potential abuse of the prescription drug (*See e.g.*, the '106 patent, claim 1). In addition, the claimed methods require "receiving, only into an exclusive computer system" the prescription requests. (*See e.g.*, the '106 patent, claim 1).

48. The '107 patent

The '107 patent is a division of the '730 patent and is generally directed to "a computerized method to control abuse" of a drug (*See*, *e.g.*, the '107 patent, claim 1). Three of the six claims specify "a computerized method to control abuse of gamma hydroxy butyrate (GHB)…" (the '107 patent, claims 4-6). The claims also require "receiving in the computer processor" all prescription requests, "determining with the computer processor current and anticipated patterns" of abuse of the drug, and "selecting with the computer processor multiple controls for distribution…" (*See*, *e.g.*, the '107 patent claim 1).

49. The '059 patent

The '059 patent is a continuation of the '730 patent and is generally directed to "a computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy…." (the '059 patent, claims 1-16). The claimed methods also require "confirming with a patient that educational material has been received and/or read" and checking the exclusive computer database for potential abuse of the prescription drug (*See e.g.*, the '059 patent, claim 1). In addition, the claimed methods require "receiving in a computer processor" the prescription requests, and all but one of the independent claims require "generating with the computer processor periodic reports via the exclusive computer database to evaluate diversion patterns." (*See e.g.*, the '059 patent, claim 1).

50. The '988 patent

The '988 patent is a grandchild of the '059 patent and is generally directed to "a method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse, or diversion of said prescription drug…" (*See*, *e.g.*, the '988 patent at claim 1). The claimed methods also require an "exclusive central pharmacy and… exclusive central database…" (*See*, *e.g*, the '988 patent at claim 1). In two claimed methods, the prescription drug "comprises a gamma hydroxybutyrate (GHB) drug product." (*See*, *e.g.*, the '988 patent at claims 8 and 15).

51. The Advisory Committee Transcript

The '730 patent lists the Advisory Committee Transcript in the References Cited section. The Advisory Committee Transcript is listed with the date of June 6, 2001. Only a 6-page excerpt of the Advisory Committee Transcript can be found in the prosecution file wrapper of the '730 patent, but the full transcript can be obtained from the FDA through a Freedom of Information Act ("FOIA") request. (*See* AMNXYR_000007365-AMNXYR_000007746).

The Advisory Committee Transcript discloses Orphan Medical, Inc.'s proposed distribution program for Xyrem, a pharmaceutical formulation comprising gamma hydroxy butyrate ("GHB"), presented to the FDA's Peripheral and Central Nervous System Drugs Advisory Committee. (the Advisory Committee Transcript, 9:12-15). GHB is a Schedule I drug under the Controlled Substances Act "for abusable versions," and is a Schedule III drug for approved medical uses. (*Id.* at 164:24 through 165:3). Orphan Medical seeks FDA approval for the use of Xyrem in treating narcolepsy. (*Id.* at 5:23 through 6:1; 144:20 through 145:2 and 369:1-3).

In the proposed distribution system, a single manufacturer produces Xyrem and supplies it to "one single national specialty pharmacy," which then distributes it to patients (*Id.* at 177:24 through 178:11). The proposed distribution system seeks to achieve 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." (*Id.* at 14:25 through 15:6). With the third goal "not only refer[ring] to diversion and its use illicitly by folks who should not be taking it, but also to the accidental use of GHB in the home…." (*Id.* at 15:6-9).

The central pharmacy maintains all the controls and records for the distribution of Xyrem, and all the prescriptions are sent to the central pharmacy to be filled. (*Id.* at 178:8-11 and 180:14-16). Upon receiving the prescription, the central pharmacy checks the physicians credentials and that the patient is eligible to receive Xyrem. (*Id.* at 181:1-22). The proposed distribution program is also disclosed as being beneficial because it allows for the identification of potential abuse situations, and if necessary, pharmacist intervention. (*Id.* at 184:23 through 185:7 and 259:4-8). Additionally, the pharmacy confirms receipt of the drug by the patient, or

the patient's designated representative, after shipment. (*Id.* at 182:17 through 183:1 and 184:10-15).

In addition to the above, the program was presented as requiring educational materials to accompany the first shipment of Xyrem. (*Id.* at 182:5-8). The patient would then send back confirmation that the materials were read. (*Id.* at 357:9-13). However, the other participants at the presentation suggested to Orphan that the patient should confirm that he read the materials before receiving Xyrem. (*Id.* at 371:10-13 and 374:14-20).

The 6-page excerpt of the Advisory Committee Transcript submitted during prosecution of the '730 patent does not contain the disclosure related to the goals of the Xyrem distribution program (*Id.* at 14:25 through 15:6-9; 259:4-8). Nor does it contain any disclosure related to the patient confirming that he has read the educational materials. (*Id.* at 357:9-13; 371:10-13; and 374:14-20).

52. The NADDI Presentation

The NADDI Presentation was presented at the National Association of Drug Diversion Investigators National Conference in November 2001. The NADDI Presentation was cited during prosecution of the '730, '059 patents, and '988 patents.

The NADDI Presentation is slides presented by Orphan Medical disclosing their proposed distribution system for Xyrem, a "medical form of GHB," for which they seek FDA approval for use in treating narcolepsy. (the NADDI Presentation, pgs. 4-14). Orphan presented a "closed loop distribution" system in which Orphan manufactures Xyrem and supplies it to a "single-dedicated pharmacy" that keeps inventories, collects and maintains doctor and patient registry information, as well as reports prescription information to state authorities. (*Id.* at pgs. 6-7). Furthermore, the proposed system can "proactively prevent diversion and facilitate law enforcement investigations." (*Id.*).

In the proposed system, a physician faxes a "unique" prescription form to the central pharmacy. (*Id.* at pg. 8). The pharmacy then "verifies [the] physician is 'eligible' [to prescribe Xyrem]" by checking the physicians credentials. (*Id.* at pgs. 8-9). The pharmacy then ships "educational materials to [the] patient before dispensing Xyrem." (*Id.* at pg. 10). The pharmacy "verifies [the] patient has read [the] educational materials" and "sets up a time for Xyrem to be shipped via FedEx." (*Id.* at pg. 10). The shipment is tracked, and authorities are notified if it is diverted. (*Id.*). Upon receipt of the shipment by the patient, the central pharmacy contacts the patient within 24 hours to confirm delivery. (*Id.* at pg. 12). The central pharmacy also calls the patient prior to any further shipments of Xyrem to "monitor use, provide additional information, and asses[] patient compliance." (*Id.*).

The central pharmacy also maintains a registry of information about the patient, such as the patient's name, social security number, date of birth, and address. (*Id.*). Additionally, the registry maintains information on the physician such as the physicians name, address, specialty, prescriptions by dose, and prescriptions by volume. (*Id.*). From this data, the pharmacy can generate reports for federal and state authorities, to provide information to law enforcement, and to "[a]lert state medical board[s] of any troubling physician activities." (*Id.* at pg. 13).

The proposed system is disclosed as being able to prevent diversion and illicit use, as well as stop prescriptions from being filled. (*Id.*). The system is also beneficial because it maintains all physician and patient data in one location, is able to provide this information to "authorities as required and upon request," and because the pharmacy performs "[o]n-going monitoring and calls [to] identify potential overuse." (*Id.* at pg. 14).

53. The Advisory Committee Slides

The Advisory Committee Slides were presented at the FDA's Peripheral and Central Nervous System Drugs Advisory Committee Meeting on June 6, 2001. The Advisory Committee

Slides describe the Xyrem distribution system as "[a] comprehensive system designed to ensure responsible distribution and use of Xyrem." (the Advisory Committee Slides, 142). The proposed distribution system is disclosed as a "closed distribution system" in which a single manufacturing facility produces Xyrem and delivers it to a "single specialty pharmacy." (*Id.* at 146). Furthermore, the specialty pharmacy is described as distributing Xyrem from a single location that maintains controls and records. (*Id.* at 147).

The Advisory Committee Slides disclose that the prescription process as follows: (1) the physician faxes a prescription to the specialty pharmacy, (2) the specialty pharmacy verifies that the physician is eligible to prescribe Xyrem by checking the physicians credentials, (3) the ability of the patient to receive Xyrem is then verified, (4) the pharmacy then contacts the patient and discuss the prescription with the patient, and (5) the single specialty pharmacy then ships the Xyrem to the patient via overnight courier, confirms receipt of the shipment of Xyrem, and again discusses the prescription with the patient. (*Id.* at 146 and 151-157).

In addition, the program is disclosed as being beneficial because it allows for identification of forms of abuse and allows appropriate pharmacist intervention. (*Id.* at 158-159).

54. The Advisory Committee Minutes

The Advisory Committee Minutes disclose the votes taken by members of the Peripheral and Central Nervous System Drugs Advisory Committee on questions presented after Orphan Medical's presentation before the committee on June 6, 2001. When the committee members were asked if the patient should sign an informed consent before receiving the initial shipment of Xyrem, five out of nine committee members voted yes, four voted no. (the Advisory Committee Minutes, question 5). The minutes state, "[t]he dissenter's [sic] thought that without details it was hard to vote on. What would be the informed consent? One person suggested that contract might

be better choice of words where the patient could acknowledge the dispensing of the drug and risks." (*Id.*).

55. Xyrem Video and Transcript

The Xyrem Video and Transcript became publicly available at the latest on July 13, 2001. The Xyrem Video Transcript is a transcript of the Xyrem Video discussing a proposed distribution system for Xyrem. The transcript discloses that "[a] crucial component of the secure distribution of Xyrem is the use of a specialty pharmacy," and that "[t]he specialty pharmacy is a single, centrally-located facility that will have a variety of distribution, documentation, and security responsibilities." (Xyrem Video Transcript, pg. 4). In addition, the transcript states that the specialty pharmacy will "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." (*Id.*). Furthermore, an advantage of utilizing the central pharmacy is described as "keep[ing] all the data about inventory, physicians, reimbursement, patients, and delivery in one efficient and quickly-accessible location." (*Id.* at pg. 6).

In the proposed distribution system, a physician faxes or mails a prescription for Xyrem to the specialty pharmacy. (*Id.* at pg. 5). Upon receipt of the prescription, the specialty pharmacy then checks the physicians credentials and ability to prescribe Xyrem. (*Id.* at pg. 6). The specialty pharmacy then contacts the patient to arrange for the shipment of Xyrem, which is shipped by Federal Express to the patient. (*Id.* at pgs. 7-8). After receipt of the shipment by the patient, the specialty pharmacy contacts the patient to confirm its receipt. (*Id.* at pg. 9).

Other aspects of the proposed system disclose the ability of the specialty pharmacy to detect and prevent abuse. The transcript states that "[t]hroughout [the] 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." (*Id.* at pg. 8). Moreover, "[t]he specialty pharmacy also keeps track of expected prescription refill dates and … [p]atients who request a refill before their refill date will be flagged and their physician contacted." (*Id.* at pg. 9). As such, these "security and verification protocols will minimize diversion of the medication to unauthorized individuals." (*Id.* at pg. 10).

56. Moradi

Moradi was filed as U.S. Appl. No. 10/207,402 on July 29, 2002. Moradi is directed to "[a] system for securely providing prescription medication to patients." (Moradi, Abstract). Moradi discloses that "[its] invention generally relates to the field of prescription delivery systems, and more particularly to the field of automated prescription handling." (*Id.* at ¶[0003]).

In the method of Moradi, the system receives a prescription request from a doctor that identifies the patient, the drug to be dispensed, and various credentials of the doctor, which are then verified. (*Id.* at ¶¶[0035] and [0116]-[0118]). The system "includes several processing components that are located at various physical locations … which may each have one or more computers or processing devices…." (*Id.* at ¶[0022]). Additionally, the system of Moradi is designed to prevent potential abuse of the prescribed drug and includes a step of confirming receipt of the drug. (*Id.* at ¶[0043], ¶[0045], Fig. 3, and Abstract).

57. Califano

Califano was filed as U.S. Appl. No. 10/122,711 on April 15, 2002. Califano is directed to "systems and methods … for obtaining and managing informed consent documentation." (Califano, Abstract). Califano discloses confirming with a patient that educational material has been read and documenting that the patient understands the risks associated with a drug prior to providing the patient with the drug. (*Id.* at ¶¶[0043] and [0084]). Califano also discloses that an authorized biomedical professional logged onto the system via a secure internet session may submit a query. (*Id.* at ¶[0057]).

58. Lilly

Lilly was filed as U.S. Appl. No. 10/803,259 on January 31, 2002. Lilly is directed to "an improved method for controlling information related to controlled substances and/or prescriptive medications." (Lilly, ¶[0033]). Furthermore, Lilly discloses that it is "desirable to provide a healthcare utility that can assist substantially in reducing [the] misuse[] and abuse[] [of] prescriptions," (*Id.* at ¶[0012]). To that end, Lilly maintains a data storage unit, *e.g.*, a computer, that "provides a scalable, robust data store that maintains all pertinent information about prescriptive medication activities." (*Id.* at ¶[0062]). Physicians, pharmacies, and government agencies all have the ability to access the data storage unit to determine if any abuse is taking place, and to act proactively to prevent such abuse. (*Id.* at ¶¶[0043], [0044], [0054], [0057], and [0058]). In addition, the data storage unit generates reports. (*Id.* at ¶[0069]).

59. Elsayed

Elsayed issued on April 4, 2000, and discloses "[n]ovel methods for delivering a drug to patient … in which the involved prescribers, pharmacies and patients are registered in one or more computer databases [and] registered patients receive counseling information concerning the risks [associated with the drug]." (Elsayed, Abstract). The method "permit[s] the distribution to patients of drugs … in ways wherein such distribution can or must be carefully monitored and controlled." (*Id.* at 1:14-17).

Elsayed discloses a method of distributing the teratogen thalidomide. (*Id.* at claim 2). However, the methods disclosed in Elsayed are "not limited to the distribution of teratogenic drugs," and "other potentially hazardous drugs may also be distributed in accordance with embodiments of [the disclosed] invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them." (*Id.* at 3:10-15). Elsayed defines the term contraindicated as "any condition in a patient which renders a particular

line of treatment, including the administration of one or more drugs, undesirable or improper." (*Id.* at 3:45-50).

Elsayed's method registers prescribers in a computer readable storage medium to authorize them to prescribe the controlled drug. (*Id.* at 4:10-16). Additionally, pharmacies can become registered in a computer readable storage medium to become eligible to dispense a drug. (*Id.* at 4:50-54). The pharmacy must agree to comply with the controls placed on the dispensing of the drug to become registered. (*Id.* at 4:57-66). Furthermore, a patient becomes eligible to receive the drug by registering in a computer readable storage medium as well. (*Id.* at 5:25-37). The same computer readable storage medium can be used to register the prescriber, pharmacy, and patient. (*Id.* at 4:54-57 and 5:30-33).

The patient acknowledges that he understands the risks associated with taking a drug by filling out and signing an informed consent form. (*Id.* 7:40-45). In the informed consent form, the patient agrees to abide in a manner consistent with the prescriber's counsel in regards to the risk of using the drug. (*Id.* at 7:42-45). Such counseling can include information regarding the dangers of sharing the prescribed drug. (*Id.* at 7:13-15).

Furthermore, presentation of the informed consent form to the pharmacy can be required for filling of the prescription. (*Id.* at 9:10-12). Moreover, the disclosed method requires the patient to undergo counseling, fill out an informed consent form, and provide data before receiving a refill on their prescription. (*Id.* at 7:24-39; 8:9-13; and 9:30-50). For example, if the patient is prescribed thalidomide, the patient agrees in the informed consent form to use birth control, and if female, to undergo pregnancy testing before receiving a supply of the drug each time. (*Id.* at 7:42-65, 9:30-50, and claim 1).

In addition, Elsayed discloses controlling the prescription by providing only a limited supply of a drug to a patient at one time to promote patient compliance with the counseling received. (*Id.* at 9:30-50). The patient receives only a one-month's supply of the prescribed drug with no refills available. (*Id.* at 9:30-33). Thus, for the patient to receive a new supply, he must meet with his prescriber in a follow-up visit, during which he will receive counseling again, fill out the informed consent form another time, and provide data to be collected. (*Id.* at 9:34-50).

The method also envisions maintaining data in a computer readable storage medium to determine patients for which a drug has become contraindicated. (*Id.* at 8:26-36). If analysis of this data indicates that a drug has become contraindicated, "treatment of the patient with the involved drug may be terminated…." (*Id.* at 8:45-48). Additionally, the pharmacy can keep track of the patients prescription to prevent filling of the prescription before the patient has used up the patient's current supply. (*Id.* at 10:7-12). "Thus, the computer readable storage medium may serve to deny access, dispension or prescriptions of contraindicated drugs … to patients … or prescribers who fail to abide by" the disclosed methods. (*Id.* at 10:17-21).

60. Williams

Williams issued on November 13, 2001, and discloses a method "in which prescriptions for [a] drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber, pharmacy and patient have been properly registered in the medium before the patient is approved to receive the drug." (Williams, Abstract). Williams states, "the methods of the … invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients … prescribers … and pharmacies … to ensure proper prescribing and dispensing of [a] drug, as well as patient compliance with taking the drug." (*Id.* at 3:49-59).

Williams discloses a method of distributing the teratogen thalidomide. (*Id.* at claim 22). However, the methods disclosed in Williams are "not limited to the distribution of teratogenic drugs," and "other potentially hazardous drugs may also be distributed in accordance with embodiments of [the disclosed] invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them." (*Id.* at 3:21-26). Williams defines the term contraindicated as "any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper." (*Id.* at 4:5-8).

Williams's method registers prescribers in a computer readable storage medium to authorize them to prescribe the controlled drug. (*Id.* at 4:43-46). Additionally, pharmacies can become registered in a computer readable storage medium to become eligible to dispense a drug. (*Id.* at 5:17-21). The pharmacy must agree to comply with the controls placed on the dispensing of the drug to become registered. (*Id.* at 5:24-35). Furthermore, a patient becomes eligible to receive the drug by registering in a computer readable storage medium as well. (*Id.* at 5:61-63). The same computer readable storage medium can be used to register the prescriber, pharmacy, and patient. (*Id.* at 5:21-24 and 5:63-67).

The patient acknowledges that he understands the risks associated with taking a drug by filling out and signing an informed consent form. (*Id.* at 5:67 through 6:3; 10:23-28). In the informed consent form, the patient agrees to abide in a manner consistent with the prescriber's counsel in regards to the risk of using the drug. (*Id.* at 10:41-46). Such counseling can include information regarding the dangers of sharing the prescribed drug. (*Id.* at 10:3-5).

Furthermore, presentation of the informed consent form to the pharmacy can be required for filling of the prescription. (*Id.* at 12:8-11). Verification that the patient has supplied the

informed consent form can be stored on the computer readable storage medium as well. (*Id.* at 10:30-32). Moreover, the disclosed method requires the patient to undergo counseling, fill out an informed consent form, and provide data before receiving the a refill on their prescription. (*Id.* at 12:35-55). For example, if the patient is prescribed thalidomide, the patient agrees in the informed consent form to use birth control, and if female, to undergo pregnancy testing before receiving a supply of the drug each time. (*Id.* at 10:7-17 and 12:35-55).

In addition, Williams discloses controlling the prescription by providing only a limited supply of a drug to a patient at one time to promote patient compliance with the counseling received. (*Id.* at 12:35-55). The patient receives only a one-month's supply of the prescribed drug with no refills available. (*Id.* at 12:35-38). Thus, for the patient to receive a new supply, he must meet with his prescriber in a follow-up visit, during which he will receive counseling again, fill out the informed consent form another time, and provide data to be collected. (*Id.* at 12:39-55).

The method also envisions maintaining data in a computer readable storage medium to determine patients for which a drug has become contraindicated. (*Id.* at 11:32-42). If analysis of this data indicates that a drug has become contraindicated, "treatment of the patient with the involved drug may be terminated…." (*Id.* at 11:51-54). Additionally, the pharmacy can keep track of the patients prescription to prevent filling of the prescription before the patient has used up the patient's current supply. (*Id.* at 13:7-18). "Thus, the computer readable storage medium may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs … to patients … or prescribers who fail to abide by" the disclosed methods. (*Id.* at 13:23-27).

61. Melker

Melker was filed as U.S. Appl. No. 10/154,201 on May 22, 2002. Melker is directed to "a method and apparatus for detecting use of illicit substances…." (Melker, Abstract). Melker

discloses that GHB is an illicit drug, "the use of which leads to risks of coma and death." (*Id.* at ¶[0003]). Also, Melker teaches that GHB can be used for the treatment of narcolepsy. (*Id.*).

62. Borsand

Borsand was filed as U.S. Appl. No. 09/976,650 on October 12, 2001. Borsand is directed to "[a] system that facilitates direct, efficient, non-liner, integrated and proactive communications between a payor, a PBM, a pharmacy, and health care provider such as a physician." (Borsand, Abstract). Borsand teaches that "[i]t would be desirable for pharmaceutical information to be stored only once and in a centralized location accessible by the appropriate parties." (*Id.* at ¶[0003]). To that end, "in a preferred embodiment … 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." (*Id.* at ¶[0043] and Fig. 3). The single database maintains, *inter alia*, prescription, patient, and provider (*e.g.*, physician) information. (*Id.* at Fig. 3 and ¶[0030]). Borsand also discloses an electronic formulary that is housed in a computer that can be a single centralized computer or server, a single network, or a series of interconnected networks. (*Id.* at ¶[0031]).

In addition, the system of Borsand detects prescription abuse. (*Id.* at ¶¶[0034] and [0120]). The system tracks if a patient attempts to refill a prescription before his current prescription has run out, and the system is capable of cancelling a prescription if evidence of fraud or misuse on the part of the provider or patient is detected. (*Id.* at ¶[0120]). Furthermore, the system of Borsand can track such abuse or misuse in the form of reports. (*Id.* at ¶[0034]).

63. Ukens

Ukens was published on June 5, 2000. Ukens discusses specialty pharmacies and discloses restricting the distribution of pharmaceuticals to only one pharmacy. (Ukens, 42:2, ¶1 through 3, ¶1). Furthermore, Ukens teaches a reason for such restriction is to limit access to

dangerous drugs. (*Id.* at 42:3, ¶1). The specialty pharmacies that dispense such prescriptions can also monitor dosage and patient compliance. (*Id.* at 41:3, ¶1).

In addition to being the sole pharmacy distributing a drug, the specialty pharmacies of Ukens can authorize other pharmacies to distribute specialty prescriptions. (*Id.* at 44:1, ¶3 through 3, ¶2). For example, a specialty pharmacy, TheraCom, set up a network of 4,000 independent pharmacies to distribute specialty pharmaceuticals. The independent pharmacies can "pick and choose which drugs to stock and provide patient support for." (*Id.* at 44:1, ¶1 through 2, ¶2). The network also provides "face-to-face counseling" to patients and "compliance monitoring and follow-ups." (*Id.* at 44:2, ¶3). Ukens also discloses that restricting pharmaceuticals to only one pharmacy can cause problems with discovering drug interactions or cause a patient to fail to receive his prescription should there be a delivery failure. (*Id.* at 42:2, ¶1 through 3, ¶1).

64. Talk About Sleep

Talk About Sleep was published online on February 12, 2001, and discloses distributing Xyrem, *i.e.*, GHB, through a central pharmacy. (Talk About Sleep, pg. 1, ¶¶8-10). Such a method will promote the distribution and use of Xyrem in a responsible manner. (*Id.* at pg. 2, ¶10). Also, Talk About Sleep discloses that the Xyrem distribution program was developed with "assistance and input from State Scheduling authorities, experts in specialty distribution, drug diversion investigators, field law enforcement, narcolepsy patient groups, and pharmacists experienced in dealing with Scheduled medicines." (*Id.* at pg. 1, ¶10). Talk About Sleep also discloses that Xyrem is a treatment for the symptoms of narcolepsy, and that the drug will not be available to prescribe until after it is approved. (*Id.* at pg. 1, ¶¶1,4,5,11).

65. EP '027

EP '027 published on February 10, 1993, and is directed to a fluid dispenser having a mixing cylinder in which a movable piston divides a liquid additive chamber from a displacing liquid chamber. (EP '027 at Abstract.) It discloses that there are instances when it is desirable to add more than one additive liquid to the carrier liquid, and illustrates a system having multiple measuring cylinders, each of which contains a different additive that can be added, *inter alia*, sequentially or simultaneously. (*Id.* at 2:45-51 and Figure 3).

66. Oxtoby

Oxtoby published in 1996, and it is a general chemistry textbook. It teaches that salts, or ionic compounds, result from the combination of anions with cations, and that ionic compounds are named by the name of the cation followed by that of the anion. (Oxtoby at pp. 53-54). Ions can be either monatomic or polyatomic. (Oxtoby at p. 54) A monatomic cation bears the name of the parent element. (*Id.*) The ammonium ion, NH_4^+, is a polyatomic cation obtained by adding H^+ to ammonia. (Oxtoby at p. 55).

B. The '431 Patent

1. *Obviousness*

Claims 1-7 of the '431 patent are invalid under 35 U.S.C. § 103(a) because they would have been obvious to a person of ordinary skill in the art prior to the filing date of the '431 patent in view of one or more of the prior art references discussed herein.

Aqueous solutions of GHB salts are disclosed by **Vickers**, **CA 338**, **the '632 patent**, **the '619 patent**, **Mamelak (1977)**, **the '236 patent**, and **EP '804**. **The '937 patent** discloses that GHB is available as a pharmaceutical exclusively as the sodium salt, and that all experimental and clinical investigations have without exception been performed with the sodium salt, the acid

itself, or the corresponding lactone. **Vickers** discloses that gamma-hydroxybutyric acid is marketed for intravenous injection as a solution containing 2.42 g sodium 4-hydroxybutyrate in 10 ml water, with a pH between 8.2 and 8.9. **Vickers** also teaches that gamma-hydroxybutyric acid has been tried as a night sedative. **Vickers** further teaches that it is water soluble in all dilutions, and the pH of the solution is not far from physiological. **The '632 patent** and **the '619 patent** also disclose solutions containing at least 250 mg/ml sodium 4-hydroxybutyrate. **The '619 patent** states that sodium 4-hydroxybutyrate is highly soluble in water. **The '632 patent** provides pharmaceutical compositions of GHB salts in solution form and containing 12.5 to 50% GHB salt content by weight. **The '619 patent** discloses that solutions of GHB salts have pH values slightly in excess of 7; **CA 338** provides examples of solutions of alkali metal salts of GHB with pH values ranging from 7.2 to 7.7.

Nema discloses that, depending on the route of administration, preservatives may not be allowed in injectable formulations. **Nema** further states that injectable products are required to withstand sterilization processes. **Wickliffe** recites that bacterial growth has been shown to be inhibited at pH 2 without the use of additional preservative material, and that asepsis has also been reported above pH 9. **CA 338**, **the '632 patent**, **the '619 patent**, **the '236 patent**, and **EP '804** provide examples of preservative-free pharmaceutical compositions designed for administration to patients, including some which were.

The 1990 CRC Handbook discloses that gamma-hydroxybutyric acid has a dissociation constant in aqueous solution with a pK value of 4.72. **Remington's** states that hydrochloric acid is used as a pharmaceutic aid to acidify a solution. The **1995 USP** provides a list of 13 acidifying agents used as pharmaceutic ingredients, and that list includes acetic acid, citric acid, hydrochloric acid, malic acid, nitric acid, phosphoric acid, and sulfuric acid. **Nema** also lists

acetic acid, citric acid, hydrochloric acid, phosphoric acid, and sulfuric acid as pH adjusting agents used in injectable formulations.

A person of ordinary skill in the art reading Vickers would have been motivated to prepare an aqueous solution of a gamma-hydroxybutyrate salt. A person of ordinary skill in the art reading Vickers in view of the '937 patent, alone or in combination with any of the '632 patent, the '619 patent, Mamelak (1977), the '236 patent, or EP '804, would have been specifically motivated to select the sodium salt. A person of ordinary skill in the art reading Vickers in view of the '619 patent and the '632 patent would have been motivated to prepare a solution containing 500 mg/ml, or 310-750 mg/ml, sodium gamma-hydroxybutyrate, with a reasonable expectation of success. A person of ordinary skill in the art reading Vickers in view of CA 338 and the '619 patent would have reasonably expected such a solution to have a pH between 6 and 10.

Furthermore, a person of ordinary skill in the art reading Vickers in view of the 1990 CRC Handbook would have recognized that the aqueous solution containing 242 mg/ml sodium 4-hydroxybutyrate disclosed in Vickers would inherently have a pH of about 9.5. Accordingly, a person of ordinary skill in the art would have recognized that, in order to attain the reported pH of 8.2 to 8.9, it would be necessary to use a pH-adjusting agent, specifically, an acidifying agent. In further view of any of Remington's, the 1995 USP, or Nema, a person of ordinary skill in the art would have routinely used any of malic acid, citric acid, acetic acid, lactic acid, hydrochloric acid, phosphoric acid, or sulfuric acid to adjust the pH of the Vickers formulation from 9.5 to the reported 8.2-8.9 range. Furthermore, a person of ordinary skill in the art would have known that malic acid, citric acid, acetic acid, and lactic acid are organic acids.

Lastly, a person of ordinary skill in the art reading Vickers in view of CA 338, the '632 patent, the '619 patent, the '236 patent, or EP '804 would have recognized that, in order for the preservative-free pharmaceutical compositions disclosed therein to be administered to patients, they would have had to be inherently chemically stable and resistant to microbial growth. In further view of Nema or Wickliffe, a person of ordinary skill in the art would have been motivated to exclude preservatives from the aqueous formulation.

2. *35 U.S.C. § 112, ¶1*

Claims 1-7 are invalid under 35 U.S.C. § 112, ¶1 for lacking written description support and enablement. Specifically, in view of statements made by the applicant during prosecution, each of these claims require the exclusion of a preservative. But in view of the Court's construction in the corresponding *Roxane* case, these claims, as drafted, do in fact include a preservative. Thus, the specification neither enables nor provides written description support for claims that require the exclusion of a preservative, as argued in the prosecution history.

Claim 6 explicitly requires a pH-adjusting agent. Claim 7 depends from claim 6 and therefore also requires the same pH-adjusting agent. And claim 1 and all claims dependent therefrom require the step of adjusting the pH, thereby also requiring the addition of a pH-adjusting agent.

Under the Court's construction in Jazz's case against Roxane, the pH-adjusting agent required by claims 1-7 must be construed as a "preservative." The Court construed "preservative" to mean "a substance or substances added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action." *See Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.,* 2:10-cv-06108-ES-SCM (consolidated) (D.N.J. Nov. 22, 2010), D.I. 151, at p. 16 ("*Roxane Markman* Order"). The '431 patent asserts that adjusting the

pH is a means to inhibit chemical change or microbial action. So, under the Court's construction, a pH-adjusting required in the claims is properly construed as a "preservative."

But, during prosecution of the '431 patent, to overcome the Examiner's prior art rejections, Applicants argued that the cited prior art references do not teach any way to make aqueous GHB solutions resistant to microbial degradation other than by the addition of a preservative. Specifically, the Applicants argued that:

> Gessa does not disclose any way to make GHB aqueous solutions stable to microbial degradation ***other than by using conventional preservatives*** in Examples 1 and 2. … 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***…. [N]one of the references teach or suggest solutions of GHB salt that are resistant to microbial growth ***without an added preservative***.

(Prosecution History of the '431 patent, Amendment and Reply submitted on August 10, 2001 (emphasis added).) (*See, e.g.,* AMNXYR_000002621-AMNXYR_000002625.). In so arguing, Applicants clearly and unmistakably surrendered a method of making gamma-hydroxybutyrate formulations using preservatives. Yet, claim 1 (and all claims dependent therefrom) must be held to require such a method comprising a preservative.

Claims 1-7 explicitly require adjusting the pH, and, in view of the prosecution history, also require the exclusion of preservatives. But, under the Court's definition of "preservative" in the *Roxane* case, the required pH-adjusting agent necessarily acts as a preservative. As a result, claims 1-7 lack enablement and written description support, since the specification does not teach any way to exclude preservatives while also using a preservative, as required by the claims.

3. *35 U.S.C. § 112, ¶2*

Claims 1-7 are invalid under 35 U.S.C. § 112, ¶2 for being indefinite on multiple grounds.

First, each of claims 1-7 are invalid as indefinite for lacking a proper antecedent basis. For example, claim 1 of the '431 patent recites, "… the gamma-hydroxybutyrate salt." In addition, claim 6 recites, "… said pH-adjusting agent." But there is no antecedent basis for either "the gamma-hydroxybutyrate salt" or "said pH-adjusting agent" recited respectively in these claims. And since claims 2-7 all depend, directly or indirectly, from claims 1 or 6, they too are invalid as indefinite for the same reasons.

Next, each of claims 1-7 are also invalid as indefinite because their terms are hopelessly vague and insolubly ambiguous, thus rendering their scope unascertainable. Claim 6 explicitly requires a pH-adjusting agent. Claim 7 depends from claim 6 and therefore also requires the same pH-adjusting agent. And claim 1 and all claims dependent therefrom require the step of adjusting the pH, thereby also requiring the addition of a pH-adjusting agent.

Under the Court's construction in Jazz's case against Roxane, the pH-adjusting agent required by claims 1-7 must be construed as a "preservative." In the *Markman* order in *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, the Court construed "preservative" to mean "a substance or substances added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action." (*See Roxane Markman* Order at p. 16). The '431 patent asserts that adjusting the pH is a means to inhibit chemical change or microbial action. So, under the Court's construction, a pH-adjusting required in the claims is properly construed as a "preservative."

But, during prosecution of the '431 patent, to overcome the Examiner's prior art rejections, Applicants argued that the cited prior art references do not teach any way to make aqueous GHB solutions resistant to microbial degradation other than by the addition of a preservative. Specifically, the Applicants argued that:

> Gessa does not disclose any way to make GHB aqueous solutions stable to microbial degradation ***other than by using conventional preservatives*** in Examples 1 and 2. … 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***…. [N]one of the references teach or suggest solutions of GHB salt that are resistant to microbial growth ***without an added preservative***.

(Prosecution History of the '431 patent, Amendment and Reply submitted on August 10, 2001 (emphasis added).) (*See, e.g.,* AMNXYR_000002621-AMNXYR_000002625.). In so arguing, Applicants clearly and unmistakably surrendered a method of making gamma-hydroxybutyrate formulations using preservatives. Yet, claim 1 (and all claims dependent therefrom) must be held to require such a method comprising a preservative. As a result, the requirement of a pH-adjusting agent in claims 1-7, which acts as a preservative under the Court's construction, contradicts the express requirement from the prosecution history that these claims do not utilize a preservatives in the aqueous medium. That is, even though the claims purport to require the exclusion of a preservative, they do in fact require a preservative, as written, under the Court's construction of "preservative." As a consequence, claims 1-7 are hopelessly vague and insolubly ambiguous, leading to a finding that they are indefinite.

Lastly, Claim 7 is invalid as indefinite because it requires the selection of an organic acid from a list that also includes inorganic acids. Claim 7 depends from claim 6, which requires that the pH-adjusting agent is an organic acid. However, the list of acids in claim 7 provides a list that includes both organic and inorganic acids, *i.e.*, boric acid, hydrochloric acid, phosphoric acid, sulfuric acid, sulfonic acid, and nitric acid. Therefore, Claim 7 requires the selection of an organic acid from a list that also includes inorganic acids, rendering it indefinite.

4. *35 U.S.C. § 112, ¶4*

Claims 4 and 7 are invalid under 35 U.S.C. § 112, ¶4 for being improper dependent claims.

First, claim 4 is an improper dependent claim. As discussed *supra*, during prosecution of the application that issued as the '431 patent, the Applicants argued that their invention was patentable over the prior art because none of the prior art references taught a way to make aqueous GHB solutions resistant to microbial degradation other than by the addition of a conventional preservative. In arguing this, Applicants clearly and unmistakably surrendered a method of making gamma-hydroxybutyrate formulations using conventional preservatives, and claim 1 must be held to require a method wherein an aqueous medium containing a gamma-hydroxybutyrate salt is free of a preservative. As a result, claim 4, which explicitly requires the absence of a preservative, is not narrower than claim 1, from which it depends, and it is therefore an improper dependent claim.

Lastly, claim 7 is an improper dependent claim. Claim 7 depends from claim 6, which requires that the pH-adjusting agent is an organic acid. However, the list of acids in claim 7 includes six inorganic acids. As a result, claim 7 is an improper dependent claim, since it is not narrower than the claim from which it depends.

5. *35 U.S.C. § 112, ¶5*

Claim 4 is invalid under 35 U.S.C. § 112, ¶5 for being an improper multiple dependent claim. Claim 4 is a multiple dependent claim that depends from any of claims 1, 2, or 3. However, claim 3 is also a multiple dependent claim that depends from claims 1 or 2. Since a multiple dependent claim may not depend from another multiple dependent claim, claim 4 is invalid for being an improper multiple dependent claim.

'431 Patent Claim	Invalidity
1. 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.	**The '937 patent** discloses that GHB is available as a pharmaceutical exclusively as the sodium salt, and that all experimental and clinical investigations have without exception been performed with the sodium salt, the acid itself, or the corresponding lactone. *See*, *e.g.*, 1:7-15. **Nema** discloses that injectable products are required to withstand sterilization processes such as autoclaving. It is also disclosed that preservatives may not be allowed in some injectable products, depending on the route of administration. It is also disclosed that chelating agents are used in parenteral products to complex heavy metals, thereby improving the efficacy of antioxidants or preservatives. Also disclosed are buffers and chemicals used to adjust the pH of formulations, and a table of 32 buffers and pH-adjusting agents, including organic and inorganic acids. *See*, *e.g.*, pp. 166-169. **Vickers** discloses that gamma-hydroxybutyrate is water soluble in all dilutions, and that the pH of the solution is not far from physiological. It is also disclosed that gamma-hydroxybutyric acid is marketed for intravenous injection as a solution containing 2.42 g sodium 4-hydroxybutyrate in 10 ml water, with a pH between 8.2 and 8.9. *See*, *e.g.*, pp. 75, 82-87. **CA 338** discloses the preparation of 4-hydroxybutyric acid salt solutions of pH 7.2-7.7 for injection. *See* abstract. **The '632 patent** discloses the use of gamma-hydroxybutyric acid salts for preparing pharmaceutical compositions. It is also disclosed that suitable gamma-hydroxybutyric acid salts include the sodium salt, and that the GHB salt content of the compositions can vary from 12.5 to 50% by weight. Also disclosed are a bottle containing 140 ml of solution containing 42.35 g of sodium gamma-hydroxybutyric acid, a bottle containing 20 ml of solution containing 6.05 g of sodium gamma-hydroxybutyric acid, and an injectable formulation of sodium gamma-hydroxybutyrate free of preservatives. *See*, *e.g.*, abstract, 7:32-33, 7:47-49, examples 1-2, 8:57-59. **The '619 patent** discloses that sodium 4-hydroxybutyrate is highly soluble in water and, in aqueous solution, has a pH slightly in excess of 7. It also discloses formulations that are free of preservatives, including one that was administered to a patient just prior to undergoing surgery. *See*, *e.g.*, 1:61-66, examples 1-

'431 Patent Claim	Invalidity
	3. **Mamelak (1977)** discloses that γ-hydroxybutyrate is marketed by Laboratoire Egic of Paris, France, as a banana-flavored syrup. It also discloses the use of GHB, obtained as a banana-flavored syrup, in a dose of 1.0-4.5 g and placebo in a dose of 5 cc banana flavoring in water, and exploring the use of sodium gamma-hydroxybutyrate to treat insomnia. *See*, *e.g.*, pp. 273, 274, 275. **The '236 patent** discloses that the calcium and magnesium salts of 4-hydroxybutyric acid can be dispensed as aqueous solutions, and that the sodium salt of 4-hydroxybutyric acid induces sleep. *See*, *e.g.*, 1:38-43, 4:39-47. **EP '804** discloses administration of salts of gamma-hydroxybutyric acid in the form of single or multi-dose liquid solutions, with the sodium salt being particularly preferred. It also discloses a formulation for intravenous injection that is free of preservatives. *See*, *e.g.*, 2:38-39, 6:32-34, formulation 3. **Remington's** discloses means to achieve drug stabilization from photolytic, oxidative, and solvolytic decomposition reactions. It is also disclosed that hydrochloric acid is a pharmaceutic aid that is used as an acidifying agent. *See*, *e.g.*, pp. 239, 1410. **The 1995 USP** discloses a list of 13 acidifying agents among USP and NF Pharmaceutic Ingredients, including organic and inorganic acids. *See*, *e.g.*, p. 2205. **The 1990 CRC Handbook** discloses that γ-Hydroxybutyric acid has a pK_a of 4.72 in aqueous solution. *See*, *e.g.*, p. 8-36. **Wickliffe** discloses that bacterial growth has been shown to be inhibited at pH 2 without the use of additional preservative material, and that asepsis also occurs above pH 9. *See*, *e.g.*, p. 770.
2. The method of claim 1 wherein the salt is sodium gamma-hydroxybutyrate.	*See supra* claim 1.
3. The method of claim 1 or 2 wherein the final concentration is from about 310 to about 750 mg/ml and the final pH is about 6 to about	*See supra* claim 1.

'431 Patent Claim	Invalidity
9.	
4. The method of claim 1, 2, or 3 wherein the medium does not contain a preservative.	*See supra* claim 1.
5. The method of claim 1, wherein the concentration of said gamma-hydroxybutyrate is from about 250 to about 750 mg/ml.	*See supra* claim 1.
6. The method of claim 1, wherein said pH-adjusting agent is an organic acid.	*See supra* claim 1. *See also*, 21 C.F.R. §§ 184.1005, 184.1033, 184.1061, 184.1069, 184.1081, and 184.1099.
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.	*See supra* claims 1 and 6. *See also*, 21 C.F.R. § 184.1095.

C. The '889 Patent

1. *Obviousness*

Claim 1 of the '889 patent is invalid under 35 U.S.C. § 103(a) because it would have been obvious to a person of ordinary skill in the art prior to the filing date of the '889 patent in view of one or more of the prior art references discussed herein.

Aqueous pharmaceutical compositions of gamma-hydroxybutyrate are disclosed by **Vickers**, **the '632 patent**, **EP '804**, **the '236 patent**, and **the '619 patent**. Aqueous solutions of the sodium salt are explicitly disclosed by **the '937 patent**, **the '632 patent**, **EP '804**, **the '236 patent**, **Vickers**, and **the '619 patent**.

The '632 patent discloses compositions of gamma-hydroxybutyrate salts, of which sodium is a suitable selection, containing 12.5-50% GHB salt content by weight. **Vickers** teaches that gamma-hydroxybutyric acid is soluble in water in all dilutions and the pH is not far from physiological. **Vickers** also notes that gamma-hydroxybutyric acid is marketed for intravenous injection as an aqueous solution containing 2.42 g sodium gamma-hydroxybutyrate in 10 ml water, with a pH of 8.2-8.9. **CA 338** asserts that the alkali metal salts of GHB, as usually prepared, have far too high a pH for injection as 20% solutions; in light of this problem, **CA 338** details the preparation of injectable solutions by hydrolysis of gamma-butyrolactone with slightly less than the theoretical amount of alkali hydroxide, so as to obtain solutions of pH 7.2-7.7. **The 1995 USP** includes malic acid among a list of 13 acidifying agents used as pharmaceutic ingredients.

Nema teaches that, depending on the route of administration, preservatives may not be allowed in injectable formulations. **Nema** further teaches that injectable products are required to withstand sterilization processes. **Wickliffe** states that bacterial growth has been shown to be inhibited at pH 2 without the use of additional preservative material, and that asepsis has also been reported above pH 9. **CA 338**, **the '632 patent**, **the '619 patent**, **the '236 patent**, and **EP '804** provide preservative-free pharmaceutical compositions designed for administration to patients, including some which were.

A person of ordinary skill in the art reading Vickers, alone or in combination with any of the '937 patent, the '632 patent, EP '804, the '236 patent, and the '619 patent, would have been motivated to prepare an aqueous pharmaceutical composition of sodium gamma-hydroxybutyrate. A person of ordinary skill in the art reading Vickers in view of the '632 patent

would have been motivated to prepare such a composition to have a GHB salt concentration of at least 500 mg/ml, with a reasonable expectation of success.

In addition, a person of ordinary skill in the art reading Vickers in view of CA 338 would have been motivated to lower the pH of the sodium gamma-hydroxybutyrate solution to 7.2-7.7, or about 7.5, in order to obtain a more ideal solution for injection. In further view of the 1995 USP, a person of ordinary skill in the art would have used malic acid as a pH-adjusting agent.

A person of ordinary skill in the art reading Vickers in view of CA 338, the '632 patent, the '619 patent, the '236 patent, or EP '804 would have recognized that, in order for the preservative-free pharmaceutical compositions disclosed therein to be administered to patients, they would have had to be inherently chemically stable and resistant to microbial growth. In further view of Nema or Wickliffe, a person of ordinary skill in the art would have been motivated to exclude preservatives from the aqueous formulation.

2. *35 U.S.C. § 112, ¶1*

Claim 1 is invalid under 35 U.S.C. § 112, ¶1 for lacking written description support and enablement. Specifically, in view of statements made by the applicant during prosecution, this claim requires the exclusion of a preservative. But in view of the Court's construction in the *Roxane* case, the claim, as drafted, does in fact include a preservative. Thus, the specification neither enables nor provides written description support for a claim that requires the exclusion of a preservative, as argued in the prosecution history.

Claim 1 explicitly requires a pH-adjusting agent. Under the Court's construction in Jazz's case against Roxane, the pH-adjusting agent required by claim 1 must be construed as a "preservative." The Court construed "preservative" to mean "a substance or substances added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action." (*See Roxane Markman* Order at p. 16). The '889 patent asserts that adjusting the pH is a

means to inhibit chemical change or microbial action. So, under the Court's construction, a pH-adjusting required in the claims is properly construed as a "preservative."

But, during prosecution of the '431 patent, which is the parent of the '889 patent, to overcome the Examiner's prior art rejections, Applicants argued that the cited prior art references do not teach any way to make aqueous GHB solutions resistant to microbial degradation other than by the addition of a preservative. Specifically, the Applicants argued that:

> Gessa does not disclose any way to make GHB aqueous solutions stable to microbial degradation ***other than by using conventional preservatives*** in Examples 1 and 2. … 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***…. [N]one of the references teach or suggest solutions of GHB salt that are resistant to microbial growth ***without an added preservative***.

(Prosecution History of the '431 patent, Amendment and Reply submitted on August 10, 2001 (emphasis added).) (*See, e.g.,* AMNXYR_000002621-AMNXYR_000002625.). In so arguing, Applicants clearly and unmistakably surrendered a method of making gamma-hydroxybutyrate formulations using preservatives. Yet, claim 1 of the '889 patent must be held to require such a method comprising a preservative.

Claim 1 explicitly requires adjusting the pH, and, in view of the prosecution history and the claim language, also require the exclusion of preservatives. But, under the Court's definition of "preservative" in the Roxane case, the required pH-adjusting agent necessarily acts as a preservative. As a result, claim 1 lacks enablement and written description support, since the specification does not teach any way to exclude preservatives while also using a preservative, as required by the claim.

3. *35 U.S.C. § 112, ¶2*

Claim 1 is invalid under 35 U.S.C. § 112, ¶2 for being indefinite because its terms are hopelessly vague and insolubly ambiguous, thus rendering its scope unascertainable. Claim 1 explicitly requires malic acid as a pH-adjusting agent. Under the Court's construction in Jazz's case against Roxane, the pH-adjusting agent must be construed as a "preservative." In the *Markman* order in *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, the Court construed "preservative" to mean "a substance or substances added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action." (*See Roxane Markman* Order at p. 16). The '889 patent asserts that adjusting the pH is a means to inhibit chemical change or microbial action. So, under the Court's construction, a pH-adjusting required in the claims is properly construed as a "preservative."

But, during prosecution of the '431 patent, which is the parent of the '889 patent, to overcome the Examiner's prior art rejections, Applicants argued that the cited prior art references do not teach any way to make aqueous GHB solutions resistant to microbial degradation other than by the addition of a preservative. Specifically, the Applicants argued that:

> Gessa does not disclose any way to make GHB aqueous solutions stable to microbial degradation ***other than by using conventional preservatives*** in Examples 1 and 2. … 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***…. [N]one of the references teach or suggest solutions of GHB salt that are resistant to microbial growth ***without an added preservative***.

(Prosecution History of the '431 patent, Amendment and Reply submitted on August 10, 2001 (emphasis added).) (*See, e.g.,* AMNXYR_000002621-AMNXYR_000002625.). In so arguing, Applicants clearly and unmistakably surrendered a method of making gamma-hydroxybutyrate formulations using preservatives. Yet, claim 1 of the '889 patent must be held to require such a

method comprising a preservative. As a result, the requirement of a pH-adjusting agent in claim 1, which acts as a preservative under the Court's construction, contradicts the express requirement from the prosecution history and the claim language that the claims does not utilize preservatives in the aqueous medium. That is, even though the claim purports to require the exclusion of a preservative, it does in fact require a preservative, as written, under the Court's construction of "preservative." As a consequence, claim 1 is hopelessly vague and insolubly ambiguous, leading to a finding that it is indefinite.

Claim Charts

'889 Patent Claim	Invalidity
1. A pharmaceutical composition, consisting essentially of an aqueous solution of 500 mg/ml sodium gamma-hydroxybutyrate, 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.	**The '632 patent** discloses pharmaceutical compositions of gamma-hydroxybutyric acid salts useful for treatment of alcoholism. It is also disclosed that suitable salts include the sodium salt, and that the GHB salt content of the compositions can vary from 12.5 to 50% by weight. Also disclosed is an injectable preparation of sodium gamma-hydroxybutyrate which is free of preservatives. *See*, *e.g.*, Abstract, 7:32-33, 7:47-49, 8:57-59. **The '937 patent** discloses that GHB is available as a pharmaceutical exclusively as the sodium salt, and that all experimental and clinical investigations have without exception been performed with the sodium salt, the acid itself, or the corresponding lactone. *See*, *e.g.*, 1:7-15. **EP '804** discloses the preparation of orally administrable pharmaceutical compositions of gamma-hydroxybutyric acid salts, and it also discloses a formulation for intravenous injection that is free of preservatives. *See*, *e.g.*, 6:32-34, formulation 3. **The '236 patent** discloses that sodium 4-hydroxybutyrate has been used in medicine to induce both anesthesia and sleep. *See*, *e.g.*, 1:38-43. **Vickers** discloses that gamma-hydroxybutyrate is water soluble in all dilutions, and that the pH of the solution is not far from physiological. It is also disclosed that GHB is marketed for intravenous injection as a solution of 2.42 gm sodium gamma-

'889 Patent Claim	Invalidity
	hydroxybutyrate in 10 ml water, with a pH of 8.2-8.9. *See*, *e.g.*, pp. 75, 82-87. **The 1995 USP** discloses the use of malic acid as one of 13 acidifying agents among USP and NF Pharmaceutic Ingredients. *See*, *e.g.*, p. 2205. *See also*, 21 C.F.R. § 184.1069. **CA 338** discloses that the alkali metal salts of GHB, as usually prepared, have far too high a pH for injection as 20% solutions. It also discloses the preparation of 4-hydroxybutyric acid salt solutions of pH 7.2-7.7 for injection, by hydrolysis of GBL with slightly less than the theoretical amount of alkali hydroxide. *See*, *e.g.*, Abstract. **Remington's** discloses requirements for pharmaceutical stability and some approaches to achieving stability. pp. 239 and 639-640. **Nema** discloses that injectable products are required to withstand sterilization processes such as autoclaving, and that preservatives may not be allowed in some injectable products, depending on the route of administration. *See*, *e.g.*, p. 166. **Wickliffe** discloses that bacterial growth has been shown to be inhibited at pH 2 without the use of additional preservative material, and that asepsis also occurs above pH 9. *See*, *e.g.*, p. 770. **The '619 patent** discloses preservative-free formulations of sodium 4-hydroxy-butyrate, one of which was administered to a patient to induce anesthesia prior to surgery. *See*, *e.g.*, Examples 1-3.

D. The '219 Patent

1. *Obviousness*

Claims 1-4 of the '219 patent are invalid under 35 U.S.C. § 103(a) because they would have been obvious to a person of ordinary skill in the art prior to the filing date of the '219 patent in view of one or more of the prior art references discussed herein.

Aqueous pharmaceutical compositions of sodium gamma-hydroxybutyrate are disclosed by **Vickers**, **the '632 patent**, **Mamelak (1977)**, **the '236 patent**, **EP '804**, **the '937 patent**, and **the '619 patent.**

Vickers teaches that gamma-hydroxybutyric acid is water soluble in all dilutions, and that the pH of the solution is not far from physiological. **Vickers** also notes that gamma-hydroxybutyric acid is marketed for intravenous injection as a solution of 2.42 g sodium gamma-hydroxybutyrate in 10 ml water, which has a pH of 8.2-8.9. **The '632 patent** provides pharmaceutical compositions of salts of gamma-hydroxybutyrate, of which sodium is a suitable selection, containing 12.5-50% GHB salt content by weight. **Mamelak (1977)** states that GHB is commercially available as a solution in a banana-flavored syrup. **Mamelak (1977)** further states that patients were administered either 1.0-4.5g GHB, or a placebo consisting of 5 cc banana flavoring in water.

CA 338 asserts that the alkali metal salts of GHB, as usually prepared, have far too high a pH for injection as 20% solutions; in light of this problem, **CA 338** details the preparation of injectable solutions by hydrolysis of gamma-butyrolactone with slightly less than the theoretical amount of alkali hydroxide, so as to obtain solutions of pH 7.2-7.7.

The 1995 USP includes a list of 13 acidifying agents used as pharmaceutic ingredients, and that list includes acetic acid, citric acid, hydrochloric acid, malic acid, nitric acid, phosphoric acid, and sulfuric acid. **Nema** lists acetic acid, citric acid, hydrochloric acid, phosphoric acid, and sulfuric acid as pH adjusting agents used in injectable formulations. **Remington's** teaches that hydrochloric acid is used as a pharmaceutic aid to acidify a solution.

Nema also discloses that, depending on the route of administration, preservatives may not be allowed in injectable formulations. **Nema** further teaches that injectable products are

required to withstand sterilization processes. **Wickliffe** states that bacterial growth has been shown to be inhibited at pH 2 without the use of additional preservative material, and that asepsis has also been reported above pH 9. **CA 338**, **the '632 patent**, **the '619 patent**, **the '236 patent**, and **EP '804** provide preservative-free pharmaceutical compositions designed for administration to patients, including some which were.

A person of ordinary skill in the art reading Vickers, alone or in combination with any of the '632 patent, Mamelak (1977), the '236 patent, EP '804, the '937 patent, or the '619 patent, would have been motivated to prepare a pharmaceutical composition consisting essentially of an aqueous solution of sodium gamma-hydroxybutyrate. A person of ordinary skill in the art reading Vickers, alone or in combination with any of the '236 patent, EP '804, the '937 patent, and the '619 patent, in view of the '632 patent, would have prepared such a solution to contain 125-500 mg/ml, or 400-650 mg/ml, sodium gamma-hydroxybutyrate, with a reasonable expectation of success.

Additionally, a person of ordinary skill in the art reading Vickers, alone or in combination with any of the '632 patent, Mamelak (1977), the '236 patent, EP '804, the '937 patent, and the '619 patent, in view of CA 338, would have been motivated to adjust the pH of the Vickers intravenous injection formulation from the recited 8.2-8.9 down to the range 7.2-7.7 recited in CA 338, in order to obtain a more ideal solution for injection. In trying to do so, a person of ordinary skill in the art would have consulted any of the 1995 USP, Nema, or Remington's, which disclose malic acid, citric acid, acetic acid, propionic acid, tartaric acid, hydrochloric acid, phosphoric acid, sulfuric acid, and nitric acid as acidifying agents used as pharmaceutic ingredients and in injectable formulations.

Furthermore, a person of ordinary skill in the art reading Vickers, alone or in combination with any of the '632 patent, Mamelak (1977), the '236 patent, EP '804, the '937 patent, or the '619 patent, in view of any of CA 338, the '632 patent, the '619 patent, the '236 patent, or EP '804, would have recognized that, in order for the preservative-free compositions disclosed therein to be administered to patients, they would have had to be inherently chemically stable and resistant to microbial growth. In further view of Nema or Wickliffe, a person of ordinary skill in the art would have been motivated to exclude preservatives from the aqueous formulation.

2. *35 U.S.C. § 112, ¶1*

Claims 1-4 are invalid under 35 U.S.C. § 112, ¶1 for lacking written description support and enablement. Specifically, in view of statements made by the applicant during prosecution, each of these claims require the exclusion of a preservative. But in view of the Court's construction in the *Roxane* case, these claims, as drafted, do in fact include a preservative. Thus, the specification neither enables nor provides written description support for claims that require the exclusion of a preservative, as argued in the prosecution history.

Claims 1 and 4 explicitly require a pH-adjusting agent. Claims 2 and 3 depend from claim 1 and therefore also requires the same pH-adjusting agent.

Under the Court's construction in Jazz's case against Roxane, the pH-adjusting agent required by claims 1-4 must be construed as a "preservative." The Court construed "preservative" to mean "a substance or substances added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action." (*See Roxane Markman* Order at p. 16). The '219 patent asserts that adjusting the pH is a means to inhibit chemical change or microbial action. So, under the Court's construction, a pH-adjusting required in the claims is properly construed as a "preservative."

But, during prosecution of the '431 patent, which is an ancestor of the '219 patent, to overcome the Examiner's prior art rejections, Applicants argued that the cited prior art references do not teach any way to make aqueous GHB solutions resistant to microbial degradation other than by the addition of a preservative. Specifically, the Applicants argued that:

> Gessa does not disclose any way to make GHB aqueous solutions stable to microbial degradation ***other than by using conventional preservatives*** in Examples 1 and 2. … 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***…. [N]one of the references teach or suggest solutions of GHB salt that are resistant to microbial growth ***without an added preservative***.

(Prosecution History of the '431 patent, Amendment and Reply submitted on August 10, 2001 (emphasis added).) (*See, e.g.,* AMNXYR_000002621-AMNXYR_000002625.). In so arguing, Applicants clearly and unmistakably surrendered a method of making gamma-hydroxybutyrate formulations using preservatives. Yet, claims 1 and 4 of the '219 patent (and all claims dependent therefrom) must be held to require such a method comprising a preservative.

Claims 1-4 explicitly require adjusting the pH, and, in view of the prosecution history, also require the exclusion of preservatives. But, under the Court's definition of "preservative" in the Roxane case, the required pH-adjusting agent necessarily acts as a preservative. As a result, claims 1-4 lack enablement and written description support, since the specification does not teach any way to exclude preservatives while also using a preservative, as required by the claims.

3. *35 U.S.C. § 112, ¶2*

Claims 1-4 are invalid under 35 U.S.C. § 112, ¶2 for being indefinite because their terms are hopelessly vague and insolubly ambiguous, thus rendering their scope unascertainable. Claims 1 and 4 explicitly require a pH-adjusting agent. Claims 2 and 3 depend from claim 1 and therefore also explicitly require a pH-adjusting agent. Under the Court's construction in Jazz's

case against Roxane, the pH-adjusting agent must be construed as a "preservative." In the *Markman* order in *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, the Court construed "preservative" to mean "a substance or substances added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action." (*See Roxane Markman* Order at p. 16). The '219 patent asserts that adjusting the pH is a means to inhibit chemical change or microbial action. So, under the Court's construction, a pH-adjusting required in the claims is properly construed as a "preservative."

But, during prosecution of the application that issued as the '431 patent, which is the ancestral application of the '219 patent, to overcome the Examiner's prior art rejections, Applicants argued that the cited prior art references do not teach any way to make aqueous GHB solutions resistant to microbial degradation other than by the addition of a preservative. Specifically, the Applicants argued that:

> Gessa does not disclose any way to make GHB aqueous solutions stable to microbial degradation ***other than by using conventional preservatives*** in Examples 1 and 2. … 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***…. [N]one of the references teach or suggest solutions of GHB salt that are resistant to microbial growth ***without an added preservative***.

(Prosecution History of the '431 patent, Amendment and Reply submitted on August 10, 2001 (emphasis added).) (*See, e.g.,* AMNXYR_000002621-AMNXYR_000002625.). In so arguing, Applicants clearly and unmistakably surrendered a method of making gamma-hydroxybutyrate formulations using preservatives. Yet, claims 1-4 of the '219 patent must be held to require such a method comprising a preservative. As a result, the requirement of a pH-adjusting agent in claims 1-4, which acts as a preservative under the Court's construction, contradicts the express requirement from the prosecution history and the claim language that these claims do not utilize

preservatives in the aqueous medium. That is, even though the claims purport to require the exclusion of a preservative, they do in fact require a preservative, as written, under the Court's construction of "preservative." As a consequence, claims 1-4 are hopelessly vague and insolubly ambiguous, leading to a finding that they are indefinite.

Claim Charts

'219 Patent Claim	Invalidity
1. 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.	**The '632 patent** discloses the use of gamma-hydroxybutyric acid salts for preparing pharmaceutical compositions, that suitable salts include the sodium salt, and that the GHB salt content of the compositions can vary from 12.5 to 50% by weight. It also discloses a bottle containing 20 ml of solution containing 6.05 g of sodium gamma-hydroxy butyric acid, as well as an injectable formulation of sodium gamma-hydroxybutyrate free of preservatives. *See*, *e.g.*, Abstract, 7:32-33, 7:47-49, Example 2, 8:57-59. **Vickers** discloses oral and injectable use of sodium γ-hydroxybutyrate, which is water soluble in all dilutions, to induce sleep. It is also disclosed that gamma-hydroxybutyric acid is marketed for intravenous injection as a solution containing 2.42 g sodium 4-hydroxybutyrate in 10 ml water, with a pH between 8.2 and 8.9. *See*, *e.g.*, pp. 75, 78, 82, and 87. **Mamelak (1977)** discloses that γ-hydroxybutyrate is marketed by Laboratoire Egic of Paris, France, as a banana-flavored syrup, and it further discloses the use of GHB, obtained as a banana-flavored syrup, in a dose of 1.0-4.5 g and placebo in a dose of 5 cc banana flavoring in water. *See*, *e.g.*, pp. 274-275. **The '236 patent** discloses that sodium 4-hydroxybutyrate has been used in medicine to induce both anesthesia and sleep. *See*, *e.g.*, 1:38-43. **Nema** discloses that injectable products are required to withstand sterilization processes such as autoclaving, and that preservatives may not be allowed in some injectable products, depending on the route of administration. It also discloses buffers and chemicals used to adjust the pH of formulations, including a table of 32 buffers and pH-adjusting agents, such as acetic acid, and citric acid. *See*, *e.g.*, pp. 166, 168, 169. **EP '804** discloses administration of salts of gamma-hydroxybutyric acid in the form of single or multi-dose liquid

'219 Patent Claim	Invalidity
	solutions, with the sodium salt being particularly preferred. It also discloses a formulation for intravenous injection that is free of preservatives. *See*, *e.g.*, 2:38-39, 6:32-34, Formulation 3. **The '937 patent** discloses that gamma-hydroxybutyric acid is commercially available as the sodium salt, and that all experimental and clinical investigations have without exception been performed with the sodium salt, the acid itself, or the corresponding lactone. *See*, *e.g.*, 1:7-15. **The '619 patent** discloses that sodium 4-hydroxybutyrate is highly soluble in water and, in aqueous solution, has a pH slightly in excess of 7. It also discloses formulations that are free of preservatives, including one that was administered to a patient just prior to undergoing surgery. *See*, *e.g.*, 1:61-66, examples 1-3. **The 1990 CRC Handbook** discloses that γ-Hydroxybutyric acid has a pK_a of 4.72 in aqueous solution. *See*, *e.g.*, p. 8-36. **The 1995 USP** discloses a list of 13 acidifying agents among USP and NF Pharmaceutic Ingredients, including malic acid, citric acid, acetic acid, propionic acid, and tartaric acid. *See*, *e.g.*, p. 2205. *See also*, 21 C.F.R. §§ 184.1069, 184.1033, 184.1005, 184.1061, 184.1081, 184.1099. **CA 338** discloses that the alkali metal salts of GHB, as usually prepared, have far too high a pH for injection as 20% solutions. It also discloses the preparation of injectable solutions by hydrolysis of gamma-butyrolactone with slightly less than the theoretical amount of alkali hydroxide, to obtain solutions of pH 7.2-7.7. *See*, *e.g.*, Abstract. **Roth** discloses that, of GHB and GBL, GHB is the active form, but GBL has the longer duration of action. It is also disclosed that GBL is rapidly converted to GHB in the blood and liver. *See*, *e.g.*, pp. 1333, 1342-1343. **Remington's** discloses means to achieve drug stabilization from photolytic, oxidative, and solvolytic decomposition reactions. *See*, *e.g.*, p. 239. **Wickliffe** discloses that bacterial growth has been shown to be inhibited at pH 2 without the use of additional preservative material, and that asepsis also occurs above pH 9. *See*, *e.g.*, p.

'219 Patent Claim	Invalidity
	770.
2. The pharmaceutical composition of claim 1 wherein the aqueous solution contains about 400-650 mg/ml of sodium gamma-hydroxybutyrate.	*See supra* claim 1.
3. The pharmaceutical composition of claim 1, wherein the pH adjusting agent is malic acid.	*See supra* claim 1.
4. 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 hydrochloric acid, phosphoric acid, sulphuric acid, boric acid or nitric 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.	**The '632 patent** discloses the use of gamma-hydroxybutyric acid salts for preparing pharmaceutical compositions, with suitable salts including the sodium salt, and that the GHB salt content of the compositions can vary from 12.5 to 50% by weight. Also disclosed are a bottle containing 20 ml of solution containing 6.05 g of sodium gamma-hydroxy butyric acid, and an injectable formulation of sodium gamma-hydroxybutyrate free of preservatives. *See*, *e.g.*, Abstract, 7:32-33, 7:47-49, Example 2, 8:57-59. **Vickers** discloses oral and injectable use of sodium γ-hydroxybutyrate, which is water soluble in all dilutions, to induce sleep. It is also disclosed that gamma-hydroxybutyric acid is marketed for intravenous injection as a solution containing 2.42 g sodium 4-hydroxybutyrate in 10 ml water, with a pH between 8.2 and 8.9. *See*, *e.g.*, pp. 75, 78, 82, and 87. **Mamelak (1977)** discloses that γ-hydroxybutyrate is marketed by Laboratoire Egic of Paris, France, as a banana-flavored syrup. It also discloses the use of GHB, obtained as a banana-flavored syrup, in a dose of 1.0-4.5 g and placebo in a dose of 5 cc banana flavoring in water. *See*, *e.g.*, pp. 274-275. **EP '804** discloses administration of salts of gamma-hydroxybutyric acid in the form of single or multi-dose liquid solutions, with the sodium salt being particularly preferred. It also discloses a formulation for intravenous injection that is free of preservatives. *See*, *e.g.*, 2:38-39, 6:32-34, Formulation 3. **CA 338** discloses that the alkali metal salts of GHB, as usually prepared, have far too high a pH for injection as 20% solutions. It also discloses the preparation of injectable solutions by

'219 Patent Claim	Invalidity
	hydrolysis of gamma-butyrolactone with slightly less than the theoretical amount of alkali hydroxide, to obtain solutions of pH 7.2-7.7. *See*, *e.g.*, Abstract. **The '236 patent** discloses that sodium 4-hydroxybutyrate has been used in medicine to induce both anesthesia and sleep. *See*, *e.g.*, 1:38-43. **The '619 patent** discloses that sodium 4-hydroxybutyrate is highly soluble in water and, in aqueous solution, has a pH slightly in excess of 7. It also discloses formulations that are free of preservatives, including one that was administered to a patient just prior to undergoing surgery. *See*, *e.g.*, 1:61-66, examples 1-3. **The '937 patent** discloses that gamma-hydroxybutyric acid is commercially available as the sodium salt. *See*, *e.g.*, 1:7-12. **Roth** discloses that, of GHB and GBL, GHB is the active form, but GBL has the longer duration of action. It is also disclosed that GBL is rapidly converted to GHB in the blood and liver. *See*, *e.g.*, pp. 1333, 1342-1343. **The 1995 USP** discloses a list of 13 acidifying agents among USP and NF Pharmaceutic Ingredients, including hydrochloric acid, phosphoric acid, sulfuric acid, and nitric acid. *See*, *e.g.*, p. 2205. *See also*, 21 C.F.R. § 184.1095. **The 1990 CRC Handbook** discloses that γ-Hydroxybutyric acid has a pK_a of 4.72 in aqueous solution. *See*, *e.g.*, p. 8-36. **Nema** discloses that injectable products are required to withstand sterilization processes such as autoclaving, and that preservatives may not be allowed in some injectable products, depending on the route of administration. It also discloses buffers and chemicals used to adjust the pH of formulations, including a table of 32 buffers and pH-adjusting agents, such as acetic acid, and citric acid. *See*, *e.g.*, pp. 166, 168, 169. **Remington's** discloses means to achieve drug stabilization from photolytic, oxidative, and solvolytic decomposition reactions. It is also disclosed that hydrochloric acid is a pharmaceutic aid that is used as an acidifying agent. *See*, *e.g.*, pp. 239, 1410. **Wickliffe** discloses that bacterial growth has been shown to be inhibited at pH 2 without the use of additional preservative material, and that asepsis also occurs above pH 9. *See*, *e.g.*, p.

'219 Patent Claim	Invalidity
	770.

E. The '506 Patent

1. *Obviousness*

Claims 1-3 of the '506 patent are invalid under 35 U.S.C. § 103(a) because they would have been obvious to a person of ordinary skill in the art prior to the filing date of the '506 patent in view of one or more of the prior art references discussed herein.

Scrima (1990), **the '632 patent**, **Scrima (1989)**, **Vickers**, **EP '804**, **the '331 patent**, **EP '408**, **the '937 patent**, **Scharf**, **Lammers**, **Lapierre**, **Mamelak (1977)**, **Mamelak (1989)**, **Palatini**, **Scrima (1987)**, **Laborit**, **Hoes**, and **Sériès** disclose the use of sodium gamma-hydroxybutyrate to treat one or more of conditions including narcolepsy, cataplexy, and insomnia. **Bédard**, **Sours**, **Lammers**, **Allsopp**, and **Chokroverty** teach that narcolepsy is characterized by cataplexy and/or excessive daytime sleepiness. **Scrima (1990)**, **the '632 patent**, **Ferrara**, **Lammers**, **Mamelak (1977)**, **Scrima (1989)**, **Hoes**, and **Sériès** describe treatment using an orally administered aqueous composition of sodium gamma-hydroxybutyrate.

Mamelak (1977) details administering to insomnia patients either 1.0-4.5 g sodium gamma-hydroxybutyrate, which was obtained as a banana-flavored syrup, or a placebo, consisting of 5 cc banana flavoring in water. **The '331 patent** teaches oral administration of solutions of sodium gamma-hydroxybutyrate with typical dosages between 2.0 and 5.0 grams. **Vickers** reportsthe use of 20-30 g GHB per 24-hour period without ill effect.

Scrima (1990) and **Vickers** state that oral doses of 40-50 mg/kg GHB have been reported to induce sleep. **Scrima (1990)** further discusses a sleep study in which patients were

administered 25 mg/kg GHB within the hour prior to seep and again 3 hours later. **The '632 patent** discloses dosages of 0.025-0.10 g/kg, with 0.05 g/kg in a single daily dose being preferred. **Palatini** reports administration of 12.5, 25, and 50 mg/kg doses. **Laborit** teaches the administration of 50-60 mg/kg doses. **Scrima (1987)** reports the administration of 50 mg/kg.

Scrima (1990) further reveals patient weights of 57-113 kg for females, equivalent to a body mass index (BMI) range of 17.6-45.4, and 54-90 kg for males, equivalent to a BMI range of 20.3-29.1. **CDC** categorizes of people with BMIs under 18.5 as underweight, between 18.5 and 24.9 as healthy, between 25.0 and 29.9 as overweight, and over 30 as obese.

Mamelak (1989) reports that the central effects of an intravenous dose of 60-70 mg/kg GHB run their course in about 2 hours. **EP '265** states that sodium gamma-hydroxybutyrate has to be administered more than once a day, due to its rapid absorption and elimination, with a maximum peak at about 30-45 minutes after oral administration, a half-life time of about 20-25 minutes, and elimination of principle in 4-5 hours. **EP '804** teaches oral administration of a pharmaceutically acceptable salt of gamma-hydroxybutyric acid in the form of single or multi-dose solutions. **Mamelak (1977)** reports that patients were given repeated doses of sodium gamma-hydroxybutyrate during the night. **The '331 patent** also teaches administration of one dose within the last hour prior to retiring and further states that it may be desirable to administer a second or third dose during the normal sleep period. **Vickers** discloses that GHB has been tried orally as a night sedative, and that 2 g every 2-4 hours produces sleep. **Scrima (1989)** states that patients were instructed to ingest one entire bottle immediately before going to bed and the other 3 hours later. **Scharf** discusses the administration of GHB to narcolepsy patients at lights out and again 4 hours later. **Scrima (1987)** discloses administration of GHB within the hour prior to sleep and again 3 hours later. Similarly, **Sériès** reports on the administration of

GHB diluted in orange juice at the beginning of the recording and at the first awakening 3 hours after the first drug administration.

The '619 patent teaches that sodium gamma-hydroxybutyrate is highly soluble in water. In addition, **Vickers** notes that gamma-hydroxybutyric acid is soluble in all dilutions. A more narrow range is provided in **the '632 patent**, which discusses pharmaceutical compositions of sodium gamma-hydroxybutyrate with a GHB salt content of 12.5-50% by weight.

A person of ordinary skill in the art reading Scrima (1990), alone or in combination with any of the '632 patent, Scrima (1989), Vickers, EP '804, the '331 patent, EP '408, CA 338, the '937 patent, Lammers, Lapierre, Mamelak (1977), Mamelak (1989), Palatini, Scrima (1987), Laborit, Hoes, or Sériès, alone or in further view of any of Bédard, Sours, Lammers, Allsopp, or Chokroverty, would have been motivated to treat the one or more of conditions narcolepsy, cataplexy, and insomnia using sodium gamma-hydroxybutyrate, with a reasonable expectation of success In further view of any of Scrima (1990), the '632 patent, Lammers, Mamelak (1977), Scrima (1989), Hoes, or Sériès, a person of ordinary skill in the art would have been motivated to do so by orally administering an aqueous composition of sodium gamma-hydroxybutyrate.

A person of ordinary skill in the art would have been motivated to use doses of at least 4.5 grams, in view of the above discussed and Mamelak (1977), the '331 patent, and Vickers, with a reasonable expectation of success. In addition, a person of ordinary skill in the art reading Scrima (1990) in view of CDC would recognize that the patient weights disclosed in Scrima (1990) comprise a representative sample of the general population, ranging from underweight to obese. Accordingly, a person of ordinary skill in the art would have used the patient weights in Scrima (1990) to determine that the 40 mg/kg doses in Vickers range from 2160 to 4520 mg; the 50 mg/kg doses in Vickers, the '632 patent, Palatini, and Laborit range

from 2700 to 5650 mg; the 60 mg/kg doses in Laborit range from 3420 to 6780 mg; and the 100 mg/kg doses in the '632 patent range from 5400 to 11,300 mg.

Additionally, a person of ordinary skill in the art would have been motivated to administer a second dose of the same amount, in view of the above discussed and any of Mamelak (1989), EP '265, EP '804, Mamelak (1977), the '331 patent, Vickers, Scrima (1989), and Scrima (1987), with a reasonable expectation of success.

In view of the above, a person of ordinary skill in the art would have been motivated to administer the first dose within the hour prior to sleep onset and the second dose 2-4 hours later, with a reasonable expectation of success.

Lastly, a person of ordinary skill in the art, in view of the above discussed and the '619 patent, Vickers, and the '632 patent, would have been motivated to ensure that the aqueous composition of each dose comprised at least 500 mg/ml sodium gamma-hydroxybutyrate, with a reasonable expectation of success.

2. *35 U.S.C. § 112, ¶2*

Claims 1-3 of the '506 patent are invalid under 35 U.S.C. § 112, ¶2 for being indefinite. The limitation of "greater than about 500 mg/ml" is unclear because it may be construed to include amounts both above and below 500 mg/ml.

Claim Charts

'506 Patent Claim	Invalidity
1. 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	**Scrima (1990)** discloses that most patients with narcolepsy also have cataplexy and disrupted nocturnal sleep. GHB has been reported to induce anesthesia at doses of 60-70 mg/kg and sleep at doses of 40-50 mg/kg. It is also disclosed that subjects took 25 mg/kg of GHB within the hour prior to sleep and 25 mg/kg 3 hours later, that oral doses of ~25-35 mg/kg GHB have been reported to induce rapid sleep onset and normal cycling of sleep stages at bedtime, and that GHB was mixed with sterile, distilled

'506 Patent Claim	Invalidity
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, cataplexy, sleep paralysis, hypnagogic hallucination, sleep arousal, insomnia, and nocturnal myoclonus.	water and syrup of orange. Also disclosed are mean ± SD (range) subject weights of 85.1 ± 16.4 (57-113) kg for females and 80.4 ± 11.4 (54-90) kg for males, and mean ± SD (range) body mass index values of 31.8 ± 7.8 (17.6-45.4) for females and 26.2 ± 2.8 (20.3-29.1) for males. It is also disclosed that the therapeutic effect of reduction of cataplexy in narcolepsy patients by treatment with GHB appears to be due to the improvement of nocturnal sleep quality and that that the results of this double-blind study indicate that GHB improves sleep depth and continuity. *See*, *e.g.*, summary, pp. 479-480, 482, 486. **The '632 patent** discloses that gamma-hydroxybutyric acid derivatives, including its simple salts, have therapeutic uses "due to their narcotic, hypnotic or anticonvulsive effect." It is also disclosed that suitable salts include the sodium salt, and it discloses oral administration of pharmaceutical compositions of salts of gamma-hydroxy butyric acid. Compositions disclosed include those in which the GHB salt can vary from 12.5 to 50% by weight, such as a bottle containing 20 ml of solution containing 6.05 g of sodium gamma-hydroxy butyric acid. It is also disclosed that the typical dosage for a GHB salt is from 0.025 to 0.10 g/kg, with the preferred GHB salt dosage being 0.05 g/kg in a single daily dose. *See*, *e.g.*, 3:29-32, 7:32-33, 7:44-46, 7:48-50, 7:51-52, Example 2. **Scrima (1989)** discloses the results of a study of the effects of GHB treatment on narcolepsy and cataplexy, in which cataplexy was reduced. It is also disclosed that subjects were provided pharmacy-prepared bottles of GHB mixed with distilled water and syrup of orange, and instructed to ingest one entire bottle immediately before going to bed and the other 3 hours later. *See*, *e.g.*, pp. 333, 334. **Vickers** discloses that gamma-hydroxybutryate has a possible clinical use in night sedation, that it has been tried orally as a night sedative, that 2 g every 2-4 hours produces sleep, and that the use of 20-30 g per 24 hours without ill effect. It is also disclosed that an intravenous or oral dose of 40-50 mg/kg of gammahydroxybutyric acid will, within 5-15 minutes, induce a sleeping state from which the patient can be awoken, and that gamma-hydroxybutyric acid is water soluble in all dilutions. *See*, *e.g.*, pp. 75-76, 78, 82-87. **EP '804** discloses the use of pharmaceutically acceptable salts of gamma-hydroxybutyric acid in preparing pharmaceutical compositions suitable for therapeutic use in the treatment of

'506 Patent Claim	Invalidity
	depression, with the sodium salt being particularly preferred. It also discloses oral administration of a pharmaceutically acceptable salt of gamma-hydroxybutyric acid in the form of single or multi-dose liquid solutions, as well as examples of pharmaceutical formulations containing NaGHB to be used as described in the invention. *See*, *e.g.*, Abstract, 2:38-39, 6:32-34, 6:37-38. **The '331 patent** discloses that gamma-hydroxybutyrate has such clinical effects as increased slow-wave sleep (SWS) and reduction of narcolepsy. SWS is associated with a pulse of growth hormone (GH) that may represent 50-100% of the total daily GH output. SWS decreases with age, and the reduction or absence of SWS in the elderly is a major contributor to the overall decline in GH secretion. Reduced GH secretion may be correlated with increased cardiovascular mortality, reduced exercise capacity, and other pathologic states. Also disclosed is the therapeutic use of sodium γ-hydroxybutyrate, which may be administered orally. It is also disclosed that suitable compositions include solutions, with typical dosages between 2.0 and 5.0 grams, with administration of one dose within the last hour prior to retiring, or one-half hour or less prior to retiring. It is further disclosed that it may be desirable to administer a second or third dose during the normal sleep period. *See*, *e.g.*, 1:21-25, 1:27-38, 1:42-52, 6:21-40, 7:1-15, 7:44, 7:48, 7:52-61, 7:61-63, 7:63-64. **EP '408** discloses that GHB has been demonstrated to be a safe oral drug for narcolepsy. *See*, *e.g.*, 2:45-47. **Bédard** discloses that narcolepsy is characterized by cataplexy and excessive daytime sleepiness. *See*, *e.g*, 29:1-5, 30:3-5, 30:9-17. **The '937 patent** discloses that 4-hydroxybutyric acid is available as a pharmaceutical exclusively as the sodium salt and has been in general use as a narcotic, with hypnotic effects at 35-90 mg/kg doses and a narcotic effect at dosages greater than 100 mg/kg. It is also disclosed that "the narcosis achieved with GHB broadly resembles physiological sleep," and that all experimental and clinical investigations have without exception been performed with the sodium salt, the acid itself, or the corresponding lactone. *See*, *e.g.*, 1:7-12, 1:12-15, 1:42-43, 1:62-64. **Chokroverty** discloses that the characteristic clinical picture of narcolepsy syndrome includes cataplexy and uncontrollable sleep

'506 Patent Claim	Invalidity
	attacks during the day. *See*, *e.g.*, p. 250. **Allsopp** discloses that the narcolepsy syndrome comprises sleep disturbance, cataplexy, sleep paralysis, and hypnagogic hallucinations, and that the sleep disturbance involves excessive daytime drowsiness with intermittent, irresistible naps, and a disrupted pattern of nocturnal sleep. *See*, *e.g*, p. 302. **Lammers** discloses that narcolepsy patients treated with GHB exhibited fewer daily cataplexy attacks, and that gamma-hydroxybutyrate was administered orally as a 10% aqueous solution. *See*, *e.g.*, Summary, p. 217. **Lapierre** discloses that GHB is used to treat narcolepsy, and that cataplexy is controlled by GHB. *See*, *e.g.*, summary, p. 28. **Mamelak (1977)** discloses that Laboratoire Egic of Paris, France, market GHB as a banana-flavored syrup for oral use. It also discloses a study was undertaken to explore the usefulness of sodium γ-hydroxybutyrate in the treatment of insomnia. It further discloses oral dosing of 1.0-4.5g GHB, and that the use of GHB in repeated doses during the night reduced the incidence of daytime attacks of cataplexy and improved daytime functioning. *See*, *e.g.*, pp. 273, 274, 274-275, and 286. **Mamelak (1989)** discloses the therapeutic use of GHB to consolidate night sleep in narcoleptics and improve their alertness during the day. It also discloses oral administration of GHB, with oral doses of 20 to 30 mg/kg GHB promoting the normal sequence of NREM and REM sleep in normal subjects when given at bedtime. It is also disclosed that the central effects of an intravenous dose of 60-70 mg/kg GHB run their course in about 2 hours. *See*, *e.g.*, p. 188. **Palatini** discloses that GHB has been used in the treatment of narcolepsy, and further discloses the oral administration of 12.5, 25, and 50 mg/kg GHB diluted in water. *See*, *e.g.*, pp. 353, 354. **Scrima (1987)** discloses the results of a study that found that GHB decreases sleep attacks and cataplexy in narcoleptics, in which 50 mg/kg GHB were administered within the hour prior to sleep and again 3 hours later. *See*, *e.g.*, p. 134. **Laborit** discloses that the coma-inducing action of short-chain fatty acids from C_4 to C_{10} is known, and that "molecules closely related to GHB such as 1,4-butanediol… possess hypnotic

'506 Patent Claim	Invalidity
	properties similar to those of GHB." It is also disclosed that GHB-induced sleep has been described as being close to physiological sleep, with doses of 50 to 60 mg/kg rapidly inducing slow wave sleep followed by REM sleep, and that GHB will deepen sleep. It further discloses that the use of GHB to obtain sleep should apply to insomnia. *See*, *e.g.*, pp. 257, 258, 264, 269. **Hoes** discloses the results of a study of the effects of GHB on insomniacs, in which gamma-hydroxybutyrate was dissolved at a concentration of 10 grams per 100 milliliters of chocolate-flavored water. *See*, *e.g.*, p. 94. **CDC** discloses that a person with body mass index of less than 18.5 is considered underweight, 18.5 to 24.9 is considered healthy, 25.0 to 29.9 is considered overweight, and 30 or higher is considered obese. *See*, *e.g.*, p. 1. **Sériès** discloses that gamma-hydroxybutyrate improved sleep abnormalities in a patient with narcolepsy and central sleep apnea. It is also disclosed that 30 mg/kg gamma-hydroxybutyrate was administered as a white powder diluted in orange juice at the beginning of the recording and at the first awakening 3h after the first drug administration, with each subject received two doses of the drug. It further discloses that the patients had a mean ± SEM body mass index of 35.0 ± 1.5 kg/m^2. *See*, *e.g.*, Summary, pp. 1378, 1379. **EP '265** discloses that sodium gamma-hydroxybutyrate has to be administered more than once a day, due to its rapid absorption and elimination, with a maximum peak at about 30-45 minutes after oral administration, a half-life time of about 20-25 minutes, and elimination of principle in 4-5 hours. *See*, *e.g.*, 3:14-19. **The '619 patent** discloses that sodium 4-hydroxybutyrate is highly soluble in water. *See*, *e.g.*, 1:60-66. **Sours** discloses that cataplexy, the second most common and most easily recognized narcolepsy symptom, was characterized by a sudden decrease of muscle tone, limited to particular muscle groups. *See*, *e.g.*, p. 532.
2. The method of claim 1, wherein	*See supra* claim 1.

'506 Patent Claim	Invalidity
the condition is narcolepsy.	
3. The method of claim 1, wherein the condition is a cataplexy.	*See supra* claim 1.

F. The '059 Patent

1. *Anticipation*

Claims 1-6, 9, and 12-14 of the '059 patent are invalid under 35 U.S.C. § 102(b) as explicitly or inherently anticipated by **the Advisory Committee Transcript**, which was publically available more than one year prior to the earliest effective filing date of the '059 patent. The Advisory Committee Transcript discloses a distribution system for prescriptions of Xyrem, *i.e.*, GHB. The GHB is manufactured at a single site and then sent to a single, exclusive pharmacy that is responsible for distributing the GHB to patients. All doctors that prescribe Xyrem send all prescription requests to the exclusive pharmacy. The prescription requests contain information identifying the patient and the credentials of the doctor. The doctor's credentials are verified. Additionally, the Advisory Committee transcript discloses confirming with the patient that educational materials about GHB are read before dispensing the drug to the patient. Once the prescribed GHB is shipped to the patient, the exclusive pharmacy confirms receipt of the shipment by contacting the patient. The proposed distribution program is also disclosed as being beneficial because it allows for the identification of potential abuse situations, and if necessary, pharmacist intervention. Moreover, the exclusive pharmacy maintains all the controls and records for the distribution of GHB in one location.

Additionally, Claims 1-6, 9, and 12-14 of the '059 patent are also invalid under 35 U.S.C. § 102(b) as explicitly or inherently anticipated by **the NADDI Presentation**, which was

publically available more than one year prior to the earliest effective filing date of the '059 patent. The NADDI Presentation discloses a closed loop distribution system for Xyrem, *i.e.*, GHB. The GHB is manufactured at a single site and then shipped to a single-dedicated pharmacy. The single-dedicated pharmacy maintains a registry of information on both the patient and the prescribing doctor in one location. To prescribe GHB a doctor sends a unique prescription from to the pharmacy. The pharmacy checks the credentials of the prescribing doctor and then ships education materials to the identified patient. Furthermore, the pharmacy confirms that the patient has read the education materials before shipping the prescribed GHB to the patient. Once the pharmacy makes this confirmation, it then ships the GHB to the patient and confirms its receipt. The disclosed distribution system also entails generating reports for medical authorities, as well as law enforcement authorities. These reports also allow the pharmacy to alert state medical boards of troubling physician activities, to monitor patterns of abuse or diversion, and stop prescriptions from being filled if troubling activity is found.

2. *Obviousness*

Claims 1-16 of '059 patent are invalid under 35 U.S.C. § 103(a) because they would have been obvious to a person of ordinary skill in the art prior to the filing date of the '059 patent in view of one or more of the prior art references discussed herein.

The Advisory Committee Transcript discloses a distribution system for prescriptions of Xyrem, *i.e.*, GHB. The GHB is manufactured at a single site and then sent to a single, exclusive pharmacy that is responsible for distributing the GHB to patients. All doctors that prescribe GHB send all prescription requests to the exclusive pharmacy. The prescription requests contain information identifying the patient and the credentials of the doctor. The doctors credentials are verified. Additionally, the Advisory Committee transcript discloses confirming with the patient that educational materials about GHB are read before dispensing the drug to the patient. The

proposed distribution program is also disclosed as being beneficial because it allows for the identification of potential abuse situations, and if necessary, pharmacist intervention. Moreover, the exclusive pharmacy maintains all the controls and records for the distribution of GHB in one location.

The NADDI Presentation discloses a closed loop distribution system for Xyrem, *i.e.*, GHB. The GHB is manufactured at a single site and then shipped to a single-dedicated pharmacy. The single-dedicated pharmacy maintains a registry of information on both the patient and the prescribing doctor in one location. To prescribe GHB a doctor sends a unique prescription from to the pharmacy. The pharmacy checks the credentials of the prescribing doctor and then ships education materials to the identified patient. Furthermore, the pharmacy confirms that the patient has read the education materials before shipping the prescribed GHB to the patient. Once the pharmacy makes this confirmation, it then ships the GHB to the patient and confirms its receipt. The disclosed distribution system also entails generating reports for medical authorities, as well as law enforcement authorities. These reports also allow the pharmacy to alert state medical boards of troubling physician activities, to monitor patterns of abuse or diversion, and stop prescriptions from being filled if troubling activity is found.

The Advisory Committee Slides disclose a closed loop distribution system in which a single manufacturing facility produces Xyrem to be delivered to a single specialty pharmacy. The single specialty pharmacy distributes Xyrem from a single location and maintains all the controls and records. The discloses process begins with the doctor sending a prescription to the specialty pharmacy, which then checks the doctors credentials. The pharmacy then contacts the patient to discuss the prescription with the patient. The prescription is then shipped to the patient and its receipt is confirmed. Benefits of the program includes identification of forms of abuse

and appropriate pharmacist intervention. **The Advisory Committee Minutes** disclose the recommendation that the patient fill out an informed consent form before receiving a shipment of Xyrem. **The Xyrem Video and Transcript** discloses the distribution of Xyrem from a single specialty pharmacy that has the ability to generate data to provide information to detect abuse and to facilitate investigations into abuse. In the distribution system, a physician sends a prescription to the specialty pharmacy, which then checks his credentials. The pharmacy then contacts the patient to arrange for shipment of Xyrem, and its receipt is verified

Moradi discloses a system for dispensing prescription medications. In the disclosed system a doctor sends prescription request identifying the drug to be dispensed, the patient, and credentials of the doctor. The system is designed to prevent abuse of the drug and includes a step of confirming receipt of the drug. **Califano** discloses confirming with a patient that education material has been read and documenting that the patient understands the risks associated with the drug before providing the drug to the patient. **Lilly** discloses a method for controlling information related to controlled substances. The method makes use of a data storage unit to maintain information on prescription activities. The data storage unit can be accessed to determine if any abuse is taking place.

Elsayed discloses a hazardous drug distribution program. The method seeks to prevent the distribution of drugs to patients for which a condition in the patient renders treatment undesirable or improper, *e.g.*, abuse of the hazardous drug. Patients, pharmacies, and physicians register in a computer readable storage medium to become eligible to receive the hazardous drug. The same computer readable storage medium can be used to register all three classes. Multiple pharmacies can become registered to distribute the hazardous drug, and they must agree to comply with the controls placed on the drug to become registered. The patient is required to fill

out an informed consent form to initially receive the drug and upon its refill. The computer readable storage medium can also be accessed to perform analysis to detect abuse, and thus prevent dispensing of the drug to a patient.

Williams discloses a hazardous drug distribution program. The method seeks to prevent the distribution of drugs to patients for which a condition in the patient renders treatment undesirable or improper, *e.g.*, abuse of the hazardous drug. Patients, pharmacies, and physicians register in a computer readable storage medium to become eligible to receive the hazardous drug. Multiple pharmacies can become registered to distribute the hazardous drug, and they must agree to comply with the controls placed on the drug to become registered. The same computer readable storage medium can be used to register all three classes. The patient is required to fill out an informed consent form to initially receive the drug and upon its refill. The computer readable storage medium can also be accessed to perform analysis to detect abuse, and thus prevent dispensing of the drug to a patient.

Melker discloses that GHB is an illicit drug. **Borsand** discloses a system of storing all pharmaceutical-related information in a central location. In addition, the system is able to detect abuse, generate reports to track abuse, and cancel prescriptions because of such abuse. **Ukens** discloses restricting the distribution of specialty pharmaceuticals to a single pharmacy. The single pharmacies can also monitor dosage and patient compliance. Additionally, Ukens discloses that a specialty pharmacy can authorize other pharmacies to distribute specialty prescriptions. The authorized pharmacies can provide face-to-face counseling and perform compliance monitoring and follow-ups. **Talk About Sleep** discloses the distribution of Xyrem, *i.e.*, GHB, through a central pharmacy to promote the responsible distribution and use of prescribed GHB.

A person of ordinary skill in the art reading the Advisory Committee Transcript and the NADDI Presentation, each either alone or in combination, would have been motivated to design a distribution system for a prescription drug, such as GHB, in which the distribution of the drug is limited to an exclusive central pharmacy, such that the exclusive central pharmacy receives all the prescription requests. Furthermore, a person of ordinary skill the art would have been motivated to check the prescribing doctors credentials, to make use of a database to analyze for potential abuse situations, to confirm with the patient that educational materials were read before dispensing him the drug, to prevent shipment of the drug if abuse is found, and to confirm receipt of the drug by the patient because the Advisory Committee Transcript and the NADDI Presentation disclose such a distribution system. Any alleged differences between the disclosures of these references and the claimed invention would have been merely obvious variations.

In addition, a person of ordinary skill in the art would have looked to any of the Advisory Committee Slides, the Advisory Committee Minutes, or the Xyrem Video and Transcript when designing a distribution system for a prescription drug, such as GHB, because they are all directed to methods of distributing a prescription drug. A person of ordinary skill in the art reading the Advisory Committee Presentation and the NADDI Presentation, each either alone or in combination, in view of one or more of the Advisory Committee Slides, the Advisory Committee Minutes, or the Xyrem Video and Transcript would have been motivated to design a distribution system for a prescription drug, such as GHB, in which in which the distribution of the drug is limited to an exclusive central pharmacy, such that the exclusive central pharmacy receives all the prescription requests. Furthermore, a person of ordinary skill the art would have been motivated to check the prescribing doctors credentials, to make use of a database to analyze for potential abuse situations, to confirm with the patient that educational materials were read

before dispensing him the drug, to prevent shipment of the drug if abuse is found, and to confirm receipt of the drug by the patient because these references either alone or in combination all disclose such a distribution system.

Furthermore, a person of ordinary skill in the art reading the Advisory Committee Presentation and the NADDI Presentation, each either alone or in combination, or in combination with any of the Advisory Committee Slides, the Advisory Committee Minutes, or the Xyrem Video and Transcript, in view of one or more of Moradi, Califano, Lilly, Elsayed, Williams, Melker, Borsand, Ukens, Talk About Sleep, would have been aware that methods of distributing harmful drugs, such as GHB, that involve (1) maintaining patient and doctor information in centralized databases, (2) utilizing informed consent to counsel patients on the dangers of the prescribed drug, (3) monitoring patient compliance and potential abuse through use of a database, (4) notifying the proper parties of abuse and preventing shipments were already known. In addition, a person of ordinary skill in the art reading Ukens, Elsayed, and Williams would have been aware that such methods can be restricted to a single pharmacy, or additional pharmacies could be authorized to distribute a drug under the proper controls. Additionally, a person of ordinary skill in the art reading Elsayed and Williams would have been aware that controls such as limiting a prescription supply to a limited duration were known to prevent abuse.

Moreover, during prosecution of the '730 patent, which is the parent of the '059 patent, the Examiner rejected the claims of the pending application over Moradi in view of Lilly, Califano, and Ukens. (*See* AMNXYR_000003496-AMNXYR_000003497). The Examiner found that:

> Moradi discloses a method of distributing a drug under exclusive control of an exclusive central pharmacy, the method comprising

> … receiving prescription requests from a medical doctor containing information identifying a patient, the drug, and various credentials of the doctor … checking the credentials of the doctor … checking the exclusive computer database for potential abuse of the drug and only mailing the drug to the patient if no potential abuse is found by the checking of the exclusive computer database … and confirming receipt by the patient of the drug.

(*Id.*). As for Lilly, Califano, and Ukens the Examiner stated:

> Lilly et al. disclose that the drug is a sensitive drug, entering the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, and generating periodic reports via the exclusive computer database to evaluate potential diversion patterns … Califano et al. disclose confirming with the patient that educational material has been read prior to shipping the drug … Ukens discloses restricting distribution of a specialty medication to only one pharmacy.
>
> 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 of Ukens within Moradi, Lilly, and Califano. The motivation for doing so would have been to limit access to dangerous drugs.

(*See* AMNXYR_000003497-AMNXYR_000003498). Additionally, the Examiner found the claims obvious over Moradi in view of Lilly and Melker, stating:

> Melker teaches that gamma hydroxy butyrate (GHB) is an illicit substance … At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify Moradi and Lilly to include gamma hydroxyl butyrate. The motivation for doing so would have been to include drugs of recent concern, such as GHB.

(*See* AMNXYR_000003503-AMNXYR_000003504).

Furthermore, the Examiner found the claims obvious over Moradi in view of Lilly, Califano, and Talk About Sleep. Finding that in addition to the above:

> Talk About Sleep discloses providing GHB through a specialty distribution system that utilizes a central pharmacy … 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 of

> Talk About Sleep within Moradi, Lilly, and Califano. The motivation for doing so would have been to provide this medicine to patients that need it in a responsible manner.

(*See* AMNXYR_000003506).

On appeal to the Board of Patent Appeals and Interferences ("BPAI"), the Applicants' acquiesced to all of the Examiner's findings except that Moradi and Lilly disclosed exclusive computer databases. The BPAI 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.

(*See* AMNXYR_000003541). Therefore, the Applicants of the '730 patent have admitted that Moradi, Lilly, Califano, Ukens, Melker, and Talk About Sleep disclose all the limitations of claims 1-11 of the'730 patent, except that of using an "exclusive central database."

3. *35 U.S.C. § 101*

Claims 1-16 of the '059 patent are invalid under 35 U.S.C. § 101 for not being directed to patent-eligible subject matter. When each of the '059 patent claims is viewed in its entirety, the computer database referenced in the claims is merely used as a reference tool in an otherwise abstract, manual process, checking for potential abuse of a prescription drug by a patient or the prescribing doctor and applying that concept to a specific drug, GHB. *See*, *e.g.*, *Dealertrack, Inc. v. Huber*, 674 F.3d 1315, 1333 (Fed. Cir. 2012) (citing *SiRF Tech., Inc. v. Int'l Trade Comm'n*, 601 F.3d 1319, 1333 (Fed. Cir. 2010)); *CyberSource Corp. v. Retail Decisions*, 654 F.3d 1366 (Fed. Cir. 2011); *Bilski v. Kappos*, 130 S.Ct. 3218, 3229-30 (2010). Neither the database nor the computer itself actively performs any of the recited steps of the claims.

Moreover, the steps in most of the claims of "receiving in a computer processor" prescription requests and "generating with the computer processor periodic reports" are simply insignificant post-solution activities that do not support patent-eligibility. *See*, *e.g.*, *Bilski*, 130 S.Ct. 3218, 3230 (2010).

4. *35 U.S.C. § 112, ¶2*

Claims 1-16 of the '059 patent are invalid under 35 U.S.C. § 112, ¶2 for being indefinite. "A claim term pinned solely on the 'unrestrained, subjective opinion of a particular individual purportedly practicing the invention' will not suffice." *Source Search Techs., LLC v. LendingTree, LLC*, 588 F.3d 1063, 1076 (Fed. Cir. 2009) (quoting *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1350 (Fed. Cir. 2005)). The claims of the '059 patent are invalid for indefiniteness because they require making 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. Neither the claims nor the specification of the '059 patent provides 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 person performing the claims is left to exercise his own judgment to determine whether the patient is being truthful or not. Patent claims that require such human mental participation are indefinite and not proper patent-eligible subject matter.

5. *35 U.S.C. § 102(f)*

Claims 1-16 of the '059 patent are invalid under 35 U.S.C. § 102(f) for being derived from sources other than the inventors and/or for non-joinder. The distribution methods claimed in the '059 patent were developed from collaborative efforts of others than just the inventors listed on the face of the patent. For instance, the program presented before the Peripheral and Central Nervous System Drugs Advisory Committee was not fully finalized and Orphan Medical

presented it with the intent of gathering feedback from those attending. And, indeed the concept of confirming that the patient read educational materials before receiving Xyrem was suggested at this meeting. Furthermore, Orphan stated in Talk About Sleep that the Xyrem distribution program was developed with "assistance and input from State Scheduling authorities, experts in specialty distribution, drug diversion investigators, field law enforcement, narcolepsy patient groups, and pharmacists experienced in dealing with Scheduled medicines." (Talk About Sleep, pg. 1, ¶10). At the Peripheral and Central Nervous System Drugs Advisory Committee meeting, Orphan noted this, stating: "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." (176:15-21.)

Therefore, the claimed methods are invalid for not being fully conceived by the listed inventors of the '059 patent and/or for failing to list all inventors who contributed to the conception of the subject matter of the invention claimed in the '059 patent.

At least the following individuals would qualify as inventors:

1. Claudia H. Kawas, M.D.
2. Sandra Titus, Ph.D.
3. Ella P. Lacey, Ph. D.
4. LaRoy P. Penix, M.D.
5. Richard D. Penn, M.D.
6. Gerald Van Belle, Ph.D.
7. Gustavo C. Roman, M.D.
8. Jerry S. Wolinsky M.D.

9. Pippa Simpson, Ph.D.

10. Carol Falkowski, Ph.D.

11. Christine A. Sannerud, Ph.D.

12. Jerry Frankenheim, Ph.D.

13. Jo-Ellen Dyer, Ph.D.

14. Ronald Chervin, M.D.

15. Christian Guilleminault, M.D.

16. Robert Temple, M.D.

17. Russell Katz, M.D.

18. Ranjit Mani, M.D.

19. John Feeney, M.D.

20. Deborah R. Leiderman, M.D.

Oral and written discovery related to these individuals as this case proceeds will confirm the extent of the proper inventors of the '059 patent.

Claim Charts

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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	**Anticipation** **The Advisory Committee Transcript** discloses all the limitations of claim 1, arranged as claimed. *See* 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses all the limitations of claim 1 arranged as claimed. *See* pgs. 4-14. **Obviousness**

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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; 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	**The Advisory Committee Transcript** discloses distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving Xyrem is confirmed, that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving Xyrem is confirmed, that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4-14. **The Advisory Committee Slides** disclose distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 142, 146, 147, and 151-159. **The Advisory Committee Minutes** disclose the concept of confirming with the patient that educational material has been read before shipping Xyrem. *See*, *e.g.*, Question 5.

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drug; confirming with a patient that educational material has been received and/or read prior to shipping the prescription drug; checking the exclusive computer database for potential abuse of the prescription drug; mailing or sending by courier 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 potential diversion patterns.	**The Xyrem Video and Transcript** discloses distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4, 6-9, and 10. **Moradi** discloses a system for dispensing prescription medications. In the disclosed system a doctor sends prescription request identifying the drug to be dispensed, the patient, and credentials of the doctor. The system is designed to prevent abuse of the drug and includes a step of confirming receipt of the drug. *See*, *e.g.*, Abstract, ¶¶[0003], [0022], [0035], [0043], [0045], [0116]-[0118], and Fig. 3. **Califano** discloses confirming with a patient that education material has been read and documenting that the patient understands the risks associated with the drug before providing the drug to the patient. *See*, *e.g.*, ¶¶[0043] and [0084]. **Lilly** discloses a method for controlling information related to controlled substances. The method makes use of a data storage unit to maintain information on prescription activities. The data storage unit can be accessed to determine if any abuse is taking place. *See*, *e.g.*, ¶¶[0012], [0033], [0043], [0044], [0054], [0057], [0058], [0062], and [0069]. **Elsayed** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:10-15; 4:10-16; 5:25-37; 7:13-15; 7:28-32; 7:40-45; 8:26-32; 8:45-48; 9:10-12; 9:30-50; 10:7-12; and 10:17-21. **Williams** discloses a method of distributing hazardous

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	drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:21-26; 4:43-46; 5:61-67; 5:67 through 6:3; 10:3-5; 10:18-28; 10:30-32; 12:8-11; 12:35-55; 11:32-42; 11:51-54; 13:7-18; and 13:23-27. **Borsand** discloses a system of storing all pharmaceutical-related information in a central location. In addition, the system is able to detect abuse, generate reports to track abuse, and cancel prescriptions because of such abuse. *See*, *e.g.*, ¶¶[0003], [0034], [0043], [0120], and Fig. 3. **Ukens** discloses restricting the distribution of specialty pharmaceuticals to a single pharmacy. The single pharmacies can also monitor dosage and patient compliance. *See*, *e.g.*, 41:3, ¶1 and 42:2, ¶1 through 3, ¶1.
2. The method of claim 1, wherein the exclusive central pharmacy controls the exclusive computer database.	**Anticipation** *See supra* claim 1. **Obviousness** *See supra* claim 1.
3. The method of claim 1, comprising selectively blocking shipment of the prescription drug to a patient.	**Anticipation** *See supra* claim 1. **Obviousness** *See supra* claim 1.
4. The method of claim 1, wherein an abuse pattern is associated with a patient, and shipment is blocked upon such association.	**Anticipation** *See supra* claim 1. **Obviousness** *See supra* claim 1.
5. The method of claim 1, wherein the prescription drug comprises gamma	**Anticipation** *See supra* claim 1.

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hydroxy butyrate (GHB).	**The Advisory Committee Transcript** discloses GHB. *See* 9:12-15. **The NADDI Presentation** discloses GHB. *See* pg. 9. **Obviousness** *See supra* claim 1. **The Advisory Committee Transcript** discloses GHB. *See* 9:12-15. **The NADDI Presentation** discloses GHB. *See* pg. 9. **Talk About Sleep** discloses GHB. *See* pg. 1, ¶11. **Melker** discloses that GHB is an illicit drug. *See* ¶[0003].
6. A computerized method of distributing a 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 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	**Anticipation** **The Advisory Committee Transcript** discloses all the limitations of claim 6, arranged as claimed. *See* 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses all the limitations of claim 6 arranged as claimed. *See* pgs. 4-14. **Obviousness** **The Advisory Committee Transcript** discloses distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving Xyrem is confirmed, that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through

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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 prescription drug, 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 authorized prescribers to determine the eligibility of the prescribers to prescribe the prescription drug; confirming with a patient that educational material has been received and/or read prior to	185:7; 259:4-13; 357:9-13; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving Xyrem is confirmed, that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4-14. **The Advisory Committee Slides** disclose distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 142, 146, 147, and 151-159. **The Advisory Committee Minutes** disclose the concept of confirming with the patient that educational material has been read before shipping Xyrem. *See*, *e.g.*, Question 5. **The Xyrem Video and Transcript** discloses distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4, 6-9, and 10. **Moradi** discloses a system for dispensing prescription medications. In the disclosed system a doctor sends prescription request identifying the drug to be dispensed,

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providing the 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 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; confirming receipt by the patient of the prescription drug; and generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	the patient, and credentials of the doctor. The system is designed to prevent abuse of the drug and includes a step of confirming receipt of the drug. *See*, *e.g.*, Abstract, ¶¶[0003], [0022], [0035], [0043], [0045], [0116]-[0118], and Fig. 3. **Califano** discloses confirming with a patient that education material has been read and documenting that the patient understands the risks associated with the drug before providing the drug to the patient. *See*, *e.g.*, ¶¶[0043] and [0084]. **Lilly** discloses a method for controlling information related to controlled substances. The method makes use of a data storage unit to maintain information on prescription activities. The data storage unit can be accessed to determine if any abuse is taking place. *See*, *e.g.*, ¶¶[0012], [0033], [0043], [0044], [0054], [0057], [0058], [0062], and [0069]. **Elsayed** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:10-15; 4:10-16; 5:25-37; 7:13-15; 7:28-32; 7:40-45; 8:26-32; 8:45-48; 9:10-12; 9:30-50; 10:7-12; and 10:17-21. **Williams** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:21-26; 4:43-46; 5:61-67; 5:67 through 6:3; 10:3-5; 10:18-28; 10:30-32; 12:8-11; 12:35-55; 11:32-42; 11:51-54; 13:7-18; and 13:23-27. **Borsand** discloses a system of storing all pharmaceutical-related information in a central location. In addition, the system is able to detect abuse, generate reports to track

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	abuse, and cancel prescriptions because of such abuse. *See*, *e.g.*, ¶¶[0003], [0034], [0043], [0120], and Fig. 3. **Ukens** discloses restricting the distribution of specialty pharmaceuticals to a single pharmacy. The single pharmacies can also monitor dosage and patient compliance. *See*, *e.g.*, 41:3, ¶1 and 42:2, ¶1 through 3, ¶1.
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.	**Obviousness** *See supra* claim 6. **Ukens** discloses a specialty pharmacy authorizing other pharmacies to dispense a drug. *See*, *e.g.*, 44:1, ¶3 through 3, ¶2; 44:1, ¶1 through 2, ¶3. **Elsayed** discloses registering multiple pharmacies to dispense a hazardous drug. *See*, *e.g.*, 4:50-54. **Williams** discloses registering multiple pharmacies to dispense a hazardous drug. *See*, *e.g.*, 5:24-35.
8. The computerized method of claim 7, wherein the another pharmacy places controls on the distribution of the prescription drug, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of the prescription drug by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription	**Obviousness** *See supra* claim 7. **Ukens** discloses authorized pharmacies performing face-to-face counseling with patients, performing compliance monitoring, and performing follow-ups with the patient. *See*, *e.g.*, 44:2, ¶3. **Elsayed** discloses authorized pharmacies complying with controls placed on dispensing hazardous drugs, flagging early refill requests, and limiting the prescription to a supply of limited duration. *See*, *e.g.*, 4:57-66; 9:30-50; 10:7-12; 10:17-21. **Williams** discloses authorized pharmacies complying with controls placed on dispensing hazardous drugs, flagging early refill requests, and limiting the prescription to a supply of limited duration. *See*, *e.g.*, 5:24-35; 12:35-55; 13:7-18; 13:23-27.

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drug, and limiting the prescription to a supply of limited duration.	
9. 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	**Anticipation** **The Advisory Committee Transcript** discloses all the limitations of claim 9, arranged as claimed. *See* 9:12-15; 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses all the limitations of claim 9 arranged as claimed. *See* pgs. 4-14. **Obviousness** **The Advisory Committee Transcript** discloses distributing GHB from exclusive central pharmacy, wherein all prescriptions for GHB for all patients prescribed GHB are received from all doctors prescribing GHB. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving GHB is confirmed, that receipt of the GHB by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses distributing GHB from exclusive central pharmacy, wherein all prescriptions for GHB for all patients prescribed GHB are received from all doctors prescribing GHB. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving GHB is confirmed, that receipt of the GHB by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4-14.

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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 received and/or 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	**The Advisory Committee Slides** disclose distributing GHB from exclusive central pharmacy, wherein all prescriptions for GHB for all patients prescribed GHB are received from all doctors prescribing GHB. The doctors credentials are checked. It is also disclosed that receipt of the GHB by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 142, 146, 147, and 151-159. **The Advisory Committee Minutes** disclose the concept of confirming with the patient that educational material has been read before shipping GHB. *See*, *e.g.*, Question 5. **The Xyrem Video and Transcript** discloses distributing GHB from exclusive central pharmacy, wherein all prescriptions for GHB for all patients prescribed GHB are received from all doctors prescribing GHB. The doctors credentials are checked. It is also disclosed that receipt of the GHB by the patient is confirmed, that potential abuse is monitored, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4, 6-9, and 10. **Moradi** discloses a system for dispensing prescription medications. In the disclosed system a doctor sends prescription request identifying the drug to be dispensed, the patient, and credentials of the doctor. The system is designed to prevent abuse of the drug and includes a step of confirming receipt of the drug. *See*, *e.g.*, Abstract, ¶¶[0003], [0022], [0035], [0043], [0045], [0116]-[0118], and Fig. 3. **Califano** discloses confirming with a patient that education material has been read and documenting that the patient understands the risks associated with the drug before providing the drug to the patient. *See*, *e.g.*, ¶¶[0043] and [0084]. **Lilly** discloses a method for controlling information related to controlled substances. The method makes use of a data storage unit to maintain information on prescription activities. The data storage unit can be accessed to determine if any abuse is taking place. *See*, *e.g.*, ¶¶[0012],

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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.	[0033], [0043], [0044], [0054], [0057], [0058], [0062], and [0069]. **Elsayed** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:10-15; 4:10-16; 5:25-37; 7:13-15; 7:28-32; 7:40-45; 8:26-32; 8:45-48; 9:10-12; 9:30-50; 10:7-12; and 10:17-21. **Williams** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:21-26; 4:43-46; 5:61-67; 5:67 through 6:3; 10:3-5; 10:18-28; 10:30-32; 12:8-11; 12:35-55; 11:32-42; 11:51-54; 13:7-18; and 13:23-27. **Borsand** discloses a system of storing all pharmaceutical-related information in a central location. In addition, the system is able to detect abuse, generate reports to track abuse, and cancel prescriptions because of such abuse. *See*, *e.g.*, ¶¶[0003], [0034], [0043], [0120], and Fig. 3. **Ukens** discloses restricting the distribution of specialty pharmaceuticals to a single pharmacy. The single pharmacies can also monitor dosage and patient compliance. *See*, *e.g.*, 41:3, ¶1 and 42:2, ¶1 through 3, ¶1.
10. The computerized method of claim 9, wherein providing GHB to the patient comprises the central pharmacy authorizing the prescription drug to be dispensed to the patient by another pharmacy.	**Obviousness** *See supra* claim 9. **Ukens** discloses a specialty pharmacy authorizing other pharmacies to dispense a drug. *See*, *e.g.*, 44:1, ¶3 through 3, ¶2; 44:1, ¶1 through 2, ¶3. **Elsayed** discloses registering multiple pharmacies to dispense a hazardous drug. *See*, *e.g.*, 4:50-54.

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	Williams discloses registering multiple pharmacies to dispense a hazardous drug. *See*, *e.g.*, 5:24-35.
11. The computerized method of claim 10, wherein the another pharmacy places controls on the distribution of GHB, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of GHB by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for GHB, flagging early requests to refill the GHB, and limiting the prescription to a supply of limited duration.	**Obviousness** *See supra* claim 10. **Ukens** discloses authorized pharmacies performing face-to-face counseling with patients, performing compliance monitoring, and performing follow-ups with the patient. *See*, *e.g.*, 44:2, ¶3. **Elsayed** discloses authorized pharmacies complying with controls placed on dispensing hazardous drugs, flagging early refill requests, and limiting the prescription to a supply of limited duration. *See*, *e.g.*, 4:57-66; 9:30-50; 10:7-12; 10:17-21. **Williams** discloses authorized pharmacies complying with controls placed on dispensing hazardous drugs, flagging early refill requests, and limiting the prescription to a supply of limited duration. *See*, *e.g.*, 5:24-35; 12:35-55; 13:7-18; 13:23-27.
12. 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	**Anticipation** **The Advisory Committee Transcript** discloses all the limitations of claim 12, arranged as claimed. *See* 9:12-15; 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses all the limitations of claim 12 arranged as claimed. *See* pgs. 4-14. **Obviousness** **The Advisory Committee Transcript** discloses distributing GHB from exclusive central pharmacy,

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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	wherein all prescriptions for GHB for all patients prescribed GHB are received from all doctors prescribing GHB. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving GHB is confirmed, that receipt of the GHB by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses distributing GHB from exclusive central pharmacy, wherein all prescriptions for GHB for all patients prescribed GHB are received from all doctors prescribing GHB. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving GHB is confirmed, that receipt of the GHB by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4-14. **The Advisory Committee Slides** disclose distributing GHB from exclusive central pharmacy, wherein all prescriptions for GHB for all patients prescribed GHB are received from all doctors prescribing GHB. The doctors credentials are checked. It is also disclosed that receipt of the GHB by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 142, 146, 147, and 151-159. **The Advisory Committee Minutes** disclose the concept of confirming with the patient that educational material has been read before shipping GHB. *See*, *e.g.*, Question 5. **The Xyrem Video and Transcript** discloses distributing GHB from exclusive central pharmacy, wherein all prescriptions for GHB for all patients prescribed GHB are received from all doctors prescribing GHB. The doctors

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prescribe GHB; confirming with the patient that GHB educational material has been received and/or 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 or sending by courier 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.	credentials are checked. It is also disclosed that receipt of the GHB by the patient is confirmed, that potential abuse is monitored, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4, 6-9, and 10. **Moradi** discloses a system for dispensing prescription medications. In the disclosed system a doctor sends prescription request identifying the drug to be dispensed, the patient, and credentials of the doctor. The system is designed to prevent abuse of the drug and includes a step of confirming receipt of the drug. *See*, *e.g.*, Abstract, ¶¶[0003], [0022], [0035], [0043], [0045], [0116]-[0118], and Fig. 3. **Califano** discloses confirming with a patient that education material has been read and documenting that the patient understands the risks associated with the drug before providing the drug to the patient. *See*, *e.g.*, ¶¶[0043] and [0084]. **Lilly** discloses a method for controlling information related to controlled substances. The method makes use of a data storage unit to maintain information on prescription activities. The data storage unit can be accessed to determine if any abuse is taking place. *See*, *e.g.*, ¶¶[0012], [0033], [0043], [0044], [0054], [0057], [0058], [0062], and [0069]. **Elsayed** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:10-15; 4:10-16; 5:25-37; 7:13-15; 7:28-32; 7:40-45; 8:26-32; 8:45-48; 9:10-12; 9:30-50; 10:7-12; and 10:17-21. **Williams** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to

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	the patient if abuse is found. *See*, *e.g.*, 3:21-26; 4:43-46; 5:61-67; 5:67 through 6:3; 10:3-5; 10:18-28; 10:30-32; 12:8-11; 12:35-55; 11:32-42; 11:51-54; 13:7-18; and 13:23-27. **Borsand** discloses a system of storing all pharmaceutical-related information in a central location. In addition, the system is able to detect abuse, generate reports to track abuse, and cancel prescriptions because of such abuse. *See*, *e.g.*, ¶¶[0003], [0034], [0043], [0120], and Fig. 3. **Ukens** discloses restricting the distribution of specialty pharmaceuticals to a single pharmacy. The single pharmacies can also monitor dosage and patient compliance. *See*, *e.g.*, 41:3, ¶1 and 42:2, ¶1 through 3, ¶1.
13. 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	**Anticipation** **The Advisory Committee Transcript** discloses all the limitations of claim 13, arranged as claimed. *See* 9:12-15; 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses all the limitations of claim 13 arranged as claimed. *See* pgs. 4-14. **Obviousness** **The Advisory Committee Transcript** discloses a manufacturer producing GHB and providing it to an exclusive central pharmacy for distribution, wherein all prescriptions for GHB for all patients prescribed GHB are received from all doctors prescribing GHB. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving GHB is confirmed, that receipt of the GHB by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 371:10-13; and 374:14-20.

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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 received	**The NADDI Presentation** discloses a manufacturer producing GHB and providing it to an exclusive central pharmacy for distribution, wherein all prescriptions for GHB for all patients prescribed GHB are received from all doctors prescribing GHB. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving GHB is confirmed, that receipt of the GHB by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4-14. **The Advisory Committee Slides** discloses a manufacturer producing GHB and providing it to an exclusive central pharmacy for distribution, wherein all prescriptions for GHB for all patients prescribed GHB are received from all doctors prescribing GHB. The doctors credentials are checked. It is also disclosed that receipt of the GHB by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 142, 146, 147, and 151-159. **The Advisory Committee Minutes** disclose the concept of confirming with the patient that educational material has been read before shipping GHB. *See*, *e.g.*, Question 5. **The Xyrem Video and Transcript** discloses distributing GHB from exclusive central pharmacy, wherein all prescriptions for GHB for all patients prescribed GHB are received from all doctors prescribing GHB. The doctors credentials are checked. It is also disclosed that receipt of the GHB by the patient is confirmed, that potential abuse is monitored, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4, 6-9, and 10. **Moradi** discloses a system for dispensing prescription medications. In the disclosed system a doctor sends prescription request identifying the drug to be dispensed, the patient, and credentials of the doctor. The system is designed to prevent abuse of the drug and includes a step of confirming receipt of the drug. *See*, *e.g.*, Abstract,

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and/or 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 or sending by courier 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.	¶¶[0003], [0022], [0035], [0043], [0045], [0116]-[0118], and Fig. 3. **Califano** discloses confirming with a patient that education material has been read and documenting that the patient understands the risks associated with the drug before providing the drug to the patient. *See*, *e.g.*, ¶¶[0043] and [0084]. **Lilly** discloses a method for controlling information related to controlled substances. The method makes use of a data storage unit to maintain information on prescription activities. The data storage unit can be accessed to determine if any abuse is taking place. *See*, *e.g.*, ¶¶[0012], [0033], [0043], [0044], [0054], [0057], [0058], [0062], and [0069]. **Elsayed** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:10-15; 4:10-16; 5:25-37; 7:13-15; 7:28-32; 7:40-45; 8:26-32; 8:45-48; 9:10-12; 9:30-50; 10:7-12; and 10:17-21. **Williams** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:21-26; 4:43-46; 5:61-67; 5:67 through 6:3; 10:3-5; 10:18-28; 10:30-32; 12:8-11; 12:35-55; 11:32-42; 11:51-54; 13:7-18; and 13:23-27. **Borsand** discloses a system of storing all pharmaceutical-related information in a central location. In addition, the system is able to detect abuse, generate reports to track abuse, and cancel prescriptions because of such abuse. *See*, *e.g.*, ¶¶[0003], [0034], [0043], [0120], and Fig. 3.

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	Ukens discloses restricting the distribution of specialty pharmaceuticals to a single pharmacy. The single pharmacies can also monitor dosage and patient compliance. *See*, *e.g.*, 41:3, ¶1 and 42:2, ¶1 through 3, ¶1.
14. A computerized method of distributing a 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 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; 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	**Anticipation** **The Advisory Committee Transcript** discloses all the limitations of claim 6, arranged as claimed. *See* 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses all the limitations of claim 6 arranged as claimed. *See* pgs. 4-14. **Obviousness** **The Advisory Committee Transcript** discloses distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving Xyrem is confirmed, that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving Xyrem is confirmed, that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4-14.

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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; 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 received and/or read prior to providing the prescription drug to the patient; 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 Advisory Committee Slides** disclose distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 142, 146, 147, and 151-159. **The Advisory Committee Minutes** disclose the concept of confirming with the patient that educational material has been read before shipping Xyrem. *See*, *e.g.*, Question 5. **The Xyrem Video and Transcript** discloses distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4, 6-9, and 10. **Moradi** discloses a system for dispensing prescription medications. In the disclosed system a doctor sends prescription request identifying the drug to be dispensed, the patient, and credentials of the doctor. The system is designed to prevent abuse of the drug and includes a step of confirming receipt of the drug. *See*, *e.g.*, Abstract, ¶¶[0003], [0022], [0035], [0043], [0045], [0116]-[0118], and Fig. 3. **Califano** discloses confirming with a patient that education material has been read and documenting that the patient understands the risks associated with the drug before providing the drug to the patient. *See*, *e.g.*, ¶¶[0043] and [0084]. **Lilly** discloses a method for controlling information related to controlled substances. The method makes use of

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the prescription drug; 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 confirming receipt by the patient of the prescription drug.	a data storage unit to maintain information on prescription activities. The data storage unit can be accessed to determine if any abuse is taking place. *See*, *e.g.*, ¶¶[0012], [0033], [0043], [0044], [0054], [0057], [0058], [0062], and [0069]. **Elsayed** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:10-15; 4:10-16; 5:25-37; 7:13-15; 7:28-32; 7:40-45; 8:26-32; 8:45-48; 9:10-12; 9:30-50; 10:7-12; and 10:17-21. **Williams** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:21-26; 4:43-46; 5:61-67; 5:67 through 6:3; 10:3-5; 10:18-28; 10:30-32; 12:8-11; 12:35-55; 11:32-42; 11:51-54; 13:7-18; and 13:23-27. **Borsand** discloses a system of storing all pharmaceutical-related information in a central location. In addition, the system is able to detect abuse, generate reports to track abuse, and cancel prescriptions because of such abuse. *See*, *e.g.*, ¶¶[0003], [0034], [0043], [0120], and Fig. 3. **Ukens** discloses restricting the distribution of specialty pharmaceuticals to a single pharmacy. The single pharmacies can also monitor dosage and patient compliance. *See*, *e.g.*, 41:3, ¶1 and 42:2, ¶1 through 3, ¶1
15. The computerized method of claim 14, wherein providing the prescription drug to the patient comprises the central pharmacy authorizing the prescription drug to be	**Obviousness** *See supra* claim 14. **Ukens** discloses a specialty pharmacy authorizing other pharmacies to dispense a drug. *See*, *e.g.*, 44:1, ¶3 through 3, ¶2; 44:1, ¶1 through 2, ¶3.

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dispensed to the patient by another pharmacy.	**Elsayed** discloses registering multiple pharmacies to dispense a hazardous drug. *See*, *e.g.*, 4:50-54. **Williams** discloses registering multiple pharmacies to dispense a hazardous drug. *See*, *e.g.*, 5:24-35.
16. The computerized method of claim 15, wherein the another pharmacy places controls on the distribution of the prescription drug, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of the prescription drug by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription drug, and limiting the prescription to a supply of limited duration.	**Obviousness** *See supra* claim 15. **Ukens** discloses authorized pharmacies performing face-to-face counseling with patients, performing compliance monitoring, and performing follow-ups with the patient. *See*, *e.g.*, 44:2, ¶3. **Elsayed** discloses authorized pharmacies complying with controls placed on dispensing hazardous drugs, flagging early refill requests, and limiting the prescription to a supply of limited duration. *See*, *e.g.*, 4:57-66; 9:30-50; 10:7-12; 10:17-21. **Williams** discloses authorized pharmacies complying with controls placed on dispensing hazardous drugs, flagging early refill requests, and limiting the prescription to a supply of limited duration. *See*, *e.g.*, 5:24-35; 12:35-55; 13:7-18; 13:23-27.

G. The '650 Patent

1. *Obviousness*

Claims 1-18 of the '650 patent are invalid under 35 U.S.C. § 103(a) because it would have been obvious to a person of ordinary skill in the art prior to the filing date of the '650 patent in view of one or more of the prior art references discussed herein.

Aqueous pharmaceutical compositions of gamma-hydroxybutyrate are disclosed by **Vickers**, **the '632 patent**, **Scrima (1989)**, **the '331 patent**, **Ferrara**, **Mamelak (1977)**, **Mamelak (1989)**, **Palatini**, **Scharf**, **Scrima (1990)**, **the '236 patent**, **EP '804**, **Broughton**, **the '619 patent**, and **CA 338**. The sodium salt is explicitly mentioned in **the '937 patent**, **Vickers**, **the '632 patent**, **the '331 patent**, **Mamelak (1977)**, **the '236 patent**, **EP '804**, **Broughton**, **the '937 patent**, and **the '619 patent**. **The '632 patent** provides for aqueous pharmaceutical compositions of gamma-hydroxybutyrate salts containing 12.5-50% GHB salt content by weight.

Vickers teaches that gamma-hydroxybutyric acid is marketed for intravenous injection as a solution of 2.42 g sodium gamma-hydroxybutyrate in 10 ml water, which has a pH of 8.2-8.9. **CA 338** asserts that the alkali metal salts of GHB, as usually prepared, have far too high a pH for injection as 20% solutions; in light of this problem, **CA 338** reports the preparation of injectable solutions by hydrolysis of gamma-butyrolactone with slightly less than the theoretical amount of alkali hydroxide, so as to obtain solutions of pH 7.2-7.7.

The 1990 CRC Handbook states that gamma-hydroxybutyric acid has a dissociation constant in aqueous solution with a pK value of 4.72. The **1995 USP** lists 13 acidifying agents used as pharmaceutic ingredients, and that list includes acetic acid, citric acid, hydrochloric acid, malic acid, nitric acid, phosphoric acid, and sulfuric acid. **Nema** lists acetic acid, citric acid, hydrochloric acid, phosphoric acid, and sulfuric acid as pH adjusting agents used in injectable formulations. **Remington's** also teaches that hydrochloric acid is used as a pharmaceutic aid to acidify a solution.

Nema also notes that, depending on the route of administration, preservatives may not be allowed in injectable formulations. **Nema** further teaches that injectable products are required to withstand sterilization processes. **CA 338**, **the '632 patent**, **the '619 patent**, **the '236 patent**,

and **EP '804** provide preservative-free pharmaceutical compositions designed for administration to patients, including some which were.

Scrima (1990), **the '632 patent**, **Scrima (1989)**, **Vickers**, **EP '804**, **the '331 patent**, **EP '408**, **the '937 patent**, **Scharf**, **Lammers**, **Lapierre**, **Mamelak (1977)**, **Mamelak (1989)**, **Palatini**, **Scrima (1987)**, **Laborit**, **Hoes**, and **Sériès** discuss the use of sodium gamma-hydroxybutyrate to treat one or more of conditions including narcolepsy, cataplexy, and insomnia. **Bédard**, **Sours**, **Lammers**, **Allsopp**, and **Chokroverty** further specify that narcolepsy is characterized by cataplexy and/or excessive daytime sleepiness. **Scrima (1989)**, **Scrima (1990)**, **Broughton**, **EP '265**, **Palatini**, and **Sériès** recommend treating such conditions by diluting the active principle in water, juice, and/or other aqueous medium. **Broughton** notes that dilution of sodium gamma-hydroxybutyrate retards the rate of absorption, so that sleep is induction is more gradual and normal, and reduces gastrointestinal upset in some patients. **Broughton**, **Scrima (1990)**, **the '632 patent**, **Ferrara**, **Lammers**, **Mamelak (1977)**, **Scrima (1989)**, **Hoes**, and **Sériès** suggest treatment using an orally administered aqueous composition of sodium gamma-hydroxybutyrate.

Mamelak (1989) reports that the central effects of an intravenous dose of 60-70 mg/kg GHB run their course in about 2 hours. **EP '265** cites the need to administer sodium gamma-hydroxybutyrate more than once a day, noting its rapid absorption and elimination, with a maximum peak at about 30-45 minutes after oral administration, a half-life time of about 20-25 minutes, and elimination of principle in 4-5 hours. **EP '804** teaches oral administration of a pharmaceutically acceptable salt of gamma-hydroxybutyric acid in the form of single or multi-dose solutions.

Mamelak (1977) reports that patients were given repeated doses of sodium gamma-hydroxybutyrate during the night. **The '331 patent** also teaches administration of one dose within the last hour prior to retiring and further states that it may be desirable to administer a second or third dose during the normal sleep period. **Vickers** reports that GHB has been tried orally as a night sedative, and that 2 g every 2-4 hours produces sleep. In the study of **Scrima (1989)**, patients were instructed to ingest one entire bottle immediately before going to bed and the other 3 hours later. **Scharf** reports the administration of GHB to narcolepsy patients at lights out and again 4 hours later. **Scrima (1987)** discloses administration of GHB within the hour prior to sleep and again 3 hours later. Similarly, **Sériès** discloses the administration of GHB diluted in orange juice at the beginning of the recording and at the first awakening 3 hours after the first drug administration. **Broughton** further reports the administration of an initial dose of 1.5-2.25 g sodium gamma-hydroxybutyrate in 10-15 ml of water within the hour prior to sleep, followed by further 1.0-1.5 g doses during the night with each major reawakening, it at least 2.5 hours had passed since the previous dose.

Remington's defines a pharmaceutical container as a device which holds the drug and is, or may be, in direct contact with the preparation, and that the immediate container is that which is in direct contact with the drug at all times. As an example, **Remington's** notes that light-sensitive drugs for parenteral use are usually sealed in flint ampoules and placed in a box, noting that light can catalyze drug decomposition reactions. **EP '265** mentions that aqueous solutions of sodium gamma-hydroxybutyrate are commercially available, and **the '632 patent** and **EP '804** disclose bottles containing aqueous pharmaceutical compositions of sodium gamma-hydroxybutyrate. **Palatini** shows the use of a cup to administer GHB to patients.

EP '951 provides a kit for the preparation of a parenteral formulation of an antibiotic, comprising one container of the antibiotic and another container of buffer to mix with the antibiotic. Similarly, **the '196 PCT** describes a kit containing vials of lyophilized cisplatin, a diluent for resuspension of the drug, collagen gels, and syringes for mixing and dosing. **The '688 PCT** specifies a kit for injection comprising at least two ampoules, one containing a drug, and the other containing a diluent to mix with the drug.

A person of ordinary skill in the art reading the '632 patent, alone or in combination with any of Vickers, the '632 patent, Scrima (1989), the '331 patent, Ferrara, Mamelak (1977), Mamelak (1989), Palatini, Scharf, Scrima (1990), the '236 patent, EP '804, Broughton, the '937 patent, the '619 patent, or CA 338, would have been motivated to prepare an aqueous pharmaceutical composition comprising 500 mg/ml sodium gamma-hydroxybutyrate. In further view of Vickers, a person of ordinary skill in the art would have been motivated to prepare a solution with a pH in the 8.2-8.9 range. In further view of The 1990 CRC Handbook, a person of ordinary skill in the art would have recognized that the aqueous solution containing 242 mg/ml disclosed in Vickers would inherently have a pH of about 9.5. Accordingly, a person of ordinary skill in the art would have recognized that, in order to attain the reported pH of 8.2-8.9, such a solution would have necessarily contained a pH-adjusting agent, namely, an acid.

In view of the above discussed and in further view of Vickers and CA 338, a person of ordinary skill in the art would be motivated to lower the pH to the 7.2-7.7 range, in order to make a more ideal formulation for injection. In order to lower the pH, a person of ordinary skill in the art would have consulted the 1995 USP, Nema, and/or Remington's, and would have routinely selected any of malic acid, citric acid, acetic acid, lactic acid, hydrochloric acid, phosphoric acid, sulfuric acid, nitric acid, an organic acid, or an inorganic acid. In the course of lowering the pH

from 8.2-8.9 to 7.2-7.7, a person of ordinary skill in the art would have necessarily passed through a pH of about 8.0.

A person of ordinary skill in the art reading the above discussed and Vickers in view of CA 338, the '632 patent, the '619 patent, the '236 patent, or EP '804 would have recognized that, in order for the preservative-free pharmaceutical compositions disclosed therein to be administered to patients, they would have had to be inherently chemically stable and resistant to microbial growth. In further view of Nema, a person of ordinary skill in the art would have been motivated to exclude preservatives from the aqueous formulation.

In view of the above discussed, in further view of Scrima (1990), alone or in combination with any of the '632 patent, Scrima (1989), Vickers, EP '804, the '331 patent, EP '408, CA 338, the '937 patent, Lammers, Lapierre, Mamelak (1977), Mamelak (1989), Palatini, Scrima (1987), Laborit, Hoes, or Sériès, alone or in further view of any of Bédard, Sours, Lammers, Allsopp, or Chokroverty, a person of ordinary skill in the art would have been motivated to use the pharmaceutical composition to treat cataplexy or daytime sleepiness in a narcolepsy patient. In further view of the disclosure of Broughton, a person of ordinary skill in the art would have been motivated to dilute the pharmaceutical composition and administer the dilution orally to the patient. In further view of any of Mamelak (1989), EP '265, EP '804, Mamelak (1977), the '331 patent, Vickers, Scrima (1989), Scharf, and Scrima (1987), a person of ordinary skill in the art would have been motivated to administer 2 consecutive oral doses daily, with the first dose being administered within the hour prior to sleep and the second dose 2.5-4 hrs later. Moreover, a person of ordinary skill in the art would have done so with a reasonable expectation of success, in view of the above discussed.

Accordingly, a person of ordinary skill in the art would have been motivated to create a set comprising the pharmaceutical composition. A person of ordinary skill in the art reading the disclosure of EP '265 that aqueous solutions of sodium gamma-hydroxybutyrate are commercially available would have recognized that the solution must be in a container. In further view of Remington's, a person of ordinary skill in the art would have been motivated to create a set comprising the pharmaceutical composition in one or more containers. In further view of the '632 patent and EP '804, a person of ordinary skill in the art would have been motivated to select a bottle as the container. In further view of Broughton, EP '951, the '196 PCT, the '688 PCT, and Palatini, a person of ordinary skill in the art would have been motivated to create a set comprising an outer container means capable of retaining a bottle of the pharmaceutical composition of aqueous sodium gamma-hydroxybutyrate, a container of diluent, and a dosing cup for delivering the diluted pharmaceutical composition to the patient.

2. *35 U.S.C. § 112, ¶1*

Claims 5-10 are invalid under 35 U.S.C. § 112, ¶1 for lacking written description support and enablement. Specifically, in view of statements made by the applicant during prosecution, each of these claims require the exclusion of a preservative. But in view of the Court's construction in the *Roxane* case, these claims, as drafted, do in fact include a preservative. Thus, the specification neither enables nor provides written description support for claims that require the exclusion of a preservative, as argued in the prosecution history.

Claim 5 explicitly requires a pH-adjusting or buffering agent. Claims 6-10 depend, directly or indirectly, from claim 5 and therefore also require the same pH-adjusting or buffering agent.

Under the Court's construction in Jazz's case against Roxane, the pH-adjusting or buffering agent required by claims 5-10 must be construed as a "preservative." The Court

construed "preservative" to mean "a substance or substances added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action." (*See Roxane Markman* Order at p. 16). The '650 patent asserts that adjusting the pH is a means to inhibit chemical change or microbial action. So, under the Court's construction, a pH-adjusting or buffering agent required in the claims is properly construed as a "preservative."

But, during prosecution of the '431 patent, which is an ancestor of the '650 patent, to overcome the Examiner's prior art rejections, Applicants argued that the cited prior art references do not teach any way to make aqueous GHB solutions resistant to microbial degradation other than by the addition of a preservative. Specifically, the Applicants argued that:

> Gessa does not disclose any way to make GHB aqueous solutions stable to microbial degradation ***other than by using conventional preservatives*** in Examples 1 and 2. … 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***…. [N]one of the references teach or suggest solutions of GHB salt that are resistant to microbial growth ***without an added preservative***.

(Prosecution History of the '431 patent, Amendment and Reply submitted on August 10, 2001 (emphasis added).) (*See, e.g.,* AMNXYR_000002621-AMNXYR_000002625.). In so arguing, Applicants clearly and unmistakably surrendered a method of making gamma-hydroxybutyrate formulations using preservatives. Yet, claims 5-10 of the '650 patent must be held to require such a method comprising a preservative.

Claims 5-10 explicitly require adjusting the pH, and, in view of the prosecution history, also require the exclusion of preservatives. But, under the Court's definition of "preservative" in the Roxane case, the required pH-adjusting agent necessarily acts as a preservative. As a result, claims 5-10 lack enablement and written description support, since the specification does not teach any way to exclude preservatives while also using a preservative, as required by the claims.

3. *35 U.S.C. § 112, ¶2*

Claims 5-10 are invalid under 35 U.S.C. § 112, ¶2 for being indefinite because their terms are hopelessly vague and insolubly ambiguous, thus rendering their scope unascertainable. Claim 5 explicitly requires a pH-adjusting or buffering agent. Claims 6-10 depend directly or indirectly from claim 5 and therefore also explicitly require a pH-adjusting or buffering agent. Under the Court's construction in Jazz's case against Roxane, the pH-adjusting or buffering agent must be construed as a "preservative." In the *Markman* order in *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, the Court construed "preservative" to mean "a substance or substances added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action." (*See Roxane Markman* Order at p. 16). The '650 patent asserts that adjusting the pH is a means to inhibit chemical change or microbial action. So, under the Court's construction, a pH-adjusting or buffering agent required in the claims is properly construed as a "preservative."

But, during prosecution of the '431 patent, which is the ancestor of the '650 patent, to overcome the Examiner's prior art rejections, Applicants argued that the cited prior art references do not teach any way to make aqueous GHB solutions resistant to microbial degradation other than by the addition of a preservative. Specifically, the Applicants argued that:

> Gessa does not disclose any way to make GHB aqueous solutions stable to microbial degradation ***other than by using conventional preservatives*** in Examples 1 and 2. … 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***…. [N]one of the references teach or suggest solutions of GHB salt that are resistant to microbial growth ***without an added preservative***.

(Prosecution History of the '431 patent, Amendment and Reply submitted on August 10, 2001 (emphasis added).) (*See, e.g.,* AMNXYR_000002621-AMNXYR_000002625.). In so arguing,

Applicants clearly and unmistakably surrendered a method of making gamma-hydroxybutyrate formulations using preservatives. Yet, claims 5-10 of the '650 patent must be held to require such a method comprising a preservative. As a result, the requirement of a pH-adjusting or buffering agent in claims 5-10, which acts as a preservative under the Court's construction, contradicts the express requirement from the prosecution history and the claim language that these claims do not utilize preservatives in the aqueous medium. That is, even though the claims purport to require the exclusion of a preservative, they do in fact require a preservative, as written, under the Court's construction of "preservative." As a consequence, claims 5-10 are hopelessly vague and insolubly ambiguous, leading to a finding that they are indefinite.

Claim Charts

'650 Patent Claim	Invalidity
1. 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.	**The '632 patent** discloses the use of gamma-hydroxybutyric acid salts for preparing pharmaceutical compositions, with suitable salts including the sodium salt, and that the GHB salt content of the compositions can vary from 12.5 to 50% by weight. It also discloses a bottle containing 20 ml of solution containing 6.05 g of sodium gamma-hydroxy butyric acid, and an injectable formulation of sodium gamma-hydroxybutyrate free of preservatives. *See*, *e.g.*, Abstract, 7:32-33, 7:47-49, Example 2, 8:57-59. **The '236 patent** discloses that sodium 4-hydroxybutyrate has been used in medicine to induce both anesthesia and sleep. *See*, *e.g*, 1:38-43. **EP '804** discloses administration of salts of gamma-hydroxybutyric acid in the form of single or multi-dose liquid solutions, with the sodium salt being particularly preferred. It also discloses a formulation for intravenous injection that is free of preservatives. *See*, *e.g.*, 2:38-39, 6:32-34, Formulation 3. **The '937 patent** discloses that gamma-hydroxybutyric acid is commercially available as the sodium salt. *See*, *e.g.*, 1:7-12. **Ferrara** discloses the administration of GHB dissolved in black cherry syrup as obtained from CT, Sanremo, Italy. *See*, *e.g.*, p.

'650 Patent Claim	Invalidity
	232. **Lapierre** discloses that GHB is used to treat narcolepsy and that cataplexy is controlled by GHB. *See*, *e.g.*, summary, p. 28. **Mamelak (1977)** discloses that γ-hydroxybutyrate is marketed by Laboratoire Egic of Paris, France, as a banana-flavored syrup. It also disclose the use of GHB, obtained as a banana-flavored syrup, in a dose of 1.0-4.5 g and placebo in a dose of 5 cc banana flavoring in water, and exploring the use of sodium gamma-hydroxybutyrate to treat insomnia. *See*, *e.g.*, pp. 273, 274-275. **Mamelak (1989)** discloses the therapeutic use of GHB to consolidate night sleep in narcoleptics and improve their alertness during the day. *See*, *e.g.*, p. 188. **Scrima (1989)** discloses the efficacy of GHB in treating narcolepsy-cataplexy, and it also discloses providing subjects with pharmacy-prepared bottles of GHB mixed with distilled water and syrup of orange. *See*, *e.g.*, p. 333. **Palatini** discloses that GHB is available dissolved in a black cherry syrup from CT. *See*, *e.g.*, p. 354. **Vickers** discloses that gamma-hydroxybutyrate is water soluble in all dilutions, and that the pH of the solution is not far from physiological. It is also disclosed that gamma-hydroxybutyric acid is marketed for intravenous injection as a solution containing 2.42 g sodium 4-hydroxybutyrate in 10 ml water, with a pH between 8.2 and 8.9. *See*, *e.g.*, pp. 75, 82-87. **Scrima (1990)** discloses the results of a double-blind study which indicate that GHB improves sleep depth and continuity. It is also disclosed that GHB was mixed with sterile, distilled water and syrup of orange. *See*, *e.g.*, pp. 482, 486. **Lammers** discloses that gamma-hydroxybutyrate was administered orally as a 10% aqueous solution. *See*, *e.g.*, p. 217. **EP '408** discloses that GHB has been demonstrated in clinical trials to be a safe, oral drug for treatment of narcolepsy, and that GHB is also known as sodium oxybate and is commercially available. It is also disclosed that ethyl 4-acetoxybutanoate may be compounded and administered in dosage levels similar to those used for GHB, and that ethyl 4-acetoxybutanoate may be taken orally as a solution or suspension. *See*, *e.g.*, 2:21-22, 2:45-46, 3:22-23, 3:26-27. **The '331 patent** discloses the therapeutic use of sodium γ-

'650 Patent Claim	Invalidity
	hydroxybutyrate, which may be orally administered, with suitable compositions including solutions. *See*, *e.g.*, 7:1-15, 7:44, 7:63-64. **CA 338** discloses that the alkali metal salts of GHB, as usually prepared, have far too high a pH for injection as 20% solutions. Also disclosed is the preparation of injectable solutions by hydrolysis of gamma-butyrolactone with slightly less than the theoretical amount of alkali hydroxide, so as to obtain solutions of pH 7.2-7.7. *See*, *e.g.*, Abstract. **Roth** discloses that, of GHB and GBL, GHB is the active form, but GBL has the longer duration of action. It is further disclosed that GBL is rapidly converted to GHB in the blood and liver. *See*, *e.g.*, pp. 1333, 1342-1343. **The 1990 CRC Handbook** discloses that γ-Hydroxybutyric acid has a pK_a of 4.72 in aqueous solution. *See*, *e.g.*, p. 8-36. **The '619 patent** discloses that sodium 4-hydroxybutyrate is highly soluble in water and, in aqueous solution, has a pH slightly in excess of 7. It is also disclosed that the equilibrium between GBL and GHB lies toward GHB at pH values above 7. Also disclosed are formulations that are free of preservatives, including one that was administered to a patient just prior to undergoing surgery. *See*, *e.g.*, 1:27-37, 1:61-66, examples 1-3. **Remington's** discloses means to achieve drug stabilization from photolytic, oxidative, and solvolytic decomposition reactions. Also disclosed is the use of hydrochloric acid as a pharmaceutic aid used to acidify. *See*, *e.g.*, pp. 239, 1410. **The 1995 USP** discloses a list of 13 acidifying agents, including organic and inorganic acids, and nine alkalizing agents among USP and NF Pharmaceutic Ingredients. *See*, *e.g.*, p. 2205. **Nema** discloses that injectable products are required to withstand sterilization processes such as autoclaving, and that preservatives may not be allowed in some injectable products, depending on the route of administration. It is also disclosed that chelating agents are used in parenteral products to complex heavy metals, thereby improving the efficacy of antioxidants or preservatives. Also disclosed are buffers and chemicals used to adjust the pH of formulations, including a table of 32 buffers and pH-adjusting agents, including organic and inorganic acids. *See*, *e.g.*, pp. 166, 167-168, 169.

'650 Patent Claim	Invalidity
2. The pharmaceutical composition of claim 1, wherein the composition has a pH of about 7.5.	*See supra* claim 1.
3. The pharmaceutical composition of claim 1, wherein the composition has a pH of about 8.0.	*See supra* claim 1.
4. The pharmaceutical composition of claim 1, wherein the composition has a pH of about 8.5.	*See supra* claim 1.
5. The pharmaceutical composition of claim 1, wherein the composition additionally comprises a pH adjusting or buffering agent.	*See supra* claim 1. **EP '804** also discloses that pharmaceutical compositions of sodium 4-hydroxybutyrate may be buffered. *See*, *e.g.*, 6:34. *See also*, 21 C.F.R. §§ 184.1005, 184.1033, 184.1061, 184.1069, 184.1081, 184.1095, and 184.1099.
6. The pharmaceutical composition of claim 5, wherein the pH adjusting or buffering agent is an acid.	*See supra* claim 5.
7. The pharmaceutical composition of claim 6, wherein the acid is an inorganic acid.	*See supra* claim 6.
8. The pharmaceutical composition of claim 6, wherein the acid is an organic acid.	*See supra* claim 6.
9. The pharmaceutical composition of claim 6, wherein the acid is selected from the group consisting of malic acid, citric acid, acetic acid, boric acid, lactic acid, hydrochloric acid, phosphoric acid, sulfuric acid, and nitric acid.	*See supra* claim 6.
10. The pharmaceutical composition of claim 6, wherein the acid is malic acid.	*See supra* claim 6.

'650 Patent Claim	Invalidity
11. A method of treating cataplexy or daytime sleepiness in a patient having narcolepsy comprising diluting the pharmaceutical composition of claim 1, and administering to the patient the diluted pharmaceutical composition.	*See supra* claim 1. **Scrima (1987)** discloses the results of a study on the effects of GHB treatment on cataplexy and sleep attacks in narcoleptics, administering 25 mg/kg GHB (50 mg/kg in two doses is 25 mg/kg per dose) within the hour prior to sleep and again 3 hours later. *See*, *e.g.*, p. 134. **Scrima (1990)** discloses that the therapeutic reduction of cataplexy in narcolepsy patients treated with GHB, mixed with syrup and juice, appears to be due to its improving sleep quality. *See*, *e.g.*, Summary, p. 482. **Broughton** discloses the results of a study in which "sixteen patients with narcolepsy and cataplexy were treated with gamma-hydroxybutyrate (GHB)," and "the subjective quality of night sleep improved in all patients and the number of irresistable (sic) daytime attacks of sleep and cataplexy substantially diminished." The use of the sodium salt of gamma-hydroxybutyrate is also disclosed. It is further disclosed that diluting the syrup in milk or juice reduced gastrointestinal upset in some patients, and that dilution retarded the rate of absorption of GHB, so that sleep induction was more gradual and normal. *See*, *e.g.*, pp. 2, 3. **Chokroverty** discloses that the characteristic clinical picture of narcolepsy syndrome includes cataplexy and uncontrollable sleep attacks during the day. *See*, *e.g.*, p. 250. **Sours** discloses that cataplexy, the second most common and most easily recognized narcolepsy symptom, was characterized by a sudden decrease of muscle tone, limited to particular muscle groups. *See*, *e.g.*, p. 532. **The '937 patent** discloses that "the narcosis achieved with GHB broadly resembles physiological sleep." *See*, *e.g.*, 1:62-64. **Bédard** discloses that narcolepsy is characterized by cataplexy and excessive daytime sleepiness and also discloses administration of GHB at bedtime, with one repetition during the night. *See*, *e.g.*, 29:1-5, 30:3-5, 30:9-17. **The '331 patent** discloses that GHB has such clinical effects as reduction of narcolepsy and increased short-wave sleep. *See*, *e.g.*, 6:21-40. **Allsopp** discloses that the narcolepsy syndrome comprises sleep disturbance, cataplexy, sleep paralysis, and hypnagogic hallucinations, and that the sleep disturbance involves excessive daytime drowsiness with intermittent, irresistible naps, and a

'650 Patent Claim	Invalidity
	disrupted pattern of nocturnal sleep. *See*, *e.g.*, p. 302. **Lammers** discloses that narcolepsy is clinically characterized by excessive daytime sleepiness, disturbed nocturnal sleep, cataplexy, hypnagogic hallucinations, and sleep paralysis. *See*, *e.g.*, p. 216. **Mamelak (1977)** discloses that the use of GHB in repeated doses during the night reduced the incidence of daytime attacks of cataplexy and improved daytime functioning. *See*, *e.g.*, p. 286. **Palatini** discloses that GHB has been used in the treatment of narcolepsy. Also disclosed is the oral administration of 12.5, 25, and 50 mg/kg GHB diluted in water, with the black cherry GHB syrup being diluted to 100 ml with water and the cup rinsed with an additional 50 ml water. *See*, *e.g.*, pp. 353, 354. **Scharf** discloses that treatment of narcoleptics with GHB significantly improved the clinical symptoms of cataplexy, sleep paralysis, hypnogogic hallucinations, daily naps, and sleep attacks. Subjects were administered 2 doses of 20-25 ml of 150 mg/ml GHB, the first at lights out, and the second 4 hours later. *See*, *e.g.*, Abstract, p. 222. **Laborit** discloses that the coma-inducing action of short-chain fatty acids from C_4 to C_{10} is known, with "molecules closely related to GHB such as 1,4-butanediol… possess hypnotic properties similar to those of GHB." It is further disclosed that GHB-induced sleep has been described as being close to physiological sleep, with doses of 50 to 60 mg/kg rapidly inducing slow wave sleep followed by REM sleep, and that GHB will deepen sleep. *See*, *e.g.*, pp. 257, 258, 264, 269. **Sériès** discloses that gamma-hydroxybutyrate improved sleep abnormalities in a patient with narcolepsy and central sleep apnea, with 30 mg/kg gamma-hydroxybutyrate administered as a white powder diluted in orange juice at the beginning of the recording and at the first awakening 3h after the first drug administration. *See*, *e.g.*, pp. 1378, 1379. **Scrima (1989)** discloses that patients were provided aqueous solutions of GHB and instructed to ingest them. *See*, *e.g.*, p. 333-334.
12. The method of claim 11, wherein the pharmaceutical composition is administered orally.	*See supra* claim 11. **The '632 patent** discloses that compositions may be syrups to be

'650 Patent Claim	Invalidity
	administered orally. *See*, *e.g.*, 7:51-53. **Broughton** discloses oral administration of sodium gamma-hydroxybutyrate. *See*, *e.g.*, p. 2. **EP '804** discloses oral administration of a pharmaceutically acceptable salt of gamma-hydroxybutyric acid in the form of single or multi-dose liquid solutions. *See*, *e.g.*, 6:32-34. **EP '265** discloses that sodium gamma hydroxy butyrate was previously available as a syrupy solution. *See*, *e.g.*, 3:23. **Mamelak (1977)** discloses oral dosing of 1.0-4.5g GHB. *See*, *e.g.*, p. 274. **Vickers** discloses that gamma-hydroxybutryate has a possible clinical use in night sedation, that GHB has been tried orally as a night sedative, and that 2 g every 2-4 hours produces sleep. It is further disclosed that an intravenous or oral dose of 40-50 mg/kg of gammahydroxybutyric acid will, within 5-15 minutes, induce a sleeping state from which the patient can be awoken. *See*, *e.g.*, pp. 78, 82-87. **Hoes** discloses the results of a study of the effects of GHB on insomniacs in which gamma-hydroxybutyrate was dissolved at a concentration of 10 grams per 100 milliliters of chocolate-flavored water. *See*, *e.g.*, p. 94. **Ferrara** discloses that GHB has been used in the treatment of sleep disorders and orally administered to treat the effects of alcohol withdrawal in man. *See*, *e.g.*, p. 231. **Lapierre** discloses oral administration of GHB. *See*, *e.g.*, p. 25. **Mamelak (1989)** discloses oral administration of GHB. *See*, *e.g.*, p. 188.
13. The method of claim 12, wherein the pharmaceutical composition is administered orally as two consecutive single doses daily.	*See supra* claim 12. **Scrima (1990)** discloses that GHB was mixed with sterile, distilled water and syrup of orange, and that subjects took 25 mg/kg of GHB within the hour prior to sleep and 25 mg/kg 3 hours later. *See*, *e.g.*, p. 482. **Broughton** discloses administering an initial dose of 1.5-2.25 g NaGHB in 10-15 ml within the hour prior to sleep, followed by further 1.0-1.5 g doses during the night with each major reawakening, if at least 2.5 hours had passed since the previous dose. *See*, *e.g.*, p. 2.

'650 Patent Claim	Invalidity
	EP '265 discloses that sodium gamma hydroxy butyrate has to be administered more than once a day, due to its rapid absorption and elimination. *See*, *e.g.*, 3:14-19. **The '236 patent** discloses that certain dosage levels of sodium 4-hydroxybutyrate generate a sleeping state from which the patient can be awoken. *See*, *e.g.*, 1:38-43. **Mamelak (1989)** discloses that GHB is rapidly metabolized and the central effects of an intravenous dose of GHB last about 2 hours. *See*, *e.g.*, p. 188. **Scrima (1989)** discloses that patients were instructed to ingest one entire bottle immediately before going to bed and the other 3 hours later. *See*, *e.g.*, p. 334. **The '331 patent** discloses administration of one dose within the last hour prior to retiring, or one-half hour or less prior to retiring, and that it may be desirable to administer a second or third dose during the normal sleep period. *See*, *e.g.*, 7:52-61, 7:61-63. **Lammers** discloses the administration of one 30 mg/kg dose of GHB shortly before nocturnal sleep and a second 30 mg/kg dose 4 hours later. *See*, *e.g.*, p. 217.
14. The method of claim 13, wherein the first dose is administered prior to bedtime and the second dose is administered from about 2.5 to about 4.0 hours after administration of the first dose.	*See supra* claim 13. **EP '265** discloses that the principle is eliminated within 4-5 hours. *See*, *e.g.*, 3:17. **Mamelak (1989)** discloses that the central effects of an intravenous dose of 60-70 mg/kg GHB run their course in about 2 hours. *See*, *e.g.*, p. 188.
15. A set comprising the pharmaceutical composition of claim 1 in one or more container means.	*See supra* claim 1. **The '632 patent** discloses a bottle containing 140 ml of solution containing 42.35 g sodium gamma-hydroxybutyric acid and a bottle containing 20 ml of solution containing 6.05 g sodium gamma-hydroxybutyric acid. *See*, *e.g.*, Examples 1-2. **EP '265** discloses that aqueous liquid solutions of sodium gamma-hydroxybutyrate are commercially available. *See*, *e.g.*, 7:22-23. **Remington's** discloses that a pharmaceutical container has been defined as a device which holds the drug and is, or may be, in direct contact with the preparation, with the immediate container being that which is in direct contact with the drug at all times. It

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	is also disclosed that light-sensitive drugs for parenteral use are usually sealed in flint ampules and placed in a box. *See*, *e.g.*, p. 646.
16. The set of claim 15, wherein the one or more container means are selected from the group consisting of a drinking cup, a dosing cup, a syringe, a pipette, a vial, an ampule, a test tube, a flask, a bottle, and a pouch syringe.	*See supra* claim 15. **EP '804** discloses a single-dose 10-ml bottle containing sodium 4-hydroxybutyrate as the active ingredient in water and a 14-dose 140-ml bottle containing 4-hydroxybutyrate as the active ingredient in water. *See*, *e.g.*, Formulations 1-2. **Palatini** discloses the use of a cup to administer the GHB. *See*, *e.g.*, p. 354.
17. The set of claim 15, comprising a third container means capable of retaining a first container means, a second container means, and one or more delivery vehicles capable of administering the pharmaceutical composition to the patient.	*See supra* claim 15. **EP '951** discloses a therapeutic kit for the preparation of a parenteral formulation of an antibiotic, wherein the kit comprises a container of the antibiotic and a container of buffer to be missed with the antibiotic. *See*, *e.g.*, 14:29-33. **The '196 PCT** discloses a kit containing vials of lyophilized cisplatin, diluent for cisplatin resuspension, collagen gels, and syringes for mixing and dosing. *See*, *e.g.*, 8:9-12. **The '688 PCT** discloses a kit for injection which comprises two or more ampoules each comprising a powdery component and a diluent for mixing and dissolving two or more components when administered. *See*, *e.g.*, 28:26-33.
18. The set of claim 17, wherein the first container means comprises the pharmaceutical composition, and the second container means comprises a diluent.	*See supra* claim 15.

H. The '275 Patent

1. *Obviousness*

Claims 1-4 of the '275 patent are invalid under 35 U.S.C. § 103(a) because they would have been obvious to a person of ordinary skill in the art prior to the filing date of the '275 patent in view of one or more of the prior art references discussed herein.

Scrima (1989), **Scrima (1990)**, **Broughton**, **the '632 patent**, **the '937 patent**, **the '331 patent**, **Vickers**, **Lammers**, **Mamelak (1977)**, **Mamelak (1989)**, **Palatini**, **Scharf**, **Laborit**, and **Sériès** disclose the treatment of cataplexy and/or daytime sleepiness in narcoleptics using sodium gamma-hydroxybutyrate. **Scrima (1989)**, **Scrima (1990)**, **Broughton**, **EP '265**, **Palatini**, and **Sériès** discuss doing so by diluting the active principle in water, juice, and/or other aqueous medium. **The '632 patent** provides aqueous compositions of sodium gamma-hydroxybutyrate ranging from 12.5 to 50% GHB salt content by weight.

Mamelak (1977) describes administering to insomnia patients either 1.0-4.5 g sodium gamma-hydroxybutyrate, which was obtained as a banana-flavored syrup, or a placebo, consisting of 5 cc banana flavoring in water. Similarly, **the '331 patent** details oral administration of solutions of sodium gamma-hydroxybutyrate with typical dosages between 2.0 and 5.0 grams. **Vickers** reports the use of 20-30 g GHB per 24-hour period without ill effect.

Scrima (1990) and **Vickers** cite reports of oral doses of 40-50 mg/kg GHB inducing sleep. **Scrima (1990)** further describes a sleep study in which patients were administered 25 mg/kg GHB within the hour prior to seep and again 3 hours later. **The '632 patent** provides dosages of 0.025-0.10 g/kg, with 0.05 g/kg in a single daily dose being preferred. **Palatini** reports administration of 12.5, 25, and 50 mg/kg doses. **Laborit** discusses the administration of 50-60 mg/kg doses.

Scrima (1990) cites patient weights of 57-113 kg for females, and a body mass index (BMI) range of 17.6-45.4, and 54-90 kg for males, and a BMI range of 20.3-29.1. **CDC** categorizes people with BMIs under 18.5 as underweight, between 18.5 and 24.9 as healthy, between 25.0 and 29.9 as overweight, and over 30 as obese.

Mamelak (1989) reports that the central effects of an intravenous dose of 60-70 mg/kg GHB run their course in about 2 hours. **EP '265** cites the need to administer sodium gamma-hydroxybutyrate more than once a day, due to its rapid absorption and elimination, with a maximum peak at about 30-45 minutes after oral administration, a half-life time of about 20-25 minutes, and elimination of principle in 4-5 hours. **EP '804** describe oral administration of a pharmaceutically acceptable salt of gamma-hydroxybutyric acid in the form of single or multi-dose solutions.

Mamelak (1977) reports that patients were given repeated doses of sodium gamma-hydroxybutyrate during the night. **The '331 patent** also teaches administration of one dose within the last hour prior to retiring and further states that it may be desirable to administer a second or third dose during the normal sleep period. **Vickers** states that GHB has been tried orally as a night sedative, and that 2 g every 2-4 hours produces sleep. In **Scrima (1989)**, patients were instructed to ingest one entire bottle immediately before going to bed and the other 3 hours later. In **Scharf**, GHB was given to narcolepsy patients at lights out and again 4 hours later. **Scrima (1987)** teaches administration of GHB within the hour prior to sleep and again 3 hours later. **Sériès** discloses the administration of GHB diluted in orange juice at the beginning of the recording and at the first awakening 3 hours after the first drug administration.

Broughton, **Scrima (1990)**, **the '632 patent**, **Lammers**, **Mamelak (1977)**, **Scrima (1989)**, **Hoes**, and **Sériès** disclose treatment using an orally administered aqueous composition of sodium gamma-hydroxybutyrate. In **Broughton**, an initial dose of 1.5-2.25 g sodium gamma-hydroxybutyrate in 10-15 ml of water was given within the hour prior to sleep, followed by further 1.0-1.5 g doses during the night with each major reawakening, it at least 2.5 hours had passed since the previous dose. **Lammers** reports the oral administration of gamma-

hydroxybutyrate as a 10% aqueous solution. **Broughton** further notes that dilution of sodium gamma-hydroxybutyrate retards the rate of absorption, so that sleep is induction is more gradual and normal, and reduces gastrointestinal upset in some patients.

A person of ordinary skill in the art reading Scrima (1990), alone or in combination with any of Scrima (1989), Broughton, Palatini, EP '265, Sériès, or the '632 patent, alone or in further view of any of the '937 patent, the '331 patent, Vickers, Lammers, Mamelak (1977), Mamelak (1989), Scharf, or Laborit, would have been motivated to use an aqueous composition of sodium gamma-hydroxybutyrate to treat cataplexy and/or daytime sleepiness in narcolepsy patients, with a reasonable expectation of success. In view of the above discussed and the '632 patent, a person of ordinary skill in the art would have started with a composition containing 50% sodium gamma-hydroxybutyrate by weight, or 500 mg/ml sodium gamma-hydroxybutyrate.

A person of ordinary skill in the art would have been motivated to use doses of 1.0-4.5 g or 2.0-5.0 g of sodium gamma-hydroxybutyrate, in view of the above discussed Mamelak (1977) and the '331 patent, with a reasonable expectation of success, based on the disclosures of the above discussed alone or in combination with Vickers.

In addition, a person of ordinary skill in the art reading Scrima (1990) in view of CDC would recognize that the patient weights disclosed in Scrima (1990) comprise a representative sample of the general population, ranging from underweight to obese. Accordingly, a person of ordinary skill in the art would have used the patient weights in Scrima (1990) to determine that the 40 mg/kg doses in Vickers range from 2160 to 4520 mg; the 50 mg/kg doses in Vickers, the '632 patent, Palatini, and Laborit range from 2700 to 5650 mg; the 60 mg/kg doses in Laborit range from 3420 to 6780 mg; and the 100 mg/kg doses in the '632 patent range from 5400 to

11,300 mg. Accordingly, a person of ordinary skill in the art would have recognized the therapeutic values of both the 4.5-9 g and 3-9 g dose ranges required by the '275 patent.

Additionally, a person of ordinary skill in the art would have been motivated to administer a second dose of the same amount, in view of the above discussed and any of Mamelak (1989), EP '265, EP '804, Mamelak (1977), the '331 patent, Vickers, Scrima (1989), Scharf, and Scrima (1987), with a reasonable expectation of success. In view of the above, a person of ordinary skill in the art would have been motivated to administer the first dose within the hour prior to sleep onset and the second dose 2-4 hours later, with a reasonable expectation of success.

Lastly, in view of the above discussed, a person of ordinary skill in the art would have been motivated to administer the aqueous composition of sodium gamma-hydroxybutyrate orally. In administering the solution, a person of ordinary skill in the art would have been motivated to prepare each dose to contain a concentration of 100 mg/ml, or 50-150 mg/ml, sodium gamma-hydroxybutyrate, in further view of Broughton, Lammers, Palatini, Scrima (1990), Hoes, and Scharf. A person of ordinary skill in the art would have been motivated to further dilute the formulation based on the disclosure in Broughton.

Claim Charts

'275 Patent Claim	Invalidity
1. A method of 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-	**Scrima (1987)** discloses the results of a study on the effects of GHB treatment on cataplexy and sleep attacks in narcoleptics, and the administration of 25 mg/kg GHB within the hour prior to sleep and again 3 hours later. *See*, *e.g.*, p. 134. **Scrima (1989)** discloses the efficacy of GHB in treating narcolepsy-cataplexy, with subjects provided pharmacy-prepared bottles of GHB mixed with distilled water and syrup of orange and instructed to ingest one entire bottle immediately before going to bed and the other 3 hours later. pp. 333, 334.

'275 Patent Claim	Invalidity
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; and (iv) orally administering to the patient having narcolepsy the second dose within 2.5 to 4 hours following initial sleep onset.	**Scrima (1990)** disclose that narcolepsy is a chronic disorder characterized by cataplexy and daytime sleepiness, and disclose the results of a double-blind study indicating that GHB improves sleep depth and continuity compared to placebo. It is also disclosed that sterile, distilled water and syrup of orange were used to mix the GHB administered to subjects in a narcolepsy study, and that subjects took 25 mg/kg of GHB within the hour prior to sleep and 25 mg/kg 3 hours later. Subject weights of 85.1 ± 16.4 (57-113) kg for females and 80.4 ± 11.4 (54-90) kg for males, and mean ± SD (range) body mass index values of 31.8 ± 7.8 (17.6-45.4) for females and 26.2 ± 2.8 (20.3-29.1) for males are disclosed. It is further disclosed that the therapeutic effect of reduction of cataplexy in narcolepsy patients by treatment with GHB appears to be due to the improvement of nocturnal sleep quality. Oral doses of ~25-35 mg/kg GHB have been reported to induce rapid sleep onset and normal cycling of sleep stages at bedtime, and GHB had been reported to induce anesthesia at doses of 60-70 mg/kg and sleep at doses of 40-50 mg/kg. *See*, *e.g.*, summary, pp. 479, 480, 482, 486. **Broughton** discloses the results of a study in which "sixteen patients with narcolepsy and cataplexy were treated with gamma-hydroxybutyrate (GHB)," and "the subjective quality of night sleep improved in all patients and the number of irresistable (sic) daytime attacks of sleep and cataplexy substantially diminished." It is also disclosed that the sodium salt of gamma-hydroxybutyrate was used, and that diluting the syrup in milk or juice reduced gastrointestinal upset in some patients and also retarded the rate of absorption of GHB, so that sleep induction was more gradual and normal. Oral doses of GHB are disclosed to induce sleep, and subjects were administered an initial dose of 1.5-2.25 g NaGHB in 10-15 ml within the hour prior to sleep, followed by further 1.0-1.5 g doses during the night with each major reawakening, if at least 2.5 hours had passed since the previous dose. *See*, *e.g.*, pp. 2, 3. **The '632 patent** discloses that gamma-hydroxybutyric acid derivatives, including its simple salts, have therapeutic uses "due to their narcotic, hypnotic or anticonvulsive effect," with suitable salts including the sodium salt. Also disclosed are compositions in which the GHB salt can vary from 12.5 to 50% by weight, including pharmaceutical compositions for oral administration, and a bottle containing 20 ml of solution containing 6.05 g of sodium gamma-hydroxy butyric acid. *See*, *e.g.*, Example 2, 3:29-32, 7:32-33, 7:48-50, 7:51-52.

'275 Patent Claim	Invalidity
	The '937 patent discloses that "the narcosis achieved with GHB broadly resembles physiological sleep." *See*, *e.g.*, 1:62-64. **The '331 patent** discloses that GHB has such clinical effects as reduction of narcolepsy and increased short-wave sleep. Also disclosed is the therapeutic use of sodium γ-hydroxybutyrate, with typical dosages between 2.0 and 5.0 grams, with administration of one dose within the last hour prior to retiring, or one-half hour or less prior to retiring, and that administration may be oral. It is further disclosed that it may be desirable to administer a second or third dose during the normal sleep period. *See*, *e.g.*, 6:21-40, 7:1-15, 7:48, 7:52-61, 7:61-63, 7:63-64. **Vickers** discloses that gamma-hydroxybutryate has a possible clinical use in night sedation, that GHB has been tried orally as a night sedative, and that 2 g every 2-4 hours produces sleep. It is also disclosed that an intravenous or oral dose of 40-50 mg/kg of gammahydroxybutyric acid will, within 5-15 minutes, induce a sleeping state from which the patient can be awoken, and that the use of 20-30 g per 24 hours without ill effect. *See*, *e.g.*, pp. 75-76, 78, 82-87. **Lammers** discloses that narcolepsy patients treated with GHB exhibited fewer daily cataplexy attacks. *See*, *e.g.*, Summary. **Mamelak (1977)** discloses exploring the use of sodium gamma-hydroxybutyrate to treat insomnia, and that the use of GHB in repeated doses during the night reduced the incidence of daytime attacks of cataplexy and improved daytime functioning. Also disclosed is oral dosing of 1.0-4.5g GHB, with repeat dosing two to three times during the night to maintain sleep in cases of severe insomnia. *See*, *e.g.*, pp. 273, 274, 286. **Mamelak (1989)** discloses the therapeutic use of GHB, which may be orally administered, to consolidate night sleep in narcoleptics and improve their alertness during the day. It is also disclosed that oral doses of 20 to 30 mg/kg GHB promote the normal sequence of NREM and REM sleep in normal subjects when given at bedtime, and that GHB is rapidly metabolized and the central effects of an intravenous dose of GHB last about 2 hours. *See*, *e.g.*, p. 188. **Palatini** discloses that GHB has been used in the treatment of narcolepsy. It is also disclosed that the black cherry GHB syrup was diluted to 100 ml with water and the cup rinsed with a further

'275 Patent Claim	Invalidity
	50 ml water, and that GHB was orally administered at doses of 12.5, 25, and 50 mg/kg GHB diluted in water. *See*, *e.g.*, pp. 353, 354. **Scharf** discloses that treatment of narcoleptics with GHB significantly improved the clinical symptoms of cataplexy, sleep paralysis, hypnogogic hallucinations, daily naps, and sleep attacks, with administration of GHB to narcolepsy patients at lights out and again 4 hours later. *See*, *e.g.*, Abstract. p. 222. **Laborit** discloses that the coma-inducing action of short-chain fatty acids from C_4 to C_{10} is known, and that "molecules closely related to GHB such as 1,4-butanediol… possess hypnotic properties similar to those of GHB." It is also disclosed that GHB-induced sleep has been described as being close to physiological sleep, with doses of 50 to 60 mg/kg rapidly inducing slow wave sleep followed by REM sleep, and that GHB will deepen sleep. *See*, *e.g.*, pp. 257, 258, 264, 269. **Sériès** discloses that gamma-hydroxybutyrate improved sleep abnormalities in a patient with narcolepsy and central sleep apnea. It is also discloses that 30 mg/kg gamma-hydroxybutyrate was administered as a white powder diluted in orange juice in two doses, at the beginning of the recording and at the first awakening 3 hours after the first drug administration. *See*, *e.g.*, pp. 1378, 1379. **EP '265** discloses that sodium gamma hydroxy butyrate is absorbed by the gastroenteric apparatus with a maximum peak at about 30-45 minutes after administration and has a half-life of 20-25 minutes, and that it has to be administered more than once a day, due to its rapid absorption and elimination. It is also disclosed that sodium gamma hydroxy butyrate was previously available as a syrupy solution. *See*, *e.g.*, 3:14-19, 3:9-23. **Strong** discloses the administration of gamma-hydroxybutyrate as its sodium salt. *See*, *e.g.*, p. 1304. **Hoes** discloses that "GOH was dissolved at a concentration of 10 grams per 100 milliliter [sic] of chocolate flavored [sic] water." *See*, *e.g.*, p. 94.
2. A method of treating cataplexy or daytime sleepiness in a patient who has been diagnosed with	**Scrima (1989)** discloses the efficacy of GHB in treating narcolepsy-cataplexy, with subjects provided pharmacy-prepared bottles of GHB, at a concentration of 25 mg/kg per dose, mixed

'275 Patent Claim	Invalidity
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 3 to about 9 grams of 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 3 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; and (iv) orally administering to the patient having narcolepsy the second dose within 2.5 to 4 hours following initial sleep onset.	with distilled water and syrup of orange and instructed to ingest one entire bottle immediately before going to bed and the other 3 hours later. *See*, *e.g.*, pp. 333, 334. **Scharf** discloses that treatment of narcoleptics with GHB significantly improved the clinical symptoms of cataplexy, sleep paralysis, hypnogogic hallucinations, daily naps, and sleep attacks, with administration of 2 doses of 20-25 ml of 150 mg/ml GHB to narcolepsy patients, the first at lights out and second 4 hours later. *See*, *e.g.*, Abstract. p. 222. **Palatini** discloses that GHB has been used in the treatment of narcolepsy. It is also disclosed that the black cherry GHB syrup was diluted to 100 ml with water and the cup rinsed with a further 50 ml water, and that GHB was orally administered at doses of 12.5, 25, and 50 mg/kg GHB diluted in water. *See*, *e.g.*, pp. 353, 354. **Lammers** discloses that narcolepsy patients treated with GHB exhibited fewer daily cataplexy attacks. *See*, *e.g.*, Summary. **The '937 patent** discloses that "the narcosis achieved with GHB broadly resembles physiological sleep." *See*, *e.g.*, 1:62-64. **Scrima (1987)** discloses the results of a study on the effects of GHB treatment on cataplexy and sleep attacks in narcoleptics, and the administration of 25 mg/kg GHB within the hour prior to sleep and again 3 hours later. *See*, *e.g.*, p. 134. **Scrima (1990)** disclose that narcolepsy is a chronic disorder characterized by cataplexy and daytime sleepiness, and disclose the results of a double-blind study indicating that GHB improves sleep depth and continuity compared to placebo. It is also disclosed that sterile, distilled water and syrup of orange were used to mix the GHB administered to subjects in a narcolepsy study, and that subjects took 25 mg/kg of GHB within the hour prior to sleep and 25 mg/kg 3 hours later. Subject weights of 85.1 ± 16.4 (57-113) kg for females and 80.4 ± 11.4 (54-90) kg for males, and mean ± SD (range) body mass index values of 31.8 ± 7.8 (17.6-45.4) for females and 26.2 ± 2.8 (20.3-29.1) for males are disclosed. It is further disclosed that the therapeutic effect of reduction of cataplexy in narcolepsy patients by treatment with GHB appears to be due to the improvement of nocturnal sleep quality. Oral doses of ~25-35 mg/kg GHB have been reported to induce rapid sleep onset and normal cycling of sleep stages at bedtime, and GHB had been reported to induce anesthesia at doses of 60-70 mg/kg and sleep at doses of 40-50 mg/kg. *See*,

'275 Patent Claim	Invalidity
	e.g., summary, pp. 479, 480, 482, 486. **Mamelak (1977)** discloses that the use of GHB in repeated doses during the night reduced the incidence of daytime attacks of cataplexy and improved daytime functioning, and sicloses exploring the use of sodium gamma-hydroxybutyrate to treat insomnia. Also disclosed are oral dosing of 1.0-4.5g GHB and repeat dosing of GHB two or three times during the night to maintain sleep in cases of severe insomnia. *See*, *e.g.*, pp. 273, 274, 286. **Vickers** discloses that gamma-hydroxybutryate has a possible clinical use in night sedation, that GHB has been tried orally as a night sedative, and that 2 g every 2-4 hours produces sleep. It is also disclosed that an intravenous or oral dose of 40-50 mg/kg of gammahydroxybutyric acid will, within 5-15 minutes, induce a sleeping state from which the patient can be awoken, and that the use of 20-30 g per 24 hours is without ill effect. *See*, *e.g.*, pp. 75-76, 78, 82-87. **Laborit** discloses that the coma-inducing action of short-chain fatty acids from C_4 to C_{10} is known, and that "molecules closely related to GHB such as 1,4-butanediol… possess hypnotic properties similar to those of GHB." It is also disclosed that GHB-induced sleep has been described as being close to physiological sleep, that doses of 50 to 60 mg/kg rapidly induce slow wave sleep followed by REM sleep, and that GHB will deepen sleep. *See*, *e.g.*, pp. 257, 258, 264, 269. **Sériès** discloses that gamma-hydroxybutyrate improved sleep abnormalities in a patient with narcolepsy and central sleep apnea. It is disclosed that the patients had a mean ± SEM body mass index of 35.0 ± 1.5 kg/m^2 and were administered 30 mg/kg gamma-hydroxybutyrate as a white powder diluted in orange juice at the beginning of the recording and at the first awakening 3h after the first drug administration, with each subject receiving two doses of the drug. *See*, *e.g.*, Summary, pp. 1378, 1379. **Broughton** discloses the use of the sodium salt of gamma-hydroxybutyrate, and that diluting the syrup in milk or juice reduced gastrointestinal upset in some patients and retarded the rate of absorption of GHB, so that sleep induction was more gradual and normal. It is also disclosed that administering an initial dose of 1.5-2.25 g NaGHB in 10-15 ml within the hour prior to sleep, followed by further 1.0-1.5 g doses during the night with each major reawakening, if at least 2.5 hours had

'275 Patent Claim	Invalidity
	passed since the previous dose. *See*, *e.g.*, pp. 2, 3. **EP '265** discloses that sodium gamma hydroxy butyrate is absorbed by the gastroenteric apparatus with a maximum peak at about 30-45 minutes after administration and has a half-life of 20-25 minutes, and that it has to be administered more than once a day, due to its rapid absorption and elimination. It is also disclosed that sodium gamma hydroxy butyrate was previously available as a syrupy solution. *See*, *e.g.*, 3:14-19, 3:9-23. **The '632 patent** discloses that gamma-hydroxybutyric acid derivatives, including its simple salts, have therapeutic uses "due to their narcotic, hypnotic or anticonvulsive effect," with suitable salts including the sodium salt. Also disclosed are compositions in which the GHB salt can vary from 12.5 to 50% by weight, including pharmaceutical compositions for oral administration, and a bottle containing 20 ml of solution containing 6.05 g of sodium gamma-hydroxy butyric acid. *See*, *e.g.*, Example 2, 3:29-32, 7:32-33, 7:48-50, 7:51-52. **Mamelak (1977)** discloses exploring the use of sodium gamma-hydroxybutyrate to treat insomnia, and that the use of GHB in repeated doses during the night reduced the incidence of daytime attacks of cataplexy and improved daytime functioning. Also disclosed is oral dosing of 1.0-4.5g GHB, with repeat dosing two to three times during the night to maintain sleep in cases of severe insomnia. *See*, *e.g.*, pp. 273, 274, 286. **Mamelak (1989)** discloses the therapeutic use of GHB, which may be orally administered, to consolidate night sleep in narcoleptics and improve their alertness during the day. It is also disclosed that oral doses of 20 to 30 mg/kg GHB promote the normal sequence of NREM and REM sleep in normal subjects when given at bedtime, and that GHB is rapidly metabolized and the central effects of an intravenous dose of GHB last about 2 hours. *See*, *e.g.*, p. 188. **The '331 patent** discloses that GHB has such clinical effects as reduction of narcolepsy and increased short-wave sleep. Also disclosed is the therapeutic use of sodium γ-hydroxybutyrate, with typical dosages between 2.0 and 5.0 grams, with administration of one dose within the last hour prior to retiring, or one-half hour or less prior to retiring, and that administration may be oral. It is further disclosed that it may be desirable to administer a second or third dose during the normal sleep period.

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	See, *e.g.*, 6:21-40, 7:1-15, 7:48, 7:52-61, 7:61-63, 7:63-64. **CDC** discloses that a person with body mass index of less than 18.5 is considered underweight, 18.5 to 24.9 is considered healthy, 25.0 to 29.9 is considered overweight, and 30 or higher is considered obese. *See*, *e.g.*, p. 1. **EP '804** discloses oral administration of a pharmaceutically acceptable salt of gamma-hydroxybutyric acid in the form of single or multi-dose liquid solutions, with examples of pharmaceutical formulations containing NaGHB to be used as described in the invention. *See*, *e.g.*, 6:32-34, 6:37-38.
3. The method of claim 1 or 2 wherein each dose contains about 50-150 mg/ml of sodium gamma-hydroxybutyrate.	*See supra* claims 1 and 2. **Lammers** discloses the oral administration of gamma-hydroxybutyrate as a 10% aqueous solution, with administration of one 30 mg/kg dose shortly before nocturnal sleep and a second 30 mg/kg dose 4 hours later. *See*, *e.g.*, p. 217. **Scharf** discloses the administration of 2 doses of 20-25 ml of 150 mg/ml GHB. *See*, *e.g.*, p. 222.
4. The method of claim 3 wherein each dose contains about 50-75 mg/ml of sodium gamma-hydroxybutyrate.	*See supra* claim 3.

I. The '988 Patent

1. *Anticipation*

Claims 1 and 4-8 of the '988 patent are invalid under 35 U.S.C. § 102(b) as explicitly or inherently anticipated by **the Advisory Committee Transcript**, which was publically available more than one year prior to the earliest effective filing date of the '988 patent. The Advisory Committee Transcript discloses a distribution system for prescriptions of Xyrem, *i.e.*, GHB, which is the subject of a New Drug Application submitted by Orphan Medical, Inc., to the FDA for which they seek approval for use in treating narcolepsy. The GHB is manufactured at a single

site and then sent to a single, exclusive pharmacy that is responsible for distributing the GHB to patients. All doctors that prescribe Xyrem send all prescription requests to the exclusive pharmacy. The prescription requests contain information identifying the patient and the credentials of the doctor. The doctors credentials are verified. Additionally, the Advisory Committee transcript discloses confirming with the patient that educational materials about GHB are read before dispensing the drug to the patient. Once the prescribed GHB is shipped to the patient, the exclusive pharmacy confirms receipt of the shipment by contacting the patient. The proposed distribution program is also disclosed as being beneficial because it allows for the identification of potential abuse situations, and if necessary, pharmacist intervention. Moreover, the exclusive pharmacy maintains all the controls and records for the distribution of GHB in one location.

Claims 1, 4-9, and 12-15 of the '988 patent are invalid under 35 U.S.C. § 102(b) as explicitly or inherently anticipated by **the NADDI Presentation**, which was publically available more than one year prior to the earliest effective filing date of the '988 patent. The NADDI Presentation discloses a closed loop distribution system for Xyrem, *i.e.*, GHB, which is the subject of a New Drug Application submitted by Orphan Medical, Inc., for which they seek approval for use in treating narcolepsy. The GHB is manufactured at a single site and then shipped to a single-dedicated pharmacy. Inventories of the drug exist at the pharmacy and are supplied by Orphan Medical. The single-dedicated pharmacy maintains a registry of information on both the patient and the prescribing doctor in one location. To prescribe GHB a doctor sends a unique prescription from to the pharmacy. The pharmacy checks the credentials of the prescribing doctor and then ships education materials to the identified patient. Furthermore, the pharmacy confirms that the patient has read the education materials before shipping the

prescribed GHB to the patient. Once the pharmacy makes this confirmation, it then ships the GHB to the patient and confirms its receipt. The disclosed distribution system also entails generating reports for medical authorities, as well as law enforcement authorities. These reports also allow the pharmacy to alert state medical boards of troubling physician activities, to monitor patterns of abuse or diversion, and stop prescriptions from being filled if troubling activity is found.

2. *Obviousness*

Claims 1-15 of '988 patent are invalid under 35 U.S.C. § 103(a) because they would have been obvious to a person of ordinary skill in the art prior to the filing date of the '988 patent in view of one or more of the prior art references discussed herein.

The Advisory Committee Transcript discloses a distribution system for prescriptions of Xyrem, *i.e.*, GHB, which is the subject of a New Drug Application submitted by Orphan Medical, Inc., to the FDA for which they seek approval for use in treating narcolepsy. The GHB is manufactured at a single site and then sent to a single, exclusive pharmacy that is responsible for distributing the GHB to patients. All doctors that prescribe GHB send all prescription requests to the exclusive pharmacy. The prescription requests contain information identifying the patient and the credentials of the doctor. The doctors credentials are verified. Additionally, the Advisory Committee transcript discloses confirming with the patient that educational materials about GHB are read before dispensing the drug to the patient. The proposed distribution program is also disclosed as being beneficial because it allows for the identification of potential abuse situations, and if necessary, pharmacist intervention. Moreover, the exclusive pharmacy maintains all the controls and records for the distribution of GHB in one location.

The NADDI Presentation discloses a closed loop distribution system for Xyrem, *i.e.*, GHB, which is the subject of a New Drug Application submitted by Orphan Medical, Inc., for

which they seek approval for use in treating narcolepsy. The GHB is manufactured at a single site and then shipped to a single-dedicated pharmacy. Inventories of the drug exist at the pharmacy and are supplied by Orphan Medical. The single-dedicated pharmacy maintains a registry of information on both the patient and the prescribing doctor in one location. To prescribe GHB a doctor sends a unique prescription from to the pharmacy. The pharmacy checks the credentials of the prescribing doctor and then ships education materials to the identified patient. Furthermore, the pharmacy confirms that the patient has read the education materials before shipping the prescribed GHB to the patient. Once the pharmacy makes this confirmation, it then ships the GHB to the patient and confirms its receipt. The disclosed distribution system also entails generating reports for medical authorities, as well as law enforcement authorities. These reports also allow the pharmacy to alert state medical boards of troubling physician activities, to monitor patterns of abuse or diversion, and stop prescriptions from being filled if troubling activity is found.

The Advisory Committee Slides disclose a closed loop distribution system in which a single manufacturing facility produces Xyrem to be delivered to a single specialty pharmacy. The single specialty pharmacy distributes Xyrem from a single location and maintains all the controls and records. The discloses process begins with the doctor sending a prescription to the specialty pharmacy, which then checks the doctors credentials. The pharmacy then contacts the patient to discuss the prescription with the patient. The prescription is then shipped to the patient and its receipt is confirmed. Benefits of the program includes identification of forms of abuse and appropriate pharmacist intervention. **The Advisory Committee Minutes** disclose the recommendation that the patient fill out an informed consent form before receiving a shipment of Xyrem. **The Xyrem Video Transcript** discloses the distribution of Xyrem from a single

specialty pharmacy that has the ability to generate data to provide information to detect abuse and to facilitate investigations into abuse. In the distribution system, a physician sends a prescription to the specialty pharmacy, which then checks his credentials. The pharmacy then contacts the patient to arrange for shipment of Xyrem, and its receipt is verified.

Moradi discloses a system for dispensing prescription medications. In the disclosed system a doctor sends prescription request identifying the drug to be dispensed, the patient, and credentials of the doctor. The system is designed to prevent abuse of the drug and includes a step of confirming receipt of the drug. The system includes several processing components that are located at various physical locations which may each have one or more computers or processing devices. **Califano** discloses systems and methods for obtaining and managing informed consent documentation. An authorized biomedical professional logged on to the system via a secure internet session may submit a query. It also discloses confirming with a patient that education material has been read and documenting that the patient understands the risks associated with the drug before providing the drug to the patient. **Lilly** discloses a method for controlling information related to controlled substances. The method makes use of a data storage unit to maintain information on prescription activities. The data storage unit can be accessed to determine if any abuse is taking place.

Elsayed discloses a hazardous drug distribution program. The method seeks to prevent the distribution of drugs to patients for which a condition in the patient renders treatment undesirable or improper, *e.g.*, abuse of the hazardous drug. Patients, pharmacies, and physicians register in a computer readable storage medium to become eligible to receive the hazardous drug. The same computer readable storage medium can be used to register all three classes. Multiple pharmacies can become registered to distribute the hazardous drug, and they must agree to

comply with the controls placed on the drug to become registered. The patient is required to fill out an informed consent form to initially receive the drug and upon its refill. The computer readable storage medium can also be accessed to perform analysis to detect abuse, and thus prevent dispensing of the drug to a patient.

Williams discloses a hazardous drug distribution program. The method seeks to prevent the distribution of drugs to patients for which a condition in the patient renders treatment undesirable or improper, *e.g.*, abuse of the hazardous drug. Patients, pharmacies, and physicians register in a computer readable storage medium to become eligible to receive the hazardous drug. Multiple pharmacies can become registered to distribute the hazardous drug, and they must agree to comply with the controls placed on the drug to become registered. The same computer readable storage medium can be used to register all three classes. The patient is required to fill out an informed consent form to initially receive the drug and upon its refill. The computer readable storage medium can also be accessed to perform analysis to detect abuse, and thus prevent dispensing of the drug to a patient.

Melker discloses that GHB is an illicit drug and that it is used outside the United States to treat narcolepsy. **Borsand** discloses a system of storing all pharmaceutical-related information in a central location. In addition, the system is able to detect abuse, generate reports to track abuse, and cancel prescriptions because of such abuse. The system may include an electronic formulary, or listing of pharmaceutical products, that is housed in a computer that can be a single centralized computer or server, a single network, or a series of interconnected networks. **Ukens** discloses restricting the distribution of specialty pharmaceuticals to a single pharmacy. The single pharmacies can also monitor dosage and patient compliance. Additionally, Ukens discloses that a specialty pharmacy can authorize other pharmacies to distribute specialty

prescriptions. The authorized pharmacies can provide face-to-face counseling and perform compliance monitoring and follow-ups. **Talk About Sleep** discloses the distribution of Xyrem, *i.e.*, GHB, as a treatment for the symptoms of narcolepsy, through a central pharmacy to promote the responsible distribution and use of prescribed GHB. Narcolepsy patients are also disclosed to be anxiously awaiting approval of the drug, which it is disclosed will not be available for prescription until after approval.

A person of ordinary skill in the art reading the Advisory Committee Transcript and the NADDI Presentation, each either alone or in combination, would have been motivated to design a distribution system for a company's prescription narcolepsy drug, such as GHB, in which the distribution of the drug, after approval for use, is limited to an exclusive central pharmacy, such that the exclusive central pharmacy receives all the prescription requests. Furthermore, a person of ordinary skill the art would have been motivated to check the prescribing doctors credentials, to make use of a database to analyze for potential abuse situations, to confirm with the patient that educational materials were read before dispensing him the drug, to prevent shipment of the drug if abuse is found, and to confirm receipt of the drug by the patient because the Advisory Committee Transcript and the NADDI Presentation disclose such a distribution system. Lastly, a person of ordinary skill in the art would have been motivated to have the pharmacy maintain an inventory of the drug, supplied by the manufacturer, and a person of ordinary skill in the art would have recognized that such an inventory would have inherently previously belonged to the drug company. Any alleged differences between the disclosures of these references and the claimed invention would have been merely obvious variations.

In addition, a person of ordinary skill in the art would have looked to any of the Advisory Committee Slides, the Advisory Committee Minutes, or the Xyrem Video Transcript when

designing a distribution system for a prescription drug, such as GHB, because they are all directed to methods of distributing a prescription drug. A person of ordinary skill in the art reading the Advisory Committee Presentation and the NADDI Presentation, each either alone or in combination, in view of one or more of the Advisory Committee Slides, the Advisory Committee Minutes, or the Xyrem Video Transcript would have been motivated to design a distribution system for a prescription drug, such as GHB, in which in which the distribution of the drug is limited to an exclusive central pharmacy, such that the exclusive central pharmacy receives all the prescription requests. Furthermore, a person of ordinary skill the art would have been motivated to check the prescribing doctors credentials, to make use of a database to analyze for potential abuse situations, to confirm with the patient that educational materials were read before dispensing him the drug, to prevent shipment of the drug if abuse is found, and to confirm receipt of the drug by the patient because these references either alone or in combination all disclose such a distribution system.

Furthermore, a person of ordinary skill in the art reading the Advisory Committee Presentation and the NADDI Presentation, each either alone or in combination, or in combination with any of the Advisory Committee Slides, the Advisory Committee Minutes, or the Xyrem Video Transcript, in view of one or more of Moradi, Califano, Lilly, Elsayed, Williams, Melker, Borsand, Ukens, Talk About Sleep, would have been aware that methods of distributing harmful drugs approved for their beneficial therapeutic properties, such as GHB for the treatment of narcolepsy, that involve (1) maintaining patient and doctor information in centralized databases, (2) utilizing informed consent to counsel patients on the dangers of the prescribed drug, (3) monitoring patient compliance and potential abuse through use of a database, (4) notifying the proper parties of abuse and preventing shipments were already

known. In addition, a person of ordinary skill in the art would have known that such databases could be distributed over multiple computers in a single centralized facility and could be queried by an authorized biomedical professional, such as a pharmacist, who would inherently work at a pharmacy. Based on the disclosure of Moradi, that a database may be distributed over multiple computers, a person of ordinary skill in the art would have been motivated to query all of the databases to conduct the most thorough search. In addition, a person of ordinary skill in the art reading Ukens, Elsayed, and Williams would have been aware that such methods can be restricted to a single pharmacy, or additional pharmacies could be authorized to distribute a drug under the proper controls. Additionally, a person of ordinary skill in the art reading Elsayed and Williams would have been aware that controls such as limiting a prescription supply to a limited duration were known to prevent abuse.

Moreover, during prosecution of the '730 patent, which is the ancestor of the '988 patent, the Examiner rejected the claims of the pending application over Moradi in view of Lilly, Califano, and Ukens. (*See* AMNXYR_000003496-AMNXYR_000003497). The Examiner found that:

> Moradi discloses a method of distributing a drug under exclusive control of an exclusive central pharmacy, the method comprising … receiving prescription requests from a medical doctor containing information identifying a patient, the drug, and various credentials of the doctor … checking the credentials of the doctor … checking the exclusive computer database for potential abuse of the drug and only mailing the drug to the patient if no potential abuse is found by the checking of the exclusive computer database … and confirming receipt by the patient of the drug.

(*Id.*). As for Lilly, Califano, and Ukens the Examiner stated:

> Lilly et al. disclose that the drug is a sensitive drug, entering the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, and generating periodic reports via the exclusive computer database to evaluate potential diversion patterns …

> Califano et al. disclose confirming with the patient that educational material has been read prior to shipping the drug … Ukens discloses restricting distribution of a specialty medication to only one pharmacy.
>
> 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 of Ukens within Moradi, Lilly, and Califano. The motivation for doing so would have been to limit access to dangerous drugs.

(*See* AMNXYR_000003497-AMNXYR_000003498). Additionally, the Examiner found the claims obvious over Moradi in view of Lilly and Melker, stating:

> Melker teaches that gamma hydroxy butyrate (GHB) is an illicit substance … At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify Moradi and Lilly to include gamma hydroxyl butyrate. The motivation for doing so would have been to include drugs of recent concern, such as GHB.

(*See* AMNXYR_000003503-AMNXYR_000003504).

Furthermore, the Examiner found the claims obvious over Moradi in view of Lilly, Califano, and Talk About Sleep. Finding that in addition to the above:

> Talk About Sleep discloses providing GHB through a specialty distribution system that utilizes a central pharmacy … 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 of Talk About Sleep within Moradi, Lilly, and Califano. The motivation for doing so would have been to provide this medicine to patients that need it in a responsible manner.

(*See* AMNXYR_000003506).

On appeal to the Board of Patent Appeals and Interferences ("BPAI"), the Applicants' acquiesced to all of the Examiner's findings except that Moradi and Lilly disclosed exclusive computer databases. The BPAI 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.

(*See* AMNXYR_000003541). Therefore, the Applicants of the '730 patent have admitted that Moradi, Lilly, Califano, Ukens, Melker, and Talk About Sleep disclose all the limitations of claims 1-11 of the '730 patent, except that of using an "exclusive central database."

3. *35 U.S.C. § 101*

Claims 1-15 of the '988 patent are invalid under 35 U.S.C. § 101 for not being directed to patent-eligible subject matter. When each of the '988 patent claims is viewed in its entirety, the computer database referenced in the claims is merely used as a reference tool in an otherwise abstract, manual process, checking for potential abuse of a prescription drug by a patient or the prescribing doctor and applying that concept to a specific drug, GHB. *See*, *e.g.*, *Dealertrack*, *Inc. v. Huber*, 674 F.3d 1315, 1333 (Fed. Cir. 2012) (citing *SiRF Tech.*, *Inc. v. Int'l Trade Comm'n*, 601 F.3d 1319, 1333 (Fed. Cir. 2010)); *CyberSource Corp. v. Retail Decisions*, 654 F.3d 1366 (Fed. Cir. 2011); *Bilski v. Kappos*, 130 S.Ct. 3218, 3229-30 (2010). Neither the database nor the computer itself actively performs any of the recited steps of the claims.

Moreover, the steps in most of the claims of "receiving in a computer processor" prescription requests and "generating with the computer processor periodic reports" are simply insignificant post-solution activity that do not support patent-eligibility. *See*, *e.g.*, *Bilski*, 130 S.Ct. 3218, 3230 (2010).

4. *35 U.S.C. § 112, ¶2*

Claims 1-15 of the '988 patent are invalid under 35 U.S.C. § 112, ¶2 for being indefinite. "A claim term pinned solely on the 'unrestrained, subjective opinion of a particular individual purportedly practicing the invention' will not suffice." *Source Search Techs.*, *LLC v. LendingTree*, *LLC*, 588 F.3d 1063, 1076 (Fed. Cir. 2009) (quoting *Datamize*, *LLC v. Plumtree*

Software, Inc., 417 F.3d 1342, 1350 (Fed. Cir. 2005)). The claims of the '988 patent are invalid for indefiniteness because they require making 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. Neither the claims nor the specification of the '059 patent provides 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 person performing the claims is left to exercise his own judgment to determine whether the patient is being truthful or not. Patent claims that require such human mental participation are indefinite and not proper patent-eligible subject matter.

In addition, claims 2 and 10 are also invalid for being indefinite because they each require that the exclusive central pharmacy and/or the exclusive central database is distributed over multiple computers, but the claims also require receiving prescription requests and checking prescriber credentials with "the computer processor." Therefore, it is not clear which of the multiple computers' processors is being used to receive prescription requests or check prescriber credentials.

In addition, claim 8 is also invalid for being indefinite because there is no antecedent basis for "the computerized method." Claim 9 is also invalid as indefinite because there is a lack of antecedent basis for "the prescription drug inventory."

5. *35 U.S.C. § 102(f)*

Claims 1-15 of the '988 patent are invalid under 35 U.S.C. § 102(f) for being derived from sources other than the inventors and/or for non-joinder. The distribution methods claimed in the '059 patent were developed from collaborative efforts of others than just the inventors listed on the face of the patent. For instance, the program presented before the Peripheral and Central Nervous System Drugs Advisory Committee was not fully finalized and Orphan Medical

presented it with the intent of gathering feedback from those attending. And, indeed the concept of confirming that the patient read educational materials before receiving Xyrem was suggested at this meeting. Furthermore, Orphan stated in Talk About Sleep that the Xyrem distribution program was developed with "assistance and input from State Scheduling authorities, experts in specialty distribution, drug diversion investigators, field law enforcement, narcolepsy patient groups, and pharmacists experienced in dealing with Scheduled medicines." (Talk About Sleep, pg. 1, ¶10). At the Peripheral and Central Nervous System Drugs Advisory Committee meeting, Orphan noted this, stating: "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." (176:15-21.)

Therefore, the claimed methods are invalid for not being fully conceived by the listed inventors of the '988 patent and/or for failing to list all inventors who contributed to the conception of the subject matter of the invention claimed in the '988 patent.

Therefore, the claimed methods are invalid for not being fully conceived by the listed inventors of the '059 patent and/or for failing to list all inventors who contributed to the conception of the subject matter of the invention claimed in the '059 patent.

At least the following individuals would qualify as inventors:

1. Claudia H. Kawas, M.D.
2. Sandra Titus, Ph.D.
3. Ella P. Lacey, Ph. D.
4. LaRoy P. Penix, M.D.
5. Richard D. Penn, M.D.

6. Gerald Van Belle, Ph.D.

7. Gustavo C. Roman, M.D.

8. Jerry S. Wolinsky M.D.

9. Pippa Simpson, Ph.D.

10. Carol Falkowski, Ph.D.

11. Christine A. Sannerud, Ph.D.

12. Jerry Frankenheim, Ph.D.

13. Jo-Ellen Dyer, Ph.D.

14. Ronald Chervin, M.D.

15. Christian Guilleminault, M.D.

16. Robert Temple, M.D.

17. Russell Katz, M.D.

18. Ranjit Mani, M.D.

19. John Feeney, M.D.

20. Deborah R. Leiderman, M.D.

Oral and written discovery related to these individuals as this case proceeds will confirm the extent of the proper inventors of the '059 patent.

Claim Charts

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1. A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising: receiving in a computer processor all prescription requests, for any	**Anticipation** **The Advisory Committee Transcript** discloses all the limitations of claim 1, arranged as claimed. *See* 5:23 through 6:1; 6:20; 9:12-15; 144:20 through 145:2; 145:1-2; 176:8-13; 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18;

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and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic 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, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's 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 company's prescription drug; confirming with a narcoleptic patient that educational material has been read prior to shipping	184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 369:1-3; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses all the limitations of claim 1 arranged as claimed. *See* pgs. 4-14. **Obviousness** **The Advisory Committee Transcript** discloses distributing Orphan Medical's narcolepsy drug Xyrem (gamma-hydroxybutyrate) from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. It is also disclosed that Orphan Medical seeks approval of Xyrem. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving Xyrem is confirmed, that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. It is also disclosed that patients who desperately need Xyrem can get it, while the drug will be kept out of the hands of people who might abuse it. *See*, *e.g.*, 5:23 through 6:1; 6:20; 9:12-15; 144:20 through 145:2; 145:1-2; 176:8-13; 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 369:1-3; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses distributing Orphan Medical's narcolepsy drug Xyrem (gamma-hydroxybutyrate) from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients

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the company's prescription drug; checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug; providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug; confirming receipt by the narcoleptic patient of the company's prescription drug; and generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	prescribed Xyrem are received from all doctors prescribing Xyrem. It is also disclosed that Orphan Medical seeks approval of Xyrem. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving Xyrem is confirmed, that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, that the central pharmacy maintains inventories supplied by the manufacturer, and that pharmacist intervention can occur if abuse is found. It is also disclosed that patients who desperately need Xyrem can get it, while the drug will be kept out of the hands of people who might abuse it. *See*, *e.g.*, pgs. 4-14. **The Advisory Committee Slides** disclose distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 142, 146, 147, and 151-159. **The Advisory Committee Minutes** disclose the concept of confirming with the patient that educational material has been read before shipping Xyrem. *See*, *e.g.*, Question 5. **The Xyrem Video and Transcript** discloses distributing Xyrem from

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	exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4, 6-9, and 10. **Moradi** discloses a system for dispensing prescription medications. In the disclosed system a doctor sends prescription request identifying the drug to be dispensed, the patient, and credentials of the doctor. The system is designed to prevent abuse of the drug and includes a step of confirming receipt of the drug. *See*, *e.g.*, Abstract, ¶¶[0003], [0022], [0035], [0043], [0045], [0116]-[0118], and Fig. 3. **Califano** discloses confirming with a patient that education material has been read and documenting that the patient understands the risks associated with the drug before providing the drug to the patient. *See*, *e.g.*, ¶¶[0043] and [0084]. **Lilly** discloses a method for controlling information related to controlled substances. The method makes use of a data storage unit to maintain information on prescription activities. The data storage unit can be accessed to determine if any abuse is taking place. *See*, *e.g.*, ¶¶[0012], [0033], [0043], [0044], [0054], [0057], [0058], [0062], and [0069]. **Elsayed** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling

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	of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:10-15; 4:10-16; 5:25-37; 7:13-15; 7:28-32; 7:40-45; 8:26-32; 8:45-48; 9:10-12; 9:30-50; 10:7-12; and 10:17-21. **Williams** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:21-26; 4:43-46; 5:61-67; 5:67 through 6:3; 10:3-5; 10:18-28; 10:30-32; 12:8-11; 12:35-55; 11:32-42; 11:51-54; 13:7-18; and 13:23-27. **Borsand** discloses a system of storing all pharmaceutical-related information in a central location. In addition, the system is able to detect abuse, generate reports to track abuse, and cancel prescriptions because of such abuse. *See*, *e.g.*, ¶¶[0003], [0034], [0043], [0120], and Fig. 3. **Ukens** discloses restricting the distribution of specialty pharmaceuticals to a single pharmacy. The single pharmacies can also monitor dosage and patient compliance. *See*, *e.g.*, 41:3, ¶1 and 42:2, ¶1 through 3, ¶1.
2. The method of claim 1, wherein one or more of the exclusive central pharmacy and the exclusive central database are distributed over multiple computers, and wherein a query operates over all data in all the distributed databases relating to the prescriptions, the doctors, and the narcoleptic patients.	**Obviousness** *See supra* claim 1. **Moradi** also discloses that the system includes several processing components that are located at various physical locations which may each have one or more computers or processing devices. *See*, *e.g.*, ¶[0022].

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	Califano also discloses that an authorized biomedical professional logged onto the system via a secure internet connection may submit a query. *See*, *e.g.*, ¶[0057]. **Borsand** also discloses an electronic listing that is housed in a computer that can be a single centralized computer or server, a single network, or a series of networks. *See*, *e.g.*, ¶[0031].
3. The method of claim 1, wherein the providing the company's prescription drug to the narcoleptic patient comprises the exclusive central pharmacy authorizing the company's prescription drug to be dispensed to the narcoleptic patient by another pharmacy.	**Obviousness** *See supra* claim 1. **Ukens** discloses a specialty pharmacy authorizing other pharmacies to dispense a drug. *See*, *e.g.*, 44:1, ¶3 through 3, ¶2; 44:1, ¶1 through 2, ¶3. **Elsayed** discloses registering multiple pharmacies to dispense a hazardous drug. *See*, *e.g.*, 4:50-54. **Williams** discloses registering multiple pharmacies to dispense a hazardous drug. *See*, *e.g.*, 5:24-35.
4. The method of claim 1, comprising delivering the company's prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the company's prescription drug.	**Anticipation** *See supra* claim 1. **The Advisory Committee Transcript** discloses the Rapid Trac System for tracking a shipment of a package of Xyrem to a patient. It is also disclosed that if the patient is not available, the package will be returned to the specialty pharmacy after one delivery reattempt. *See*, *e.g.*, 182:17 to 183:1. **The NADDI Presenation** discloses the Rapid Trac System, under which the Xyrem package is delivered to the patient only with an authorized signature. *See*, *e.g.*, p. 10.

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	Obviousness *See supra* claim 1.
5. The method of claim 1, wherein the exclusive central pharmacy enters data into the exclusive computer database.	**Anticipation** *See supra* claim 1. **The Advisory Committee Transcript** discloses that the single specialty pharmacy receives all prescription requests and maintains all controls and records for distribution of GHB in one location. It also states that all patient and prescriber data are in the exclusive database. *See*, *e.g.*, 178:8-11. Therefore, in receiving prescription requests, the pharmacy would necessarily have to enter data such as, *inter alia*, prescriber and patient information, into their exclusive computer database. **The NADDI Presentation** discloses that the single-site pharmacy maintains a registry of information on the patient and the prescribing doctor, and that the pharmacy checks the credentials of the prescribing doctor. *See*, *e.g.*, p. 4-14. In order to check the credentials of the prescribing doctor, the exclusive central pharmacy would necessarily have to enter data, such as the prescriber's information, into their registry. **Obviousness** *See supra* claim 1. **The Advisory Committee Transcript** discloses that the single specialty pharmacy receives all prescription requests and maintains all controls and records for distribution of GHB in one location. It also states that all patient and prescriber data are in the exclusive database. *See*,

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	e.g., 178:8-11. Therefore, in receiving prescription requests, the pharmacy would have to enter data such as, *inter alia*, prescriber and patient information, into their exclusive computer database. **The NADDI Presentation** discloses that the single-site pharmacy maintains a registry of information on the patient and the prescribing doctor, and that the pharmacy checks the credentials of the prescribing doctor. *See*, *e.g.*, p. 4-14. In order to check the credentials of the prescribing doctor, the exclusive central pharmacy would have to enter data, such as the prescriber's information, into their registry. **Califano** also discloses that an authorized biomedical professional logged onto the system via a secure internet connection may submit a query. *See*, *e.g.*, ¶[0057].
6. The method of claim 1, comprising selectively blocking shipment of the company's prescription drug to the narcoleptic patient.	**Anticipation** *See supra* claim 1. **Obviousness** *See supra* claim 1.
7. The method of claim 1, wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the company's prescription drug is blocked based upon such association.	**Anticipation** *See supra* claim 1. **Obviousness** *See supra* claim 1. **35 U.S.C. § 101** *See supra* claim 1. **35 U.S.C. § 112, ¶2**

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	See supra claim 1. **35 U.S.C. § 102(f)** *See supra* claim 1.
8. The computerized method of claim 1, wherein the company's prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.	**Anticipation** *See supra* claim 1. **Obviousness** *See supra* claim 1. **Talk About Sleep** discloses GHB and that it is a treatment for the symptoms of narcolepsy. It is also disclosed that people are anxiously awaiting approval of the drug, and that the drug will not be available for prescription until after it is approved. *See*, *e.g.*, pg. 1, ¶¶1,4,5, and 11. **Melker** discloses that GHB is an illicit drug, and that it is used outside of the United States to treat narcolepsy. *See*, *e.g.*, ¶[0003].
9. A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising: receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug inventory is owned by a company, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic patients,	**Anticipation** **The NADDI Presentation** discloses all the limitations of claim 9 arranged as claimed. *See* pgs. 4-14. **Obviousness** **The Advisory Committee Transcript** discloses distributing Orphan Medical's narcolepsy drug Xyrem (gamma-hydroxybutyrate) from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving Xyrem is confirmed, that receipt

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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, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's 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 company's prescription drug; confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug; checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug; providing the company's	of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. It is also disclosed that patients who desperately need Xyrem can get it, while the drug will be kept out of the hands of people who might abuse it. *See*, *e.g.*, 5:23 through 6:1; 6:20; 9:12-15; 145:1-2; 176:8-13; 177:24 through 178:11; 180:14-16; 181:1-22; 182:5-8 and 17-18; 184:10-15; 184:23 through 185:7; 259:4-13; 357:9-13; 371:10-13; and 374:14-20. **The NADDI Presentation** discloses distributing Orphan Medical's narcolepsy drug Xyrem (gamma-hydroxybutyrate) from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. It is also disclosed that Orphan Medical seeks approval of Xyrem. The doctors credentials are checked. It is also disclosed that the patient has read educational materials before receiving Xyrem is confirmed, that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, that there are inventories of Xyrem, and that pharmacist intervention can occur if abuse is found. It is also disclosed that patients who desperately need Xyrem can get it, while the drug will be kept out of the hands of people who might abuse it. *See*, *e.g.*, pgs. 4-14. **The Advisory Committee Slides** disclose distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing

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prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug; confirming receipt by the narcoleptic patient of the company's prescription drug; and generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.	Xyrem. The doctors credentials are checked. It is also disclosed that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that all the controls and records are maintained by the exclusive central pharmacy, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 142, 146, 147, and 151-159. **The Advisory Committee Minutes** disclose the concept of confirming with the patient that educational material has been read before shipping Xyrem. *See*, *e.g.*, Question 5. **The Xyrem Video and Transcript** disclose distributing Xyrem from exclusive central pharmacy, wherein all prescriptions for Xyrem for all patients prescribed Xyrem are received from all doctors prescribing Xyrem. The doctors credentials are checked. It is also disclosed that receipt of the Xyrem by the patient is confirmed, that potential abuse is monitored, that the pharmacy maintains an inventory, and that pharmacist intervention can occur if abuse is found. *See*, *e.g.*, pgs. 4, 6-9, and 10. **Moradi** discloses a system for dispensing prescription medications. In the disclosed system a doctor sends prescription request identifying the drug to be dispensed, the patient, and credentials of the doctor. The system is designed to prevent abuse of the drug and includes a step of confirming receipt of the drug. *See*, *e.g.*, Abstract, ¶¶[0003], [0022], [0035], [0043], [0045], [0116]-[0118], and Fig. 3. **Califano** discloses confirming with a patient that education material has been read and documenting that the patient understands the risks associated with the

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	drug before providing the drug to the patient. *See*, *e.g.*, ¶¶[0043] and [0084]. **Lilly** discloses a method for controlling information related to controlled substances. The method makes use of a data storage unit to maintain information on prescription activities. The data storage unit can be accessed to determine if any abuse is taking place. *See*, *e.g.*, ¶¶[0012], [0033], [0043], [0044], [0054], [0057], [0058], [0062], and [0069]. **Elsayed** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:10-15; 4:10-16; 5:25-37; 7:13-15; 7:28-32; 7:40-45; 8:26-32; 8:45-48; 9:10-12; 9:30-50; 10:7-12; and 10:17-21. **Williams** discloses a method of distributing hazardous drugs by registering patients and doctors in a computer readable storage medium. The patient must provide an informed consent form before every filling of the prescription. The computer readable storage medium can be used to detect abuse and prevent dispensing the drug to the patient if abuse is found. *See*, *e.g.*, 3:21-26; 4:43-46; 5:61-67; 5:67 through 6:3; 10:3-5; 10:18-28; 10:30-32; 12:8-11; 12:35-55; 11:32-42; 11:51-54; 13:7-18; and 13:23-27. **Borsand** discloses a system of storing all pharmaceutical-related information in a central location. In addition, the system is able to detect abuse, generate reports to

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	track abuse, and cancel prescriptions because of such abuse. *See*, *e.g.*, ¶¶[0003], [0034], [0043], [0120], and Fig. 3. **Ukens** discloses restricting the distribution of specialty pharmaceuticals to a single pharmacy. The single pharmacies can also monitor dosage and patient compliance. *See*, *e.g.*, 41:3, ¶1 and 42:2, ¶1 through 3, ¶1.
10. The method of claim 9, wherein one or more of the exclusive central pharmacy and the exclusive central database are distributed over multiple computers, and wherein a query operates over all data in all the distributed databases relating to the prescriptions, the doctors, and the narcoleptic patients.	**Obviousness** See *supra* claim 9. **Moradi** also discloses that the system includes several processing components that are located at various physical locations which may each have one or more computers or processing devices. *See*, *e.g.*, ¶[0022]. **Califano** also discloses that an authorized biomedical professional logged onto the system via a secure internet connection may submit a query. *See*, *e.g.*, ¶[0057]. **Borsand** also discloses an electronic listing that is housed in a computer that can be a single centralized computer or server, a single network, or a series of networks. *See*, *e.g.*, ¶[0031].
11. The method of claim 9, wherein the providing the company's prescription drug to the narcoleptic patient comprises the exclusive central pharmacy authorizing the company's prescription drug to be dispensed to the narcoleptic patient by another pharmacy.	**Obviousness** *See supra* claim 9. **Ukens** discloses a specialty pharmacy authorizing other pharmacies to dispense a drug. *See*, *e.g.*, 44:1, ¶3 through 3, ¶2; 44:1, ¶1 through 2, ¶3. **Elsayed** discloses registering multiple pharmacies to dispense a hazardous drug. *See*, *e.g.*, 4:50-54. **Williams** discloses registering multiple pharmacies to dispense a hazardous drug.

'988 Patent Claim	Invalidity
	See, *e.g.*, 5:24-35.
12. The method of claim 9, comprising delivering the company's prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the company's prescription drug.	**Anticipation** *See supra* claim 9. **The NADDI Presenation** discloses the Rapid Trac System, under which the Xyrem package is delivered to the patient only with an authorized signature. *See*, *e.g.*, p. 10. **Obviousness** *See supra* claim 9. **The Advisory Committee Transcript** discloses the Rapid Trac System for tracking a shipment of a package of Xyrem to a patient. It is also disclosed that if the patient is not available, the package will be returned to the specialty pharmacy after one delivery reattempt. *See*, *e.g.*, 182:17 to 183:1. **The NADDI Presenation** discloses the Rapid Trac System, under which the Xyrem package is delivered to the patient only with an authorized signature. *See*, *e.g.*, p. 10.
13. The method of claim 9, wherein the exclusive central pharmacy enters data into the exclusive computer database.	**Anticipation** *See supra* claim 9. **The NADDI Presentation** discloses that the single-site pharmacy maintains a registry of information on the patient and the prescribing doctor, and that the pharmacy checks the credentials of the prescribing doctor. *See*, *e.g.*, p. 4-14. In order to check the credentials of the prescribing doctor, the exclusive central pharmacy would necessarily have to enter data, such as the prescriber's information, into their registry.

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	Obviousness *See supra* claim 9. **The Advisory Committee Transcript** discloses that the single specialty pharmacy receives all prescription requests and maintains all controls and records for distribution of GHB in one location. It is also disclosed that all patient and prescriber data are in the exclusive database. *See*, *e.g.*, 178:8-11. Therefore, in receiving prescription requests, the pharmacy would have to enter data such as, *inter alia*, prescriber and patient information, into their exclusive computer database. **The NADDI Presentation** discloses that the single-site pharmacy maintains a registry of information on the patient and the prescribing doctor, and that the pharmacy checks the credentials of the prescribing doctor. *See*, *e.g.*, p. 4-14. In order to check the credentials of the prescribing doctor, the exclusive central pharmacy would have to enter data, such as the prescriber's information, into their registry. **Califano** also discloses that an authorized biomedical professional logged onto the system via a secure internet connection may submit a query. *See*, *e.g.*, ¶[0057].
14. The method of claim 9, wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the company's prescription drug is blocked based upon such association.	**Anticipation** *See supra* claim 9. **Obviousness** *See supra* claim 9.
15. The method of claim 9, wherein the	**Anticipation**

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company's prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.	*See supra* claim 9. **Obviousness** *See supra* claim 9. **Talk About Sleep** discloses GHB and that it is a treatment for the symptoms of narcolepsy. It is also disclosed that people are anxiously awaiting approval of the drug, and that the drug will not be available for prescription until after it is approved. *See*, *e.g.*, pg. 1, ¶¶1,4,5, and 11. **Melker** discloses that GHB is an illicit drug, and that it is used outside of the United States to treat narcolepsy. *See*, *e.g.*, ¶[0003].

J. The '203 Patent

1. *Obviousness*

Claims 1-18 of the '203 patent are invalid under 35 U.S.C. § 103(a) because they would have been obvious to a person of ordinary skill in the art prior to the filing date of the '203 patent in view of one or more of the prior art references discussed herein.

Aqueous solutions of GHB salts are disclosed by **Vickers**, **CA 338**, **the '632 patent**, **the '619 patent**, **Mamelak (1977)**, **the '236 patent**, and **EP '804**. **The '937 patent** states that GHB is available as a pharmaceutical exclusively as the sodium salt, and it asserts that all experimental and clinical investigations have without exception been performed with the sodium salt, the acid itself, or the corresponding lactone. **Vickers** notes that gamma-hydroxybutyric acid is marketed for intravenous injection as a solution containing 2.42 g sodium 4-hydroxybutyrate in 10 ml water, with a pH between 8.2 and 8.9. **Vickers** also reports that gamma-hydroxybutyric acid

has been tried as a night sedative. **Vickers** further teaches that gamma-hydroxybutyric acid is water soluble in all dilutions, and the pH of the solution is not far from physiological. **The '619 patent** states that sodium 4-hydroxybutyrate is highly soluble in water. **The '632 patent** provides pharmaceutical compositions of GHB salts in solution form and containing 12.5 to 50% GHB salt content by weight. **The '619 patent** notes that solutions of GHB salts have pH values slightly in excess of 7. **CA 338** discusses solutions of alkali metal salts of GHB with pH values ranging from 7.2 to 7.7 and preparation of aqueous sodium 4-hydroxybutyrate by sequential addition of γ-butyrolactone, water, and sodium hydroxide. **EP '027** describes a fluid dispensing system which can add multiple additive liquids to a carrier liquid, using multiple measuring cylinders, each containing a different additive that can be added sequentially or simultaneously to the carrier liquid.

Nema discloses that, depending on the route of administration, preservatives may not be allowed in injectable formulations. **Nema** further teaches that injectable products are required to withstand sterilization processes. **Wickliffe** discloses that bacterial growth has been shown to be inhibited at pH 2 without the use of additional preservative material, and that asepsis has also been reported above pH 9. **CA 338**, **the '632 patent**, **the '619 patent**, and **EP '804** provide preservative-free pharmaceutical compositions designed for administration to patients, including some which were.

The 1990 CRC Handbook states that gamma-hydroxybutyric acid has a dissociation constant in aqueous solution with a pK value of 4.72. **Remington's** lists hydrochloric acid as a pharmaceutic aid used to acidify a solution. The **1995 USP** discloses a list of 13 acidifying agents used as pharmaceutic ingredients, and that list includes acetic acid, citric acid, hydrochloric acid, lactic acid, malic acid, nitric acid, phosphoric acid, and sulfuric acid. **Nema**

also lists acetic acid, citric acid, hydrochloric acid, phosphoric acid, and sulfuric acid as pH adjusting agents used in injectable formulations.

A person of ordinary skill in the art reading Vickers would have been motivated to prepare an aqueous solution of a gamma-hydroxybutyrate salt. A person of ordinary skill in the art reading Vickers in view of the '937 patent, alone or in combination with any of the '632 patent, the '619 patent, Mamelak (1977), the '236 patent, or EP '804, would have been specifically motivated to select the sodium salt; alternatively, in view of the '236 patent, a person of ordinary skill in the art would have been motivated to select calcium or magnesium. A person of ordinary skill in the art reading Vickers in view of the '619 patent and the '632 patent would have been motivated to prepare a solution containing 500 mg/ml, or 310-750 mg/ml, sodium gamma-hydroxybutyrate, with a reasonable expectation of success. A person of ordinary skill in the art reading Vickers in view of CA 338 and the '619 patent would have reasonably expected such a solution to have a pH between 6 and 9. In further view of EP '027, a person of ordinary skill in the art would have recognized that the components of such a solution could be admixed sequentially or simultaneously.

Furthermore, a person of ordinary skill in the art reading Vickers in view of the 1990 CRC Handbook would have recognized that the aqueous solution containing 242 mg/ml sodium 4-hydroxybutyrate disclosed in Vickers would inherently have a pH of about 9.5. Accordingly, a person of ordinary skill in the art would have recognized that, in order to attain the reported pH of 8.2 to 8.9, it would be necessary to use a pH-adjusting agent, specifically, an acidifying agent. In further view of any of Remington's, the 1995 USP, or Nema, a person of ordinary skill in the art would have routinely used any of malic acid, citric acid, acetic acid, lactic acid, hydrochloric acid, phosphoric acid, or sulfuric acid to adjust the pH of the Vickers formulation from 9.5 to the

reported 8.2-8.9 range. Furthermore, a person of ordinary skill in the art would have known that malic acid, citric acid, acetic acid, and lactic acid are organic acids.

Lastly, a person of ordinary skill in the art reading Vickers in view of CA 338, the '632 patent, the '619 patent, Remington's, or EP '804 would have recognized that, in order for the preservative-free pharmaceutical compositions disclosed therein to be administered to patients, they would have had to be inherently chemically stable and resistant to microbial growth. In further view of Nema or Wickliffe, a person of ordinary skill in the art would have been motivated to exclude preservatives from the aqueous formulation.

2. *35 U.S.C. 112, ¶1*

Claims 1-18 are invalid under 35 U.S.C. § 112, ¶1 for lacking written description support and enablement. Specifically, in view of statements made by the applicant during prosecution, each of these claims require the exclusion of a preservative. But in view of the Court's construction in the corresponding *Roxane* case, these claims, as drafted, do in fact include a preservative. Thus, the specification neither enables nor provides written description support for claims that require the exclusion of a preservative, as argued in the prosecution history.

Claims 3 and 12 explicitly require a pH-adjusting agent. Claims 4 and 13 depend from claims 3 and 12, respectively, and therefore also require the same pH-adjusting agent. And claims 1, 9, and 10 (and all claims dependent therefrom) require the step of adjusting the pH, thereby also requiring the addition of a pH-adjusting agent.

Under the Court's construction in Jazz's case against Roxane, the pH-adjusting agent required by claims 1-18 must be construed as a "preservative." The Court construed "preservative" to mean "a substance or substances added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action." (*See Roxane Markman*

Order at p. 16). The '203 patent asserts that adjusting the pH is a means to inhibit chemical change or microbial action. So, under the Court's construction, a pH-adjusting required in the claims is properly construed as a "preservative."

But, during prosecution of the '431 patent, which is the ancestor of the '203 patent, to overcome the Examiner's prior art rejections, Applicants argued that the cited prior art references do not teach any way to make aqueous GHB solutions resistant to microbial degradation other than by the addition of a preservative. Specifically, the Applicants argued that:

> Gessa does not disclose any way to make GHB aqueous solutions stable to microbial degradation ***other than by using conventional preservatives*** in Examples 1 and 2. … 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***…. [N]one of the references teach or suggest solutions of GHB salt that are resistant to microbial growth ***without an added preservative***.

(Prosecution History of the '431 patent, Amendment and Reply submitted on August 10, 2001 (emphasis added).) (*See, e.g.,* AMNXYR_000002621-AMNXYR_000002625.). In so arguing, Applicants clearly and unmistakably surrendered a method of making gamma-hydroxybutyrate formulations using preservatives. Yet, claims 1, 9, and 10 of the '203 patent (and all claims dependent therefrom) must be held to require such a method comprising a preservative.

Claims 1-18 explicitly require adjusting the pH, and, in view of the prosecution history, also require the exclusion of preservatives. But, under the Court's definition of "preservative" in the Roxane case, the required pH-adjusting agent necessarily acts as a preservative. As a result, claims 1-18 lack enablement and written description support, since the specification does not teach any way to exclude preservatives while also using a preservative, as required by the claims.

3. *35 U.S.C. § 112, ¶2*

Claims 1-18 are invalid under 35 U.S.C. § 112, ¶2 for being indefinite on multiple grounds.

First, claims 3, 4, 12, and 13 are invalid as indefinite for lacking a proper antecedent basis. For example, claims 3 and 12 of the '203 patent recite, "… said pH-adjusting agent." However, there is no antecedent basis for "said pH-adjusting agent" recited in these claims. And since claims 4 and 13 depend from claims 3 and 12, respectively, they too are invalid as indefinite for the same reasons.

Next, claims 1-18 are also invalid as indefinite because their terms are hopelessly vague and insolubly ambiguous, thus rendering their scope unascertainable. Claims 3 and 12 explicitly require a pH-adjusting agent. Claims 4 and 13 depend from claims 3 and 12, respectively, and therefore also require the same pH-adjusting agent. And claims 1, 9, and 10 (and all claims dependent therefrom) require the step of adjusting the pH, thereby also requiring the addition of a pH-adjusting agent.

Under the Court's construction in Jazz's case against Roxane, the pH-adjusting agent required by claims 1-18 must be construed as a "preservative." In the *Markman* order in *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, the Court construed "preservative" to mean "a substance or substances added in addition to the gamma-hydroxybutyrate salt to inhibit chemical change or microbial action." (*See Roxane Markman* Order at p. 16). The '203 patent asserts that adjusting the pH is a means to inhibit chemical change or microbial action. So, under the Court's construction, a pH-adjusting agent required in the claims is properly construed as a "preservative."

But, during prosecution of the '431 patent, which is the ancestor of the '203 patent, to overcome the Examiner's prior art rejections, Applicants argued that the cited prior art references

do not teach any way to make aqueous GHB solutions resistant to microbial degradation other than by the addition of a preservative. Specifically, the Applicants argued that:

> Gessa does not disclose any way to make GHB aqueous solutions stable to microbial degradation ***other than by using conventional preservatives*** in Examples 1 and 2. … 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***…. [N]one of the references teach or suggest solutions of GHB salt that are resistant to microbial growth ***without an added preservative***.

(Prosecution History of the '431 patent, Amendment and Reply submitted on August 10, 2001 (emphasis added).) (*See, e.g.,* AMNXYR_000002621-AMNXYR_000002625.). In so arguing, Applicants clearly and unmistakably surrendered a method of making gamma-hydroxybutyrate formulations using preservatives. Yet, claims 1, 9, and 10 of the '203 patent (and all claims dependent therefrom) must be held to require such a method comprising a preservative. As a result, the requirement of a pH-adjusting agent in claims 1-18, which acts as a preservative under the Court's construction, contradicts the express requirement from the prosecution history that these claims do not utilize preservatives in the aqueous medium. That is, even though the claims purport to require the exclusion of a preservative, they do in fact require a preservative, as written, under the Court's construction of "preservative." As a consequence, claims 1-18 are hopelessly vague and insolubly ambiguous, leading to a finding that they are indefinite.

Next, claim 18 is invalid as indefinite because it requires the selection of a salt from a list that does not include any salts. Claim 18 requires that the aqueous medium "contains one or more of salts selected from the group consisting of lithium, potassium, sodium, calcium, ammonium, and magnesium." Lithium, potassium, sodium, calcium, ammonium, and magnesium are not salts; instead, as written, a person of ordinary skill in the art would understand these to be either elemental (neutral) or cationic (positively charged) species. *See*

Oxtoby, pp. 53-55. In contrast, a salt or ionic compound is formed by the combination of cations with anions (negatively charged species), and salts are accordingly named by the name of the cation followed by that of the anion. *See Oxtoby*, p. 54. Therefore, claim 18 requires the selection of a salt from a list that does not include any salts, rendering it indefinite.

Lastly, claim 18 is also invalid as indefinite because it is not clear whether the medium described is that before or after the addition of the gamma-hydroxybutyrate salt. Claim 18 requires that the aqueous medium contains one or more salts. Claim 1, from which claim 18 depends, recites a method comprising admixing a salt of gamma-hydroxybutyrate with the aqueous medium. Because claim 1 uses the transitional phrase "comprising," claim 1 also permits additional elements not explicitly recited in the claim, in view of the prosecution history. Therefore, the limitations recited in claim 18 may refer to a salt other than the gamma-hydroxybutyrate salt explicitly recited in base claim 1.

4. *35 U.S.C. § 112, ¶¶ 2 and 4*

Claims 4 and 13 are invalid under 35 U.S.C. § 112, ¶¶ 2 and 4 for being indefinite and improper dependent claims. Claims 3 and 12, from which claims 4 and 13 depend, respectively, require that the pH-adjusting agent is an organic acid. However claims 4 and 13 each list five inorganic acids, *i.e.,* boric acid, hydrochloric acid, phosphoric acid, sulfuric acid, and nitric acid. Therefore, claims 4 and 13 require the selection of an organic acid from a list that also includes inorganic acids, rendering the claims indefinite. Claims 4 and 13 are also improper dependent claims, because they are not narrower than the claims from which they depend, respectively.

'203 Patent Claim	Invalidity
1. A method of rendering an aqueous medium resistant to microbial growth, said method comprising admixing a salt of gamma hydroxybutyrate with the aqueous medium, adjusting the concentration of the gamma-hydroxybutyrate salt in the aqueous medium to a final concentration of from about 310 to about 750 mg/ ml, and adjusting the pH of the medium to a final pH of about 6 to about 9, so that the medium is chemically stable and resistant to microbial growth, wherein the medium would not need to contain a preservative.	**The '937 patent** discloses that GHB is available as a pharmaceutical exclusively as the sodium salt, and that all experimental and clinical investigations have without exception been performed with the sodium salt, the acid itself, or the corresponding lactone. *See*, *e.g.*, 1:7-15. **Nema** discloses that injectable products are required to withstand sterilization processes such as autoclaving and that preservatives may not be allowed in some injectable products, depending on the route of administration, and that chelating agents are used in parenteral products to complex heavy metals, thereby improving the efficacy of antioxidants or preservatives. Also disclosed are buffers and chemicals used to adjust the pH of formulations, including a table of 32 buffers and pH-adjusting agents, including organic and inorganic acids. *See*, *e.g.*, pp. 166, 167, 168, 169. **The '632 patent** discloses the use of gamma-hydroxybutyric acid salts for preparing pharmaceutical compositions, which may vary in GHB salt content from 12.5% to 50% by weight and for which suitable salts include the sodium salt. Also disclosed is an injectable aqueous formulation of sodium gamma-hydroxybutyrate free of preservatives. *See*, *e.g.*, Abstract, 7:32-33, 7:47-49, 8:57-59. **The '236 patent** discloses that the calcium and magnesium salts of 4-hydroxybutyric acid can be dispensed as aqueous solutions and that the sodium salt of 4-hydroxybutyric acid induces sleep. *See*, *e.g.*, 1:38-43, 4:39-47. **CA 338** discloses the preparation of 4-hydroxybutyric acid salt solutions of pH 7.2-7.7 for injection. Also disclosed is the preparation of sodium 4-hydroxybutyric acid solutions of pH 7.2-7.7 for injection, by sequential addition of γ-

'203 Patent Claim	Invalidity
	butyrolactone, water, and sodium hydroxide. *See*, *e.g.*, Abstract. **EP '804** discloses the administration of salts of gamma-hydroxybutyric acid, of which the sodium salt is particularly preferred, in the form of single or multi-dose liquid solutions. Also disclosed is a formulation for intravenous injection that is free of preservatives. *See*, *e.g.*, 2:38-39, 6:32-34, Formulation 3. **The '619 patent** discloses that sodium 4-hydroxybutyrate is highly soluble in water and, in aqueous solution, has a pH slightly in excess of 7. Also disclosed are formulations that are free of preservatives, including one that was administered to a patient just prior to undergoing surgery. *See*, *e.g.*, 1:61-66, examples 1-3. **Mamelak (1977)** discloses that γ-hydroxybutyrate is marketed by Laboratoire Egic of Paris, France, as a banana-flavored syrup. Also disclosed is the use of GHB, obtained as a banana-flavored syrup, in a dose of 1.0-4.5 g and placebo in a dose of 5 cc banana flavoring in water, giving a 3-g dose on most nights. Also disclosed is exploring the use of sodium gamma-hydroxybutyrate to treat insomnia. *See*, *e.g.*, pp. 273, 274, 275. **Vickers** discloses that gamma-hydroxybutyrate is water soluble in all dilutions, and that the pH of the solution is not far from physiological. It is also disclosed that gamma-hydroxybutyric acid is marketed for intravenous injection as a solution containing 2.42 g sodium 4-hydroxybutyrate in 10 ml water, with a pH between 8.2 and 8.9. *See*, *e.g.*, pp. 75, 82-87. **The 1990 CRC Handbook** discloses that γ-Hydroxybutyric acid has a pK_a of 4.72 in aqueous solution. *See*, *e.g.*, p. 8-36. **The 1995 USP** discloses a list of 13 acidifying agents among USP and NF Pharmaceutic Ingredients, including organic and inorganic acids.

'203 Patent Claim	Invalidity
	See, *e.g.*, P. 2205. **Remington's** discloses requirements for pharmaceutical stability and some approaches to achieving stability, including stabilization from photolytic, oxidative, and solvolytic decomposition reactions. It is also disclosed that hydrochloric acid is a pharmaceutic aid that is used as an acidifying agent. *See*, *e.g.*, pp. 239, 639-640, 1410. **Wickliffe** discloses that bacterial growth has been shown to be inhibited at pH 2 without the use of additional preservative material, and that asepsis also occurs above pH 9. *See*, *e.g.*, p. 770.
2. The method of claim 1, wherein said salt is sodium gamma-hydroxybutyrate.	See *supra* claim 1. **CA 338** discloses the preparation of 4-hydroxybutyric acid salt solutions of pH 7.2-7.7 for injection, by hydrolysis of GBL with slightly less than the theoretical amount of sodium hydroxide. *See*, *e.g.*, Abstract.
3. The method of claim 1, wherein said pH-adjusting agent is an organic acid.	*See supra* claim 1. **The 1995 USP** discloses a list of 13 acidifying agents among USP and NF Pharmaceutic Ingredients, including malic acid, citric acid, acetic acid, lactic acid, propionic acid, and tartaric acid. *See*, *e.g.*, p. 2205. *See also*, 21 C.F.R. §§ 184.1069, 184.1033, 184.1005, 184.1061, 184.1081, 184.1099. **Nema** discloses a table of 32 buffers and pH-adjusting agents, including acetic acid and citric acid. *See*, *e.g.*, p. 169. **EP '804** also discloses that pharmaceutical compositions of sodium 4-hydroxybutyrate may be buffered. *See*, *e.g.*, 6:34.
4. The method of claim 3, wherein said acid is selected from the group consisting of malic acid, citric acid, acetic acid, boric acid, lactic acid, hydrochloric acid, phosphoric acid,	*See supra* claim 3. **Remington's** also discloses that hydrochloric acid is a pharmaceutic aid that is used as an acidifying agent. *See*, *e.g.*, p. 1410.

'203 Patent Claim	Invalidity
sulfuric acid, and nitric acid.	**The 1995 USP** discloses a list of 13 acidifying agents among USP and NF Pharmaceutic Ingredients, including hydrochloric acid, phosphoric acid, sulfuric acid, and nitric acid. *See*, *e.g.*, p. 2205. *See also*, 21 C.F.R. § 184.1095.
5. The method of claim 1, wherein the concentration is from about 450 to about 600 mg/ml.	*See supra* claim 1.
6. The method of claim 1, wherein the concentration is about 500 mg/ml.	*See supra* claim 1.
7. The method of claim 1, wherein the components are admixed sequentially.	*See supra* claim 1. **CA 338** discloses the preparation of sodium 4-hydroxybutyric acid solutions of pH 7.2-7.7 for injection, by sequential addition of γ-butyrolactone, water, and sodium hydroxide. *See*, *e.g.*, Abstract. **EP '027** discloses a fluid dispensing system in which different additive liquids can be added to a carrier liquid sequentially. *See*, *e.g.*, 2:45-50.
8. The method of claim 1, wherein the components are admixed simultaneously.	*See supra* claim 1. **EP '027** discloses a fluid dispensing system in which different additive liquids can be added to a carrier liquid simultaneously. *See*, *e.g.*, 2:45-50.
9. A method of rendering an aqueous medium comprising a salt of gamma-hydroxybutyrate resistant to microbial growth, said method comprising adjusting the concentration of the gamma-hydroxybutyrate salt in the aqueous medium to a final concentration of from about 310 to about 750 mg/ml, and adjusting the pH of the medium to a final pH of about 6 to about 9, so that the medium is chemically stable	**The '937 patent** discloses that GHB is available as a pharmaceutical exclusively as the sodium salt, and that all experimental and clinical investigations have without exception been performed with the sodium salt, the acid itself, or the corresponding lactone. *See*, *e.g.*, 1:7-15. **Nema** discloses that injectable products are required to withstand sterilization processes such as autoclaving and that preservatives may not be allowed in some injectable products, depending on the route of administration, and that chelating agents are used in parenteral products to complex heavy

'203 Patent Claim	Invalidity
and resistant to microbial growth, wherein the medium does not contain a preservative.	metals, thereby improving the efficacy of antioxidants or preservatives. Also disclosed are buffers and chemicals used to adjust the pH of formulations, including a table of 32 buffers and pH-adjusting agents, including organic and inorganic acids. *See*, *e.g.*, pp. 166, 167, 168, 169. **The '632 patent** discloses the use of gamma-hydroxybutyric acid salts for preparing pharmaceutical compositions, which may vary in GHB salt content from 12.5% to 50% by weight and for which suitable salts include the sodium salt. Also disclosed is an injectable aqueous formulation of sodium gamma-hydroxybutyrate free of preservatives. *See*, *e.g.*, Abstract, 7:32-33, 7:47-49, 8:57-59. **Mamelak (1977)** discloses that γ-hydroxybutyrate is marketed by Laboratoire Egic of Paris, France, as a banana-flavored syrup. Also disclosed is the use of GHB, obtained as a banana-flavored syrup, in a dose of 1.0-4.5 g and placebo in a dose of 5 cc banana flavoring in water, giving a 3-5 dose on most nights. Also disclosed is exploring the use of sodium gamma-hydroxybutyrate to treat insomnia. *See*, *e.g.*, pp. 273, 274, 275. **The '236 patent** discloses that the calcium and magnesium salts of 4-hydroxybutyric acid can be dispensed as aqueous solutions and that the sodium salt of 4-hydroxybutyric acid induces sleep. *See*, *e.g.*, 1:38-43, 4:39-47. **Vickers** discloses that gamma-hydroxybutyrate is water soluble in all dilutions, and that the pH of the solution is not far from physiological. It is also disclosed that gamma-hydroxybutyric acid is marketed for intravenous injection as a solution containing 2.42 g sodium 4-hydroxybutyrate in 10 ml water, with a pH between 8.2 and 8.9. *See*, *e.g.*, pp. 75, 82-87. **The 1990 CRC Handbook** discloses that γ-Hydroxybutyric acid has a pK_a of 4.72 in aqueous solution. *See*, *e.g.*, p. 8-36.

'203 Patent Claim	Invalidity
	The 1995 USP discloses a list of 13 acidifying agents among USP and NF Pharmaceutic Ingredients, including organic and inorganic acids. *See*, *e.g.*, p. 2205. **CA 338** discloses the preparation of 4-hydroxybutyric acid salt solutions of pH 7.2-7.7 for injection. Also disclosed is the preparation of sodium 4-hydroxybutyric acid solutions of pH 7.2-7.7 for injection, by sequential addition of γ-butyrolactone, water, and sodium hydroxide. *See*, *e.g.*, Abstract. **The '619 patent** discloses that sodium 4-hydroxybutyrate is highly soluble in water and, in aqueous solution, has a pH slightly in excess of 7. Also disclosed are formulations that are free of preservatives, including one that was administered to a patient just prior to undergoing surgery. *See*, *e.g.*, 1:61-66, examples 1-3. **Wickliffe** discloses that bacterial growth has been shown to be inhibited at pH 2 without the use of additional preservative material, and that asepsis also occurs above pH 9. *See*, *e.g.*, p. 770. **EP '804** discloses the administration of salts of gamma-hydroxybutyric acid, of which the sodium salt is particularly preferred, in the form of single or multi-dose liquid solutions. Also disclosed is a formulation for intravenous injection that is free of preservatives. *See*, *e.g.*, 2:38-39, 6:32-34, Formulation 3. **Remington's** discloses requirements for pharmaceutical stability and some approaches to achieving stability, including stabilization from photolytic, oxidative, and solvolytic decomposition reactions. It is also disclosed that hydrochloric acid is a pharmaceutic aid that is used as an acidifying agent. *See*, *e.g.*, pp. 239, 639-640, 1410.
10. A method of rendering an aqueous medium comprising a salt of gamma-hydroxybutyrate resistant to microbial growth, said method comprising	**The '937 patent** discloses that GHB is available as a pharmaceutical exclusively as the sodium salt, and that all experimental and clinical investigations have without exception been performed with the sodium

'203 Patent Claim	Invalidity
contacting a salt of gamma hydroxybutyrate with the aqueous medium, adjusting the concentration of the gamma-hydroxybutyrate salt in the aqueous medium to a final concentration of from about 310 to about 750 mg/ml, and adjusting the pH of the medium to a final pH of about 6 to about 9, so that the medium is chemically stable and resistant to microbial growth, wherein the medium does not contain a preservative.	salt, the acid itself, or the corresponding lactone. *See*, *e.g.*, 1:7-15. **Nema** discloses that injectable products are required to withstand sterilization processes such as autoclaving and that preservatives may not be allowed in some injectable products, depending on the route of administration, and that chelating agents are used in parenteral products to complex heavy metals, thereby improving the efficacy of antioxidants or preservatives. Also disclosed are buffers and chemicals used to adjust the pH of formulations, including a table of 32 buffers and pH-adjusting agents, including organic and inorganic acids. *See*, *e.g.*, pp. 166, 167, 168, 169. **The '632 patent** discloses the use of gamma-hydroxybutyric acid salts for preparing pharmaceutical compositions, which may vary in GHB salt content from 12.5% to 50% by weight and for which suitable salts include the sodium salt. Also disclosed is an injectable aqueous formulation of sodium gamma-hydroxybutyrate free of preservatives. *See*, *e.g.*, Abstract, 7:32-33, 7:47-49, 8:57-59. **The '236 patent** discloses that the calcium and magnesium salts of 4-hydroxybutyric acid can be dispensed as aqueous solutions and that the sodium salt of 4-hydroxybutyric acid induces sleep. *See*, *e.g.*, 1:38-43, 4:39-47. **Mamelak (1977)** discloses that γ-hydroxybutyrate is marketed by Laboratoire Egic of Paris, France, as a banana-flavored syrup. Also disclosed is the use of GHB, obtained as a banana-flavored syrup, in a dose of 1.0-4.5 g and placebo in a dose of 5 cc banana flavoring in water, giving a 3-g dose on most nights. Also disclosed is exploring the use of sodium gamma-hydroxybutyrate to treat insomnia. *See*, *e.g.*, pp. 273, 274, 275. **EP '804** discloses the administration of salts of gamma-hydroxybutyric acid, of which the sodium salt is particularly preferred, in the form of single or multi-dose liquid solutions. Also disclosed is a

'203 Patent Claim	Invalidity
	formulation for intravenous injection that is free of preservatives. *See*, *e.g.*, 2:38-39, 6:32-34, Formulation 3. **Vickers** discloses that gamma-hydroxybutyrate is water soluble in all dilutions, and that the pH of the solution is not far from physiological. It is also disclosed that gamma-hydroxybutyric acid is marketed for intravenous injection as a solution containing 2.42 g sodium 4-hydroxybutyrate in 10 ml water, with a pH between 8.2 and 8.9. *See*, *e.g.*, pp. 75, 82-87. **The 1990 CRC Handbook** discloses that γ-Hydroxybutyric acid has a pK_a of 4.72 in aqueous solution. *See*, *e.g.*, p. 8-36. **Remington's** discloses requirements for pharmaceutical stability and some approaches to achieving stability, including stabilization from photolytic, oxidative, and solvolytic decomposition reactions. It is also disclosed that hydrochloric acid is a pharmaceutic aid that is used as an acidifying agent. *See*, *e.g.*, pp. 239, 639-640, 1410. **The 1995 USP** discloses a list of 13 acidifying agents among USP and NF Pharmaceutic Ingredients, including organic and inorganic acids. *See*, *e.g.*, P. 2205. **CA 338** discloses the preparation of 4-hydroxybutyric acid salt solutions of pH 7.2-7.7 for injection. Also disclosed is the preparation of sodium 4-hydroxybutyric acid solutions of pH 7.2-7.7 for injection, by sequential addition of γ-butyrolactone, water, and sodium hydroxide. *See*, *e.g.*, Abstract. **The '619 patent** discloses that sodium 4-hydroxybutyrate is highly soluble in water and, in aqueous solution, has a pH slightly in excess of 7. Also disclosed are formulations that are free of preservatives, including one that was administered to a patient just prior to undergoing surgery. *See*, *e.g.*, 1:61-66, examples 1-3.

'203 Patent Claim	Invalidity
	Wickliffe discloses that bacterial growth has been shown to be inhibited at pH 2 without the use of additional preservative material, and that asepsis also occurs above pH 9. *See*, *e.g.*, p. 770.
11. The method of claim 9 or 10, wherein the salt is sodium gamma-hydroxybutyrate.	*See supra* claim 9 or 10.
12. The method of claim 9 or 10, wherein said pH-adjusting agent is an organic acid.	*See supra* claim 9 or 10. **The 1995 USP** discloses a list of 13 acidifying agents among USP and NF Pharmaceutic Ingredients, including malic acid, citric acid, acetic acid, lactic acid, propionic acid, and tartaric acid. *See*, *e.g.*, p. 2205. *See also*, 21 C.F.R. §§ 184.1069, 184.1033, 184.1005, 184.1061, 184.1081, 184.1099. **Nema** discloses a table of 32 buffers and pH-adjusting agents, including acetic acid and citric acid. *See*, *e.g.*, p. 169. **EP '804** discloses that pharmaceutical compositions of sodium 4-hydroxybutyrate may be buffered. *See*, *e.g.*, 6:34.
13. The method of claim 12, 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, and nitric acid.	*See supra* claim 12. **The 1995 USP** discloses a list of 13 acidifying agents among USP and NF Pharmaceutic Ingredients, including hydrochloric acid, phosphoric acid, sulfuric acid, and nitric acid. *See*, *e.g.*, p. 2205. *See also*, 21 C.F.R. § 184.1095.
14. The method of claim 9 or 10, wherein the concentration of the gamma-hydroxybutyrate salt is from about 450 to about 600 mg/ml.	*See supra* claim 9 or 10.
15. The method of claim 9 or 10, wherein the concentration of the gamma-hydroxybutyrate salt is about	*See supra* claim 9 or 10.

'203 Patent Claim	Invalidity
500 mg/ml.	
16. The method of claim 1, wherein the medium does not contain a preservative.	*See supra* claim 1.
17. The method of claim 1, wherein said salt is selected from the group consisting of sodium, potassium, magnesium and calcium forms of gamma-hydroxybutyrate.	*See supra* claim 1. **CA 338** discloses the preparation of 4-hydroxybutyric acid salt solutions of pH 7.2-7.7 for injection, by hydrolysis of GBL with slightly less than the theoretical amount of sodium hydroxide. *See*, *e.g.*, Abstract.
18. The method of claim 1 wherein the aqueous medium contains one or more of salts selected from the group consisting of lithium, potassium, sodium, calcium, ammonium, and magnesium.	*See supra* claim 1. **CA 338** discloses the preparation of 4-hydroxybutyric acid salt solutions of pH 7.2-7.7 for injection, by hydrolysis of GBL with slightly less than the theoretical amount of sodium hydroxide. *See*, *e.g.*, Abstract. **35 U.S.C. § 112 ¶ 2** This claim is also invalid as indefinite because "lithium, potassium, sodium, calcium, ammonium, and magnesium" as recited in the claim are not salts; these are either elemental (neutral) or cationic (positively charged) species. *See Oxtoby*, pp. 53-55. In contrast, a salt or ionic compound is formed by the combination of cations with anions (negatively charged species) and named by the name of the cation followed by the name of the anion. *See* Oxtoby, p. 54.

1766508_3

Dated: November 7, 2013

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CERTIFICATE OF SERVICE

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Electronic Patent Application Fee Transmittal

Application Number:	13592202
Filing Date:	22-Aug-2012
Title of Invention:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
First Named Inventor/Applicant Name:	Dayton T. Reardan
Filer:	Gregory M. Stark/John Gustav-Wrathall
Attorney Docket Number:	101.031US9

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Utility under 35 USC 111(a) Filing Fees

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Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for Continued Examination	1801	1	1200	1200
		Total in USD ($)		**1200**

Electronic Acknowledgement Receipt	
EFS ID:	17934506
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:	107632
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Multipart Description/PDF files in .zip description

Document Description	Start	End
Request for Continued Examination (RCE)	1	1
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Claims	3	9
Applicant Arguments/Remarks Made in an Amendment	10	11
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National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
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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	3686
	Examiner Name	Lena Najarian
Sheet 1 of 2	Attorney Docket No: 101.031US9	

US PATENT DOCUMENTS

Examiner Initial *	USP Document Number	Publication Date	Name of Patentee or Applicant of cited Document
	US-8,589,182	11/19/2013	Reardan, Dayton T, et al.

FOREIGN PATENT DOCUMENTS

Examiner Initial *	Foreign Document Number	Publication Date	Name of Patentee or Applicant of cited Document	T 1
	EP-0527027A1	2/10/1993	Poole, Neil	

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
	"Civil Action No. 2:13-cv-00391-ES-SCM (consolidated)", Defendant Amneal Pharmaceuticals, LLC's Preliminary Invalidity Contentions (United States District Court of New Jersey), 182 pgs	
	"Civil Cover Sheet", Jazz Pharmaceuticals, Inc. v. Par Pharmaceuticals, Inc., (United States District Court, District of New Jersey), (12/27/13), 1 pg	
	"Complaint for Patent Infringement", Jazz Pharmaceuticals, Inc. v. Par Pharmaceuticals, Inc, (United States District Court, District of New Jersey), (12/27/13), 26 pgs	
	"Fed. R. Civ. P. Rule 7.1 Disclosure Statement", Jazz Pharmaceuticals, Inc. v. Par Pharmaceuticals, Inc., (United States District Court, District of New Jersey), (12/27/13), 2 pgs	
	"Final Minutes: Peripheral and Central Nervous System Drugs Advisory Committee", [Online]. Retrieved from the Internet: <URL: http://www.fda.gov/ohrms/dockets/ac/01/minutes/3754m1.htm>, (Jun. 6, 2001), 6 pgs.	
	"Notice of Paragraph IV Certification", Detailed Statement of the Factual and Legal Bases for Par's Paragraph IV Patent Certification and Offer of Confidential Access, (11/20/13), 190 pgs	
	"Orphan Medical Slides: Xyrem (sodium oxybate) oral solution", Peripheral and Central Nervous System Drugs Advisory Committee Meeting, [Online]. Retrieved from the Internet: <URL: http://www.fda.gov/ohrms/dockets/ac/01/slides/3754s1_01_orphanmedical/index.htm>, (Jun. 6, 2001), 167 pgs.	
	"Report on the Filing or Determination of an Action Regarding a Patent or Trademark", Jazz Pharmaceuticals, Inc. v. Par Pharmaceuticals, Inc., United States District Court, District of New Jersey Case No. 2:13-cv-07884-ES-JAD, (12/27/2013), 1 pg	
	"Slides: Pediatric Subcommittee of the Peripheral and Central Nervous system Drugs Advisory Committee", [Online]. Retrieved from the Internet: <URL: http://www.fda.gov/ohrms/dockets/ac/01/slides/3754s1.htm>, (Jun. 6, 2001), 86 pgs.	

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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	3686
	Examiner Name	Lena Najarian
Sheet 2 of 2	Attorney Docket No: 101.031US9	

OTHER DOCUMENTS – NON PATENT LITERATURE DOCUMENTS

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	"Summons in a Civil Case", Jazz Pharmaceuticals, Inc. v. Par Pharmaceuticals, Inc., United States District Court, District of New Jersey Case No. 213-CV-07884-ES-JAD, (12/31/13), 2 pgs	
	OXTOBY, DAVID W, et al., "", Principles of Modern Chemistry, Fort Worth : Saunders College Pub., (1996), 52-56	

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Office européen des brevets

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(84) Designated Contracting States : **BE DE FR GB NL SE**

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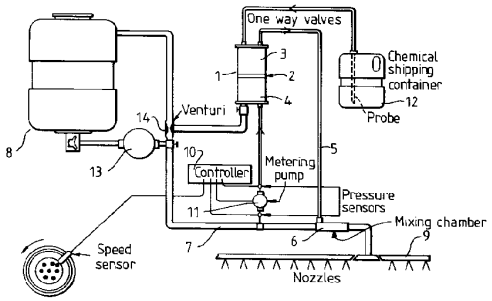
(54) Fluid dispenser.

(57) A liquid mixing system having a mixing cylinder (1) in which a movable piston (2) divides a liquid additive chamber (3) from a displacing liquid chamber (4). Displacing liquid, usually a proportion of a carrier liquid with which the additive liquid is to be mixed, is introduced to the displacing chamber to eject additive fluid to a mixing area where it is mixed with the carrier fluid. The additive chamber is connected to a bulk source of additive liquid from which it can be refilled and to which surplus additive can be returned. Displacing fluid is removed from the displacing chamber via a return line connected to a venturi. Suction is created in the venturi line through return of a carrier fluid through the venturi.

FIG.1 Schematic diagram of the concentrate metering system.



EP 0 527 027 A1

This invention relates to mixing liquids, and in particular to the mixing of one or more additive liquid, such as a concentrate, to a carrier liquid.

It will be appreciated that in such systems the additive liquid or liquids are usually supplied in lesser volume than the carrier liquid, but this is not essential.

UK Patent No. 2216817 describes a system in which the additive liquid is provided in a cylinder with a movable piston. Another liquid is used to displace the piston and cause the additive liquid to be introduced into the carrier as the mixture is used.

An advantage of this type of system is that additive and carrier are only mixed during use, i.e. it eliminates pre-mixing and waste or hazard from left over mixture. The abovementioned patent suggests a valved system using a suction pump to return carrier from the cylinder to a storage tank and for introducing additive liquid into the cylinder. However there is no detailed information concerning suitable mechanisms for achieving this.

The present invention is directed towards providing an additive liquid filling system for such a mixing apparatus that may additionally or alternatively also enable introduction of more than one additive liquid into a carrier liquid.

Accordingly the invention provides a liquid mixing system comprising at least one cylinder having a movable piston separating a first chamber from a second chamber, the first chamber being connectable via a first line and valve to a bulk source of an additive liquid and via a second line and valve to a mixing area, the second chamber being connected via a metering line having a valve and metering pump to a source of displacing liquid and via a second valve to a return line for the displacing liquid, the arrangement being that the valves in said first line and return line are opened and the valves in the second line and metering line are closed to draw displacing fluid out of the second chamber and fill the first chamber with additive liquid, the valve settings are reversed to eject additive fluid from the first chamber to the mixing area where it is mixed with a carrier fluid, and the valve in the metering line and first line are opened with the other valves closed to return remaining additive back to the bulk source.

The invention is now described by way of example with reference to the accompanying drawings, in which:

Figure 1 is a schematic diagram of a fluid mixing system incorporating a refill supply;

Figure 2 is a similar diagram showing valve locations;

Figure 3 shows in more detail the incorporation of a plurality of metering cylinders; and

Figure 4 shows a modification that permits simultaneous mixing and refilling.

Referring to Figures 1 and 2, a fluid mixing system comprises a metering cylinder 1 provided with a movable piston 2 dividing a first chamber 3 for additive liquid from a second chamber 4 for a displacing liquid. When the chamber 3 contains additive liquid it can be progressively forced out of the chamber, along line 5 to a mixing chamber 6 by the introduction of displacing liquid into chamber 4, urging piston 2 upwardly as viewed in the drawing.

In the mixing chamber the additive liquid is combined with a carrier liquid pumped by a main pump 13 along line 7 from a carrier liquid tank 8, the mixture is then supplied to a spray boom 9. The displacing fluid introduced to chamber 4 is a proportion of the carrier fluid that passes along line 7. The proportion, which in turn controls the amount of additive fluid displaced from chamber 3, and hence the concentration of the mixture, is controlled by controller 10 which monitors variables such as carrier liquid pressure and speed of travel of the spray boom over the ground (slower movement requiring a lower concentration of additive to distribute a given amount of additive per unit area).

Referring to Figure 2, valves A to F control the change from mixing cycle to refill cycle. In the mixing cycle valves A and E are closed and B and F open so that carrier liquid from the tank cannot enter chamber 4, only carrier liquid passing through a metering pump 11 and through open valve F can enter chamber 4. Valve C to an additive bulk supply 12 is closed, and if the bulk supply is remote from the sprayer the connecting pipe is disconnected. Valve D is open to allow additive liquid to flow to the mixing chamber.

To refill the chamber 3, the line to the bulk supply is connected and the valve settings are reversed. Valve C is opened to enable a refill supply to enter from the bulk container and valve D is closed to prevent a 'short circuit' of fluid from the bulk supply to the mixing chamber. Valves A and E are opened and valves B and F are closed so that the main pump 13 pumps water up (as viewed) through a venturi 14 causing carrier liquid to be sucked out of the cylinder 4, resulting in downward movement of piston 2 and suction of refilling additive into chamber 3. It will be realised that this arrangement with a venturi eliminates need for a second pump or drive for removing carrier fluid from the chamber 4.

There are instances when it is desirable to add more than one additive liquid to the carrier liquid. Figure 3 illustrates a system having multiple measuring cylinders, each of which may contain a different additive liquid that can be added sequentially, simultaneously or in varying combinations with the other liquids by selective operation of valves F, F_1, F_2 and F_3.

The system illustrated in Figure 3 may also be used with the same additive in two or more of the measuring cylinders. This is useful for example to enable higher concentrations to be released and/or to prolong the duration of application of mixed liquids between refills.

It will be appreciated that with the system descri-

bed with respect to Figure 2, during the refill operation, mixing ceases. This does not matter if the bulk storage container is static and not for example carried by the spraying vehicle. However in some instances small 'bulk' storage containers may be carried on board. In this latter instance a modification of the multi-cylinder arrangement, shown in Figure 4, enables refill of individual cylinders to take place in a staggered sequence, enabling simultaneous mixing to continue from another cylinder.

In Figure 4, each measuring cylinder is provided with a separate displacement liquid removal circuit. The main pump 13 supplies carrier along line 7 where, subject to the setting of values F, F_1, F_2 and F_3 it passes through a respective metering pump and respective measuring cylinder chamber 4. However instead of a single return line and venturi, each measuring cylinder has a separate return line 15, 15_1, 15_2 and 15_3 connecting with a respective venturi 14, 14_1, 14_2 and 14_3 on respective lines 17, 17_1, 17_2 and 17_3 with valves A, A_1, A_2 and A_3. Each of the valves A, A_1, A_2 and A_3 can be separately operated, along with the other valves associated with each measuring cylinder so that one cylinder can be refilling while others are mixing. The sequence of refilling is preferably controlled to avoid excessive pressure surges and drops in line 7, for example with one cylinder refilling while the other three are on standby or mixing.

When mixing is to be discontinued, the additive fluid in the measuring cylinders is returned to the bulk storage container by closing valve B and D and opening valve C.

The metering pumps measure, in terms of angular rate and the pressure differential, the rate of flow of carrier fluid into the second chamber of the measuring cylinders. This is directly proportional to the rate of ejection of the additive fluid from the first chamber. Thus the metering pump flow rate signal may be integrated and calibrated to be used as a measure of the quantity of additive dispensed and, from a knowledge of full or starting values, the quantity remaining in each cylinder. A predetermined level may be used as a trigger to commence a refill cycle.

The overall operation of the system especially the multi-cycle system is controlled by a digital processor, to which valve status indications, metering signals and distribution data are input in addition to concentration requirements.

Claims

1. A liquid mixing system comprising at least one cylinder (1) having a movable piston (2) separating a first chamber (3) from a second chamber (4), the first chamber being connectable via a first line and valve (C) to a bulk source (12) of an additive liquid and via a second line and valve (D) to a mixing area, the second chamber being connected via a metering line having a valve (F) and metering pump (11) to a source of displacing liquid and via a second valve (E) to a return line for the displacing liquid, the arrangement being that the valves in said first line and return line are opened and the valves in the second line and metering line are closed to draw displacing fluid out of the second chamber and fill the first chamber with additive liquid, the valve settings are reversed to eject additive fluid from the first chamber to the mixing area where it is mixed with a carrier fluid, and the valve in the metering line and first line are opened with the other valves closed to return remaining additive back to the bulk source.

2. A liquid mixing system according to claim 1 in which the displacing fluid comprises a proportion of the carrier fluid and the return line comprises a loop having a second valve and a venturi via which at least a proportion of the carrier fluid is pumped so that when the return line valve is opened the suction from the venturi withdraws the displacing carrier fluid from the second chamber.

3. A liquid mixing system according to claim 1 or claim 2 in which the valve states are controlled by digital controller.

4. A liquid mixing system according to any preceding claim in which the flow of displacing fluid into the second chamber is used to provide a measurement of dispensed additive.

FIG.1 Schematic diagram of the concentrate metering system.

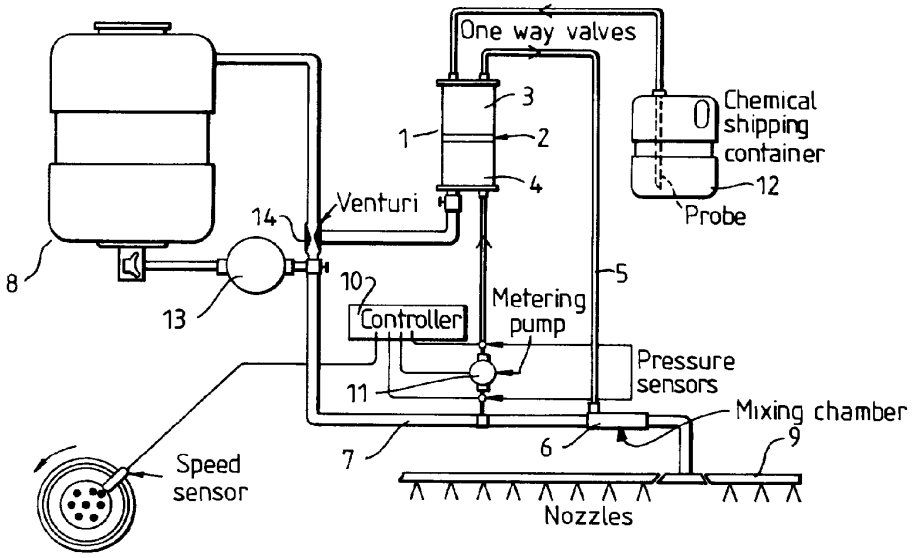


FIG. 2

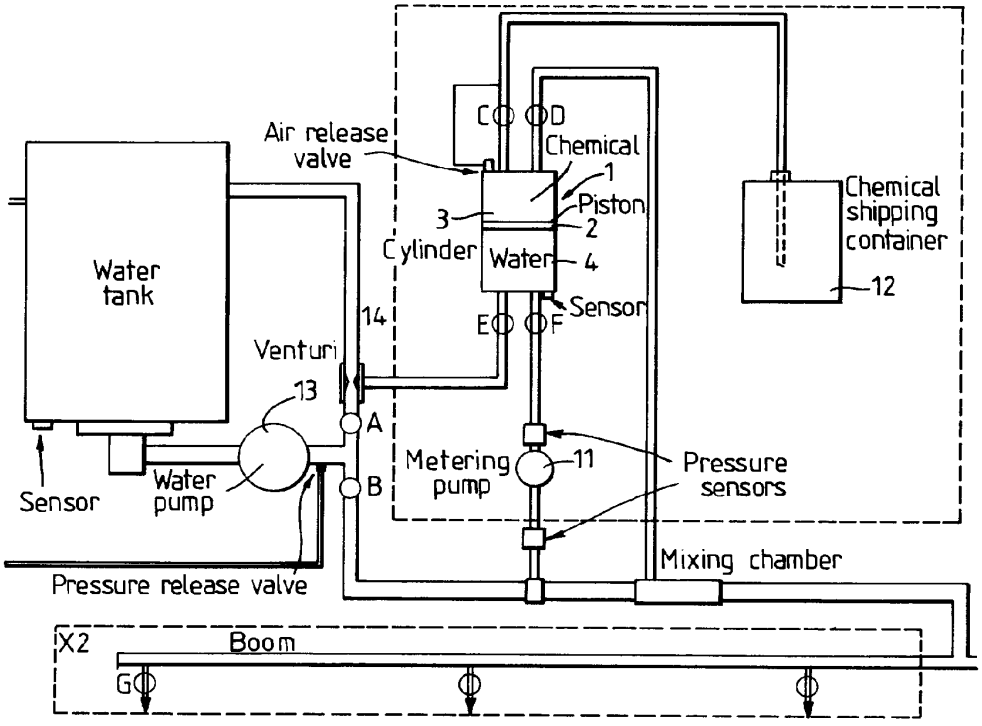


FIG.3

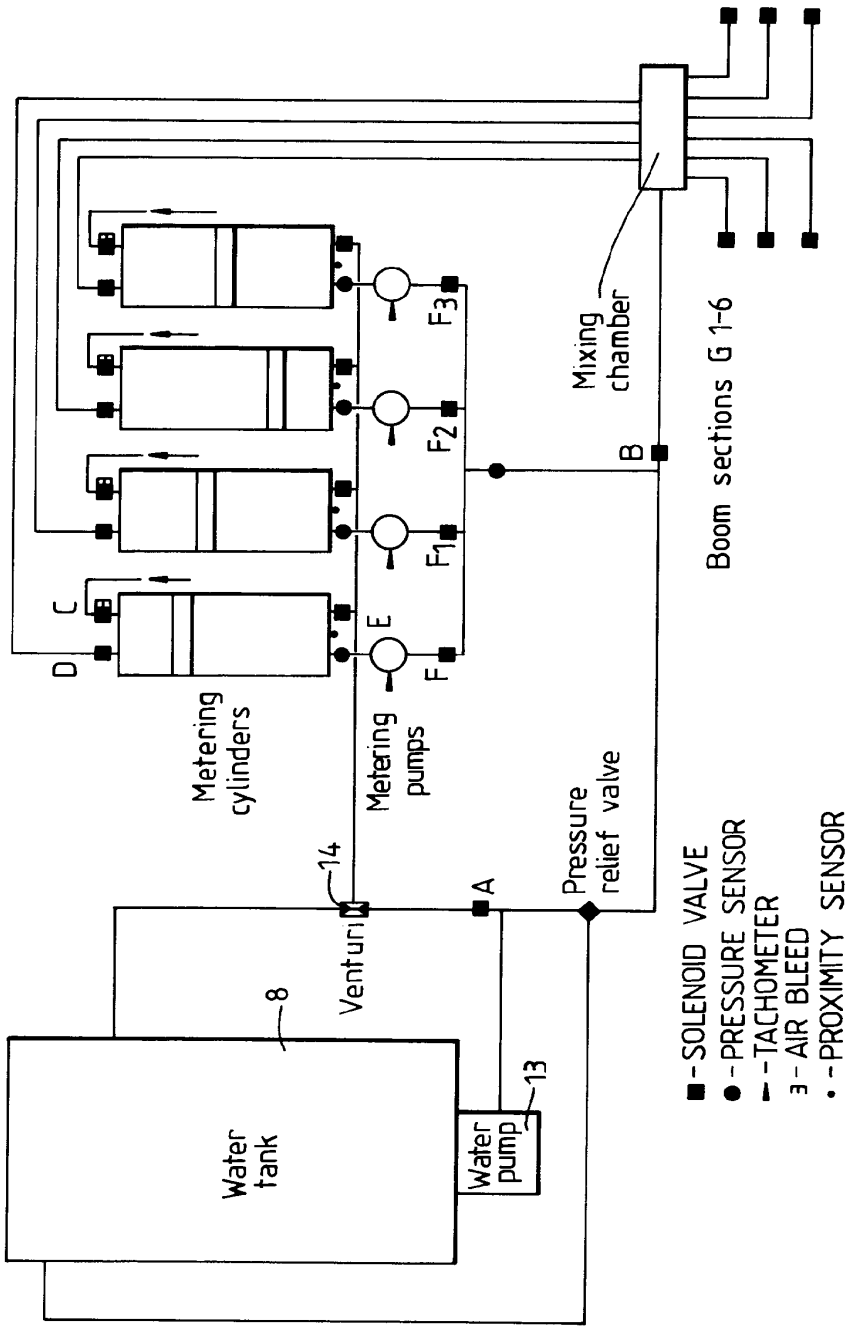
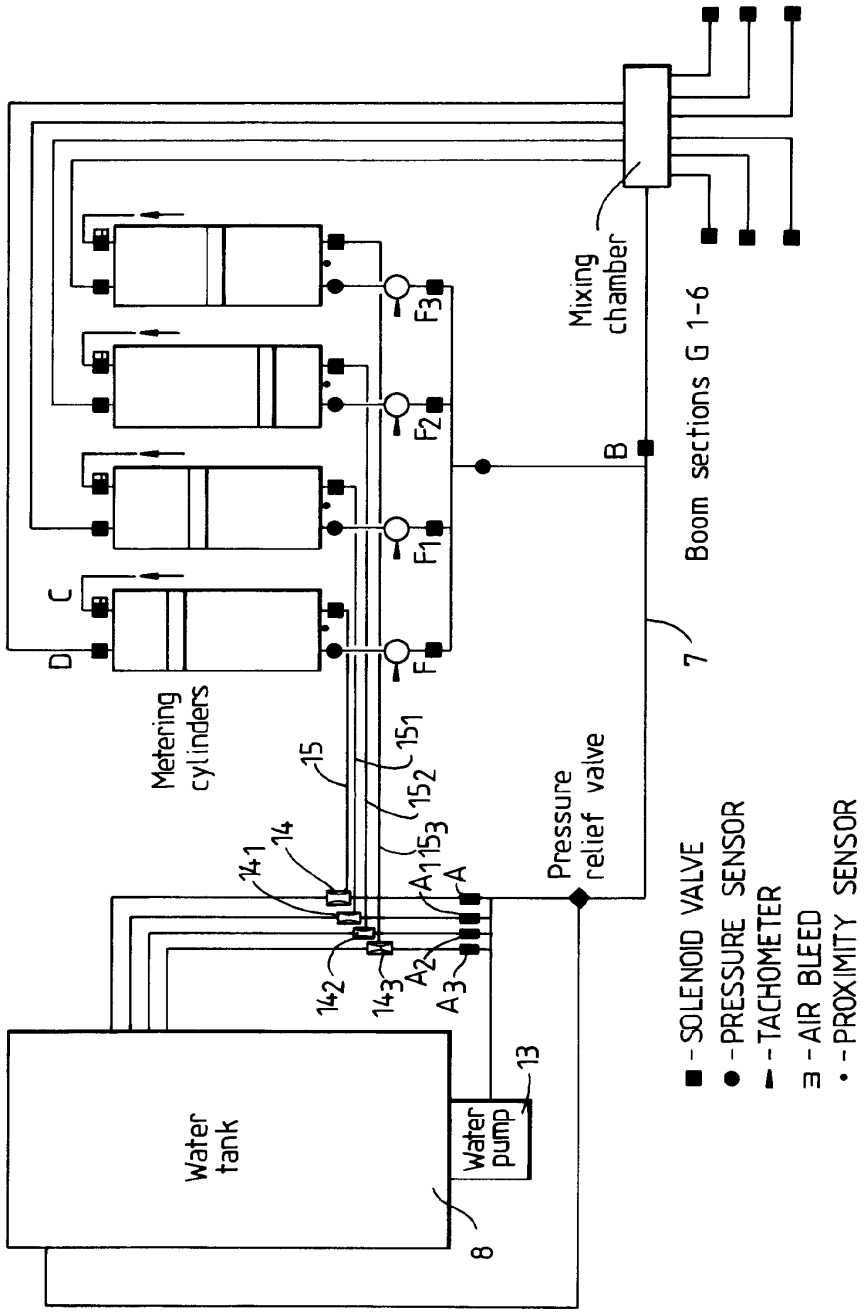


FIG. 4



European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 92 30 7070

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	POWER FARMING vol. 69, no. 7, July 1989, SUTTON, GB pages 42 - 43 A. PEARCE 'Pressure pointers' * page 42, column 1, paragraph "Up and running" - page 43, column 1, line 12; figure 1 *	1-4	A01C23/04 A01M7/00 B05B7/32
X	POWER FARMING vol. 70, no. 9, September 1990, SUTTON, GB pages 24 - 27 I. MARSHALL ET AL. 'When it's better to close for business' * page 27, "AFRC Engineering" *	1-4	
A,D	GB-A-2 216 817 (NATIONAL RESEARCH DEVELOPMENT CORPORATION) * page 5, line 6 - line 26; figure 1 *	1	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A01C
A01M
B05B

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	10 NOVEMBER 1992	MERCKX A.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **v.** **PAR PHARMACEUTICAL, 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 Par Pharmaceutical, Inc. ("Par"), 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 Par'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"), 8,263,650 (the "'650 patent"), 8,324,275 (the "'275 patent"), 8,461,203 (the "'203 patent"),

7,668,730 (the "'730 patent"), 7,765,106 (the "'106 patent"), 7,765,107 (the "'107 patent"), 7,895,059 (the "'059 patent"), 8,457,988 (the "'988 patent"), and 8,589,182 (the "'182 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 Par Pharmaceutical, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 300 Tice Boulevard, Woodcliff Lake, New Jersey.

4. On information and belief, Par develops numerous generic drugs for sale and use throughout the United States, including in this judicial district. Par has litigated patent cases in this District in the past without contesting personal jurisdiction, and, in at least some of those actions, Par 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 Par by virtue of, *inter alia,* its systematic and continuous contacts with the State of New Jersey. On information and belief, Par has its principal place of business in Woodcliff Lake, New Jersey, conducts business in this District, purposefully avails 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. Also, on information and belief,

Par has customers in the State of New Jersey. Further, on information and belief, Par is registered to conduct business in the State of New Jersey.

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

The Patent-In-Suit

8. 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.

9. 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.

10. 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.

11. 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.

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 E.

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 F.

14. On June 11, 2013, the USPTO duly and lawfully issued the '203 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 '203 patent is attached hereto as Exhibit G.

15. 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. The '730 patent was later assigned to Jazz Pharmaceuticals. A copy of the '730 patent is attached hereto as Exhibit H.

16. 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. The '106 patent was later assigned to Jazz Pharmaceuticals. A copy of the '106 patent is attached hereto as Exhibit I.

17. 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. The '107 patent was later assigned to Jazz Pharmaceuticals. A copy of the '107 patent is attached hereto as Exhibit J.

18. 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 K.

19. On June 4, 2013, the USPTO duly and lawfully issued the '988 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 '988 patent is attached hereto as Exhibit L.

20. On November 19, 2013, the USPTO duly and lawfully issued the '182 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 '182 patent is attached hereto as Exhibit M.

The XYREM® Drug Product

21. 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.

22. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the '889, '219, '506, '650, '275, '730, '106, '107, '059, '988, and '182 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

23. Pursuant to Section 505 of the FFDCA, Par filed ANDA No. 205403 ("Par'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 ("Par's Proposed Product"), before the patents-in-suit expire.

24. On information and belief, in connection with the filing of its ANDA as described in the preceding paragraph, Par 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) ("Par's Paragraph IV Certification"), alleging that the claims of the '889, '219, '506, '650, '275, '730, '106, '107, '059, and '988 patents are invalid, unenforceable, and/or will not be infringed by the activities described in Par's ANDA.

25. No earlier than November 20, 2013, Jazz Pharmaceuticals received written notice of Par's Paragraph IV Certification ("Par's Notice Letter") pursuant to 21 U.S.C. § 355(j)(2)(B). Par's Notice Letter alleged that the claims of the '889, '219, '506, '650, '275, '730, '106, '107, '059, and '988 patents are invalid, unenforceable, and/or will not be infringed by the activities described in Par's ANDA. Par's Notice Letter also informed Jazz Pharmaceuticals that Par seeks approval to market Par's Proposed Product before the patents-in-suit expire.

Count I: Infringement of the '431 Patent

26. Plaintiff repeats and realleges the allegations of paragraphs 1-25 as though fully set forth herein.

27. Par, 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. Par'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.

28. Par'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).

29. There is a justiciable controversy between the parties hereto as to the infringement of the '431 patent.

30. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will infringe the '431 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States.

31. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will induce infringement of the '431 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, upon FDA approval of Par's ANDA, Par will intentionally encourage acts of direct infringement with knowledge of the '431 patent and knowledge that its acts are encouraging infringement.

32. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will contributorily infringe the '431 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, Par has had and continues to have knowledge that Par's Proposed Product is especially adapted for a use that infringes the '431 patent and that there is no substantial non-infringing use for Par's Proposed Product.

33. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Par's infringement of the '431 patent is not enjoined.

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

35. 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

36. Plaintiff repeats and realleges the allegations of paragraphs 1-35 as though fully set forth herein.

37. Par'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).

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

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

40. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will induce infringement of the '889 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, upon FDA approval of Par's ANDA, Par will intentionally encourage acts of direct infringement with knowledge of the '889 patent and knowledge that its acts are encouraging infringement.

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

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

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

44. 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

45. Plaintiff repeats and realleges the allegations of paragraphs 1-44 as though fully set forth herein.

46. Par'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).

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

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

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

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

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

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

53. 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

54. Plaintiff repeats and realleges the allegations of paragraphs 1-53 as though fully set forth herein.

55. Par'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).

56. There is a justiciable controversy between the parties hereto as to the infringement of the '506 patent.

57. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will infringe the '506 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States.

58. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will induce infringement of the '506 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, upon FDA approval of Par's ANDA, Par will intentionally encourage acts of direct infringement with knowledge of the '506 patent and knowledge that its acts are encouraging infringement.

59. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will contributorily infringe the '506 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, Par has had and continues to have knowledge that Par's Proposed Product is especially adapted for a use that infringes the '506 patent and that there is no substantial non-infringing use for Par's Proposed Product.

60. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Par's infringement of the '506 patent is not enjoined.

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

62. 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 '650 Patent

63. Plaintiff repeats and realleges the allegations of paragraphs 1-62 as though fully set forth herein.

64. Par'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).

65. There is a justiciable controversy between the parties hereto as to the infringement of the '650 patent.

66. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will infringe the '650 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States.

67. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will induce infringement of the '650 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, upon FDA approval of Par's ANDA, Par will intentionally encourage acts of direct infringement with knowledge of the '650 patent and knowledge that its acts are encouraging infringement.

68. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will contributorily infringe the '650 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, Par has had and continues to have knowledge that Par's Proposed Product is especially adapted for a use that infringes the '650 patent and that there is no substantial non-infringing use for Par's Proposed Product.

69. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Par's infringement of the '650 patent is not enjoined.

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

71. 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 '275 Patent

72. Plaintiff repeats and realleges the allegations of paragraphs 1-71 as though fully set forth herein.

73. Par'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).

74. There is a justiciable controversy between the parties hereto as to the infringement of the '275 patent.

75. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will infringe the '275 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States.

76. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will induce infringement of the '275 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, upon FDA approval of Par's ANDA, Par will intentionally encourage acts of direct infringement with knowledge of the '275 patent and knowledge that its acts are encouraging infringement.

77. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will contributorily infringe the '275 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, Par has had and continues to have knowledge that Par's Proposed Product is especially adapted for a use that infringes the '275 patent and that there is no substantial non-infringing use for Par's Proposed Product.

78. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Par's infringement of the '275 patent is not enjoined.

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

80. 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 '203 Patent

81. Plaintiff repeats and realleges the allegations of paragraphs 1-80 as though fully set forth herein.

82. Par, 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 '203 patent. Par'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.

83. Par'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 '203 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

84. There is a justiciable controversy between the parties hereto as to the infringement of the '203 patent.

85. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will infringe the '203 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States.

86. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will induce infringement of the '203 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, upon FDA approval of Par's ANDA, Par will intentionally encourage acts of direct infringement with knowledge of the '203 patent and knowledge that its acts are encouraging infringement.

87. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will contributorily infringe the '203 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, Par has had and continues to have knowledge that Par's Proposed Product is especially adapted for a use that infringes the '203 patent and that there is no substantial non-infringing use for Par's Proposed Product.

88. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Par's infringement of the '203 patent is not enjoined.

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

90. 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 VIII: Infringement of the '730 Patent

91. Plaintiff repeats and realleges the allegations of paragraphs 1-90 as though fully set forth herein.

92. Par'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).

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

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

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

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

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

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

99. 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 IX: Infringement of the '106 Patent

100. Plaintiff repeats and realleges the allegations of paragraphs 1-99 as though fully set forth herein.

101. Par'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).

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

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

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

105. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will contributorily infringe the '106 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, Par has had and continues to have knowledge that Par's Proposed Product is especially adapted for a use that infringes the '106 patent and that there is no substantial non-infringing use for Par's Proposed Product.

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

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

108. 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 X: Infringement of the '107 Patent

109. Plaintiff repeats and realleges the allegations of paragraphs 1-108 as though fully set forth herein.

110. Par'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).

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

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

113. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will induce infringement of the '107 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, upon FDA approval of Par's ANDA, Par will intentionally encourage acts of direct infringement with knowledge of the '107 patent and knowledge that its acts are encouraging infringement.

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

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

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

117. 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 XI: Infringement of the '059 Patent

118. Plaintiff repeats and realleges the allegations of paragraphs 1-117 as though fully set forth herein.

119. Par'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).

120. There is a justiciable controversy between the parties hereto as to the infringement of the '059 patent.

121. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will infringe the '059 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States.

122. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will induce infringement of the '059 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, upon FDA approval of Par's ANDA, Par will intentionally encourage acts of direct infringement with knowledge of the '059 patent and knowledge that its acts are encouraging infringement.

123. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will contributorily infringe the '059 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, Par has had and continues to have knowledge that Par's Proposed Product is especially adapted for a use that infringes the '059 patent and that there is no substantial non-infringing use for Par's Proposed Product.

124. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Par's infringement of the '059 patent is not enjoined.

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

126. 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 XII: Infringement of the '988 Patent

127. Plaintiff repeats and realleges the allegations of paragraphs 1-126 as though fully set forth herein.

128. Par'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 '988 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

129. There is a justiciable controversy between the parties hereto as to the infringement of the '988 patent.

130. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will infringe the '988 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States.

131. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will induce infringement of the '988 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, upon FDA approval of Par's ANDA, Par will intentionally encourage acts of direct infringement with knowledge of the '988 patent and knowledge that its acts are encouraging infringement.

132. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will contributorily infringe the '988 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, Par has had and continues to have knowledge that Par's Proposed Product is especially adapted for a use that infringes the '988 patent and that there is no substantial non-infringing use for Par's Proposed Product.

133. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Par's infringement of the '988 patent is not enjoined.

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

135. 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 XIII: Infringement of the '182 Patent

136. Plaintiff repeats and realleges the allegations of paragraphs 1-135 as though fully set forth herein.

137. Par, 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 '182 patent. Par'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.

138. Par'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 '182 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

139. There is a justiciable controversy between the parties hereto as to the infringement of the '182 patent.

140. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will infringe the '182 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States.

141. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will induce infringement of the '182 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, upon FDA approval of Par's ANDA, Par will intentionally encourage acts of direct infringement with knowledge of the '182 patent and knowledge that its acts are encouraging infringement.

142. Unless enjoined by this Court, upon FDA approval of Par's ANDA, Par will contributorily infringe the '182 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Par's Proposed Product in the United States. On information and belief, Par has had and continues to have knowledge that Par's Proposed Product is especially adapted for a use that infringes the '182 patent and that there is no substantial non-infringing use for Par's Proposed Product.

143. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Par's infringement of the '182 patent is not enjoined.

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

145. 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 Par has infringed the patents-in-suit by submitting ANDA No. 205403;

(B) A Judgment be entered that Par has infringed, and that Par's making, using, selling, offering to sell, or importing Par'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. 205403 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 Par 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 Par'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 Par, 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 Par's Proposed Product will directly infringe, induce and/or contribute to infringement of the patents-in-suit;

(G) To the extent that Par 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 Par engages in the commercial manufacture, use, importation into the United States, sale, or offer for sale of Par'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: December 27, 2013

By: s/ Charles M. Lizza

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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)(JAD) and *Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC*, Civil Action No. 13-391 (ES)(JAD) 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: December 27, 2013

By: s/ Charles M. Lizza
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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **v.** **PAR PHARMACEUTICAL, INC.,** **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: December 27, 2013

By: s/ Charles M. Lizza

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Final Minutes

Peripheral and Central Nervous System Drugs Advisory Committee
June 6, 2001
Xyrem ® , Orphan Medical Inc.

Consideration of (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.

The meeting was held at the Holiday Inn, in Bethesda, Maryland. Prior to the meeting, the members, consultants and guests had reviewed background material from the FDA. In order for the public to be informed, the background material was also available on the Dockets page before the meeting. There were approximately 130 persons in attendance. The meeting started at 8 a.m. and ended at 6:00 p.m.

Attendance:
PCNS and Consultants Present: Claudia Kawas, M.D., Acting Chair ,
Gerald Van Belle, Ph.D., LeRoy Penix , M.D., Jerry Wolinsky, M.D., Richard Penn, M.D.,
Ella Lacey, Ph.D,

PCNS Consultants Absent: Howard Weiner, M.D, Michael Grundman, M.D.,

Substance Abuse Consultants: Pippa Simpson, Ph.D., Carol Falkowski, Ph.D., Christine Sannerud, Ph.D. (non-voting)

Substance Abuse Guest Speakers (non-voting): Jerry Frankenheim, Ph.D., JoEllen Dyer, Ph.D.,

Neurology – Sleep Guest Speakers (non-voting) Christian Guilleminault, M.D., Ronald Chervin, M.D. (Both receiving webcast and on direct phone link)

FDA Participants: Robert Temple, M.D., Russell Katz, M.D, Ranjit Mani, M.D., Deborah Leiderman, M.D., Sharon Yan, Ph.D.

Overview of FDA's Presentation:
Russell Katz, M.D., gave an overview of the FDA questions for the meeting.

Orphan Medical Presentations
Introduction
Dayton Reardan, Ph.D., Orphan Medical

Medical Need, Efficacy and Safety
Emanuel Mignot, M.D., Stanford University Sleep Clinic

Efficacy
William Houghton, M.D., Orphan Medical

Polysomnographic Effects of Xyrem
Jed Black, M.D., Stanford University Sleep Clinic

Safety and Summary of Risks versus Benefits
Bill Houghton, M.D., Orphan Medical

RISK MANAGEMENT PRESENTATIONS
FDA invited speakers:
Epidemiology of GHB Abuse Issues
Carol Falkowski, Hazelden Foundation, Minnesota

Adverse Medical Effects with GHB
Jo Ellen Dyer, Pharm.D. California Poison Control System -San Francisco, University of California San Francisco

Sponsor Presentations on Risk Management and Abuse Liability
Bob Balster, Ph.D., Medical College of Virginia

Risk Management
Patti Engel, RN, BSN, Orphan Medical

PUBLIC SPEAKERS:
All speakers had been asked to limit their comments to five minutes. All have also been asked to disclose any potential conflicts of interest before they begin their statement.

Sharon Fitzgerald, Littleton, Colorado

Abbey S. Meyers, President, National Organization for Rare Disorders, Inc®

Robert L. Cloud, Narcolepsy Network, Inc.

Cindy Pekarick, Pennsylvania

Eric Strain, M.D., College on Problems of Drug Dependence

Deborah Zvorsec, Ph.D., Hennepin County Medical Center, Minnesota

Trinka Porrata, California

Richard Gelula, Executive Director, National Sleep Foundation

Matt Speakman, West Virginia

Charles Cichon, President, National Association of Drug Diversion Investigators

Debbie Alumbaugh, Florida

Brian Hunter, Young Adults With Narcolepsy

Joe Spillane, Pharm.D., Florida

Mali Einen, California

Sandra Jones, California

Committee Discussion and Votes:

1. **Has the sponsor demonstrated efficacy of Xyrem® for the proposed indication to treat cataplexy and excessive daytime sleepiness in patients with narcolepsy?**

    a. If no, is there any reasonable claim for which the sponsor has presented substantial evidence of effectiveness?

The committee altered the question several times. The final vote on efficacy was changed when the committee started to discuss the safety data and decided that efficacy needed to be considered primarily in relationship to the data available to judge the safety data. Hence, this record only notes the final question which addressed efficacy and then safety in relationship to data available on 6-9 grams of Xyrem® :

Has the sponsor demonstrated efficacy (at 6 – 9 grams) of Xyrem® for the proposed indication of cataplexy?

Yes = 5 No= 4

Has the sponsor demonstrated efficacy (at 6 – 9 grams) of Xyrem® for the proposed indication of daytime sleepiness?

Yes=0 No = 9

2. **Has the sponsor established the safety of Xyrem® when used for the proposed indication for which substantial evidence of effectiveness has been submitted?**

This was only voted on in terms of cataplexy and with a dose range of 6-9grams/day.

Yes=4 No=4 Abstain=1

3. **Is the adoption of a risk management plan necessary for the safe use of Xyrem®?**

Yes=8 No=1

(The no vote was cast because it is a complicated issue and can't resolve all the issues for control. If it is limited a patient population may not be served – which was equated to pain management limitations. "The devil is in the details.")

Please evaluate the following components of the Risk Management Program:

4. **Safe Use in Home**

    a. Should there be a requirement for additional safeguards in patient's homes, e.g., keeping drugs in a locked storage space?

Yes=1 No=8 (because all drugs should be in a safe place)

b. Should there be additional warnings on the labeling of the dose cups and/or bottle of GHB?

Unanimous that labels on bottles and dose cups should indicate what the substance is and the dose in the container. (Thus if someone overdosed and went to and ER the staff would know what they had ingested.)

c. Is there any special concern or advice regarding limitations on the quantity of Xyrem ® supplied at any one time?

No consensus ; perhaps it might be extended to 3 months

d. What special concerns should be communicated in the product label and other printed materials?

Not specifically discussed but answered in other questions.

5. Safe Use by Patient

a. Should patients sign an informed consent form before receiving the initial shipment of the drug?

Yes=5 No=4

The dissenter's thought that without details it was hard to vote on. What would be in the informed consent? One person suggested that contract might be better choice of words where the patient could acknowledge the dispensing of the drug and the risks.

b. Should patients be required to return a registry form before receiving the first shipment?

Yes=2 No=1 Abstain = 6

The consensus was that maybe they won't take this seriously and how was this going to be different from consent.

6. Appropriate Prescribing

a. Should physicians document that they read the materials sent to them before the pharmacy fills the initial prescription?

Yes=7 No=2

The members cautioned that a sleep center physician should only have to sign this once. MD needs to know that it is GHB and should be definitely informed of this information.

b. 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?

The word physician staff was added to the sentence:

Yes = 1 No=7 Abstain =1

c. Should there be restricted prescribing for the product? (e.g., only to those who have a diagnosis of cataplexy)

This was discussed at great length. There are two concerns to consider: The patient's interests and protecting the public from abuse/misuse. Many felt that there was a definite need to protect the public. Since it can be miss diagnosed, a member felt that someone needs to monitor who is treated. There was concern that PK studies should be done on children before prescribed. There was also sensitivity to the fact that not all patients will be at sleep centers . One of the sleep specialists indicated that in his opinion one couldn't confirm cataplexy.

Yes=7 No=1 Abstain =1

d. Does the Risk Management Program assure appropriate prescribing or sufficiently reduce the risks of misuse or overdose from Xyrem?

The patient needs to know that the substance is GHB and that there is the potential for abuse/legal consequences.

e. Should certification of physicians for prescribing Xyrem be required?

Yes=0 No=8 Abstain=1

7. Central Pharmacy

a. Is the institution of the sponsor's central pharmacy adequate?

Not discussed

b. Should the central pharmacy be described in the product labeling, as well as educational and promotional material?

Not discussed

8. Post Market Surveillance

a. Should there be a requirement for post-marketing reporting of cases of misuse, abuse, overdose, dependence, and diversion?

Not discussed

b. Should the role of the central pharmacy include providing post-marketing and surveillance reports to the Agency in addition to the sponsor?

Not discussed

c. Should these reports be provided on a regular basis and include monitoring prescribing and dispensing patterns?

Not discussed

9. Other recommendations

a. Any other recommendations on how to protect the family of the patient, on the handling, storage, and disposal of GHB, on labeling and on post market follow-up for misuse and overdose?

The fact that Xyrem is GHB is not in the patient educational material. Although the sponsor indicated that they had intentionally not used the word GHB on advice of abuse experts, members of the committee felt that the patient definitely needed to know this information.

Since the sponsor has an investment in making a profit, members questioned if it was realistic to expect that the sponsor serve as the reporter of adverse events, abuses etc. "Who will police the police."

The committee and guests discussed the issues and their views are recorded in the transcript. A verbatim transcript of this meeting will be available on the FDA's Dockets Management Branch Website approximately 30 days after the meeting. The address is HTTP://www.fda.gov/ohrms/dockets/ac/acmenu.htm.

I certify that I attended the June 6, 2001 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Sandra Titus 6/25/01
Sandra Titus, Ph.D. Date
Executive Secretary, PCNS

Claudia Kawas M.D. 6/19/01
Claudia Kawas, M.D. Date
Acting Chair, PCNS

Prepared on June 6, 2001
Sandra Titus

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. 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

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $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).			
☐ 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	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/16/2014	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 28	Minus	** 28	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

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

LIE
/VENICE WILLIAMS/

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13592202	REARDAN ET AL.
	Examiner	**Art Unit**
	LENA NAJARIAN	3686

CPC		
Symbol	**Type**	**Version**

CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 28	
/LENA NAJARIAN/ Primary Examiner.Art Unit 3686 02/07/2014 (Primary Examiner) (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 2B

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13592202	REARDAN ET AL.
	Examiner	**Art Unit**
	LENA NAJARIAN	3686

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION												
CLASS	SUBCLASS	CLAIMED									NON-CLAIMED					
705	2	G	0	6	Q	10 / 00 (2012.01.01)										
CROSS REFERENCE(S)																
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)															
705	3															
707	803															

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 28	
/LENA NAJARIAN/ Primary Examiner.Art Unit 3686 (Primary Examiner)	02/07/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 2B

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13592202	REARDAN ET AL.
	Examiner	**Art Unit**
	LENA NAJARIAN	3686

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	15	17	27	33										
	2	16	18	28	34										
	3	17	19												
2	4	18	20												
3	5	19	21												
4	6	20	22												
5	7		23												
6	8		24												
7	9		25												
8	10		26												
9	11	21	27												
10	12	22	28												
11	13	23	29												
12	14	24	30												
13	15	25	31												
14	16	26	32												

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 28	
/LENA NAJARIAN/ Primary Examiner.Art Unit 3686 (Primary Examiner)	02/07/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 2B

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	05/30/2013	10/23/2013	01/06/2014	02/07/2014				
	1	÷	✓	✓	=	=				
	2	÷	✓	=	-	-				
	3	÷	✓	✓	-	-				
	4	÷	✓	✓	=	=				
	5	÷	✓	✓	=	=				
	6	÷	✓	✓	=	=				
	7	÷	✓	✓	=	=				
	8	÷	✓	✓	=	=				
	9	÷	✓	✓	=	=				
	10	÷	✓	✓	=	=				
	11	÷	✓	✓	=	=				
	12	÷	✓	✓	=	=				
	13	÷	✓	✓	=	=				
	14	÷	✓	✓	=	=				
	15	÷	✓	✓	=	=				
	16	÷	✓	✓	=	=				
	17	÷	✓	✓	=	=				
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	19	÷	✓	✓	=	=				
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	22	÷	✓	✓	=	=				
	23	÷	N	-	-	-				
	24	÷	N	-	-	-				
	25	÷	N	-	-	-				
	26	÷	N	-	-	-				
	27		✓	✓	=	=				
	28		✓	✓	=	=				
	29			✓	=	=				
	30			✓	=	=				
	31			✓	=	=				
	32			✓	=	=				
	33			✓	=	=				
	34			✓	=	=				

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 5805

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/592,202	08/22/2012	705	3686	101.031US9

APPLICANTS

INVENTORS

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

**** CONTINUING DATA ***************************

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 ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

08/31/2012

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /LENA NAJARIAN/ Examiner's Signature	☐ Met after Allowance LN Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		MN	16	26	3

ADDRESS

Schwegman Lundberg & Woessner/Jazz Pharmaceutical
P.O. Box 2938
Minneapolis, MN 55402
UNITED STATES

TITLE

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

FILING FEE RECEIVED		
2390	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

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NOTICE OF ALLOWANCE AND FEE(S) DUE

107632 7590 03/14/2014

Schwegman Lundberg & Woessner/Jazz Pharmaceutical
P.O. Box 2938
Minneapolis, MN 55402

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

DATE MAILED: 03/14/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/592,202	08/22/2012	Dayton T. Reardan	101.031US9	5805

TITLE OF INVENTION: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	06/16/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE 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.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

107632 7590 03/14/2014
Schwegman Lundberg & Woessner/Jazz Pharmaceutical
P.O. Box 2938
Minneapolis, MN 55402

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/592,202	08/22/2012	Dayton T. Reardan	101.031US9	5805

TITLE OF INVENTION: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	06/16/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
NAJARIAN, LENA	3686	705-002000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/592,202	08/22/2012	Dayton T. Reardan	101.031US9	5805

107632 7590 03/14/2014

Schwegman Lundberg & Woessner/Jazz Pharmaceutical
P.O. Box 2938
Minneapolis, MN 55402

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

DATE MAILED: 03/14/2014

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 0 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 0 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.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. 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.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 13/592,202	Applicant(s) REARDAN ET AL.	
	Examiner LENA NAJARIAN	Art Unit 3686	AIA (First Inventor to File) Status No

-- 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 *1/16/14*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ 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.
3. ☒ The allowed claim(s) is/are *1, 4-22, and 27-34*. As a result of the allowed claim(s), 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 .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   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.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ 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. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 20140116
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/LENA NAJARIAN/
Primary Examiner, Art Unit 3686

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 2	Attorney Docket No: 101.031US9	

US PATENT DOCUMENTS			
Examiner Initial *	**USP Document Number**	**Publication Date**	**Name of Patentee or Applicant of cited Document**
	US-8,589,182	11/19/2013	Reardan, Dayton T, et al.

FOREIGN PATENT DOCUMENTS				
Examiner Initial *	**Foreign Document Number**	**Publication Date**	**Name of Patentee or Applicant of cited Document**	**T 1**
	EP-0527027A1	2/10/1993	Poole, Neil	

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**
	"Civil Action No. 2:13-cv-00391-ES-SCM (consolidated)", Defendant Amneal Pharmaceuticals, LLC's Preliminary Invalidity Contentions (United States District Court of New Jersey), 182 pgs	
	"Civil Cover Sheet", Jazz Pharmaceuticals, Inc. v. Par Pharmaceuticals, Inc., (United States District Court, District of New Jersey), (12/27/13), 1 pg	
	"Complaint for Patent Infringement", Jazz Pharmaceuticals, Inc. v. Par Pharmaceuticals, Inc, (United States District Court, District of New Jersey), (12/27/13), 26 pgs	
	"Fed. R. Civ. P. Rule 7.1 Disclosure Statement", Jazz Pharmaceuticals, Inc. v. Par Pharmaceuticals, Inc., (United States District Court, District of New Jersey), (12/27/13), 2 pgs	
	"Final Minutes: Peripheral and Central Nervous System Drugs Advisory Committee", [Online]. Retrieved from the Internet: <URL: http://www.fda.gov/ohrms/dockets/ac/01/minutes/3754m1.htm>, (Jun. 6, 2001), 6 pgs.	
	"Notice of Paragraph IV Certification", Detailed Statement of the Factual and Legal Bases for Par's Paragraph IV Patent Certification and Offer of Confidential Access, (11/20/13), 190 pgs	
	"Orphan Medical Slides: Xyrem (sodium oxybate) oral solution", Peripheral and Central Nervous System Drugs Advisory Committee Meeting, [Online]. Retrieved from the Internet: <URL: http://www.fda.gov/ohrms/dockets/ac/01/slides/3754s1_01_orphanmedical/index.htm>, (Jun. 6, 2001), 167 pgs.	
	"Report on the Filing or Determination of an Action Regarding a Patent or Trademark", Jazz Pharmaceuticals, Inc. v. Par Pharmaceuticals, Inc., United States District Court, District of New Jersey Case No. 2:13-cv-07884-ES-JAD, (12/27/2013), 1 pg	
	"Slides: Pediatric Subcommittee of the Peripheral and Central Nervous system Drugs Advisory Committee", [Online]. Retrieved from the Internet: <URL: http://www.fda.gov/ohrms/dockets/ac/01/slides/3754s1.htm>, (Jun. 6, 2001), 86 pgs.	

EXAMINER	/Lena Najarian/	**DATE CONSIDERED**	03/10/2014

* 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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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 2 of 2	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**
	"Summons in a Civil Case", Jazz Pharmaceuticals, Inc. v. Par Pharmaceuticals, Inc., United States District Court, District of New Jersey Case No. 213-CV-07884-ES-JAD, (12/31/13), 2 pgs	
	OXTOBY, DAVID W, et al., "", Principles of Modern Chemistry, Fort Worth : Saunders College Pub., (1996), 52-56	

EXAMINER /Lena Najarian/ **DATE CONSIDERED** 03/10/2014

* 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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /L.N./

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13592202	REARDAN ET AL.
	Examiner	Art Unit
	LENA NAJARIAN	3686

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
707	803	5/29/13	LN
705	2, 3	5/29/13	LN

SEARCH NOTES		
Search Notes	Date	Examiner
East	5/28/13	LN
East	10/22/13	LN
East	10/23/13	LN
forward/backward citation search	1/6/14	LN
Google	1/6/14	LN
updated previous searches	2/7/14	LN

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
705	3	1/6/14	LN
707	803	1/6/14	LN
	PGPUB text search	1/6/14	LN
	updated previous searches	2/7/14	LN

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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

107632 7590 04/02/2014

Schwegman Lundberg & Woessner/Jazz Pharmaceutical
P.O. Box 2938
Minneapolis, MN 55402

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

NOTIFICATION DATE	DELIVERY MODE
04/02/2014	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):

slw@blackhillsip.com
uspto@slwip.com

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
13/592,202	22 August, 2012	REARDAN ET AL.	101.031US9

Schwegman Lundberg & Woessner/Jazz Pharmaceutical
P.O. Box 2938
Minneapolis, MN 55402

EXAMINER	
LENA NAJARIAN	
ART UNIT	PAPER
3686	20140325

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

IDS documents dated 5/28/13 and 10/28/13.

/LENA NAJARIAN/
Primary Examiner, Art Unit 3686

PTO-90C (Rev.04-03)

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US Patent & Trademark Office: U.S. DEPARTMENT OF COMMERCE
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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	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-8,457,988	6/4/2013	Reardan, Dayton T, 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**
	"Application Serial No. 13/595,676, Non Final Office Action mailed 03-21-13", 16 pgs	
	"Application Serial No. 13/595,757, Examiner Interview Summary mailed 03-12-13", 3 pgs	
	"Application Serial No. 13/595,757, Notice of Allowance mailed 03-21-13", 68 pgs	
	"Application Serial No. 13/595,757, Response filed 03-07-13 to Non Final Office Action mailed 01-17-13", 8 pgs	
	"Roxane Laboratories, Inc.'s Amended Answer and Affirmative Defenses to Plaintiff's Complaint Regarding U.S. Patent No. 8,234,275", Exhibit 2, (4/26/13), 15 pgs	
	"Roxane Laboratories, Inc.'s Amended Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint Regarding U.S. Patent No. 8,263,650", Exhibit 1, (4/26/13), 23 pgs	

EXAMINER /Lena Najarian/ **DATE CONSIDERED** 03/25/2014

* 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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Modified form PTO/SB/08A(04-07) OMB 651-0031
US Patent & Trademark Office: U.S. DEPARTMENT OF COMMERCE
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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	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**
	"Answer, Defenses, and Counterclaims", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey Civil Action No. 13-391 ES-SCM, (4/15/13), 22 pgs	
	"Notice of Voluntary Dismissal of Counterclaims Pertaining to U.S. Patent Nos. 7,668,730; 7,765,106; AND 7,765,107 (CONTAINED IN COUNTS I, II) PURSUANT TO FED. R. CIV. P. 41(a), (c)", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey Civil Action No. 13-391 ES-SCM, (7/15/13), 2 pgs	

EXAMINER /Lena Najarian/ **DATE CONSIDERED** 03/25/2014

* 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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /L.N./

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

107632 7590 03/14/2014
Schwegman Lundberg & Woessner/Jazz Pharmaceutical
P.O. Box 2938
Minneapolis, MN 55402

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

Melissa Cuff	(Depositor's name)
/Melissa Cuff/	(Signature)
04-03-14	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/592,202	08/22/2012	Dayton T. Reardan	101.031US9	5805

TITLE OF INVENTION: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	06/16/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
NAJARIAN, LENA	3686	705-002000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☒ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Schwegman Lundberg
2 & Woessner, P.A.
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Jazz Pharmaceuticals, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Palo Alto, California

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 19-0743 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ☐ Applicant changing to regular undiscounted fee status.
  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature / /
Typed or printed name David D'Zurilla
Date April 3, 2014
Registration No. 36,776

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal

Application Number:	13592202
Filing Date:	22-Aug-2012
Title of Invention:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
First Named Inventor/Applicant Name:	Dayton T. Reardan
Filer:	Mark Victor Muller/Melissa Cuff
Attorney Docket Number:	101.031US9

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	960	960
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**960**

Electronic Acknowledgement Receipt	
EFS ID:	18661840
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:	107632
Filer:	Mark Victor Muller/Melissa Cuff
Filer Authorized By:	Mark Victor Muller
Attorney Docket Number:	101.031US9
Receipt Date:	03-APR-2014
Filing Date:	22-AUG-2012
Time Stamp:	12:34:33
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$960
RAM confirmation Number	11163
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		101031US9SignedIFEE.pdf	1295931 97eae1318d2c2e66e56be7d239baaac0db2647c7	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	1
	Issue Fee Payment (PTO-85B)	2	2
	Miscellaneous Incoming Letter	3	3

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30172 2d61f63aff2a8261f575349f4600bc5602be8711	no	2

Warnings:

Information:

Total Files Size (in bytes):	1326103

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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

Inventor(s): 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:	June 14, 2014
Examiner:	Lena Najarian	Group Art Unit:	3686
Customer No.:	107632	Confirmation No.:	5805

Notice of Allowance Date: March 14, 2014

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We are transmitting herewith the following:

X Issue Fee Transmittal (Form PTOL-85).
X Communication Re: Fee Address (1 page).
X Authorization to charge Deposit 19-0743 in the amount of $960.00 to cover the Large Entity Issue Fee Payment.

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

SCHWEGMAN, LUNDBERG & WOESSNER, P.A. By /David D'Zurilla/
Customer No.: 107632
David D'Zurilla
Reg. No. 36,776

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 3rd day of April, 2014.

Melissa Cuff
Name

/Melissa Cuff/
Signature

S/N 13/592,202 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Dayton T. Reardan Ph.D et al.	Examiner: Lena Najarian	
Serial No.:	13/592,202	Group Art Unit: 3686	
Filed:	August 22, 2012	Docket No.: 101.031US9	
Customer No.:	107632	Confirmation No.: 5805	
Title:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD		

COMMUNICATION RE: FEE ADDRESS

Mail Stop Issue Fee
Commissioner for Patents
P.O.Box 1450
Alexandria, VA 22313-1450

In response to the Notice of Allowance and Issue Fee Due, please record the Fee Address under the provisions of 37 CFR 1.363 as the following:

Customer Number 107632

which is associated with Jazz Pharmaceuticals, Inc..

Please direct any inquiries to the undersigned attorney at (612) 371-2140.

Respectfully submitted,

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

/ /

Date April 3, 2014 By _____
David D'Zurilla
Reg. No. 36,776

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 3rd day of April, 2014.

Melissa Cuff — Name

/Melissa Cuff/ — Signature

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	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
	US-20120209623 A1	8/16/2012	Reardan, Dayton T, et al.
	US-3,556,342	1/19/1971	Guarr, J. S.
	US-4,847,764	7/11/1989	Halvorson, J. L
	US-4,976,351	12/11/1990	Mangini, R. J, et al.
	US-5,737,539	4/7/1998	Edelson, J., et al.
	US-5,845,255	12/1/1998	Mayaud, Christian
	US-5,924,074	7/13/1999	Evans, Jae A.
	US-6,021,392	2/1/2000	Lester, Douglas D., et al.
	US-6,045,501	4/4/2000	Elsayed, Marc, et al.
	US-6,055,507	4/25/2000	Cunningham, David W.
	US-6,112,182	8/29/2000	Akers, William Rex, et al.
	US-6,315,720	11/13/2001	Williams, Bruce A., et al.
	US-6,347,329	2/12/2002	Evans, Jae A.
Change(s) applied to document, /M.A./ 2/18/2014	~~US-6,561,977~~	2/3/2004	Denny, Lawrence A. 6,687,676
	US-6,564,121	5/13/2003	Wallace, R. L, et al.
	US-6,755,784	6/29/2004	Williams, Bruce A., et al.
	US-6,952,681	10/4/2005	McQuade, R., et al.
	US-7,058,584	6/6/2006	Kosinski, D. L, et al.
	US-7,668,730	2/23/2010	Reardon, D. T, et al.
	US-7,765,106	7/27/2010	~~Dayton, T. R.~~, et al. Reardan
	US-7,765,107	7/27/2010	~~Dayton, T. R.~~, et al. Reardan
	US-7,797,171	9/14/2010	Reardan, D T, et al.
	US-7,895,059	2/22/2011	Reardan, D. T, 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
	"An Interview with Orphan Medical about Xyrem", http://www.talkaboutsleep.com/sleepdisorders/archives/Narcolepsy_xyrem_interview.htm, (Feb. 12, 2001), 3 pgs.	
	"Application Serial No. 10/322,348, Advisory Action mailed 02-05-07", 3 pgs	
	"Application Serial No. 10/322,348, Appeal Brief filed 05-21-07", 32 pgs	
	"Application Serial No. 10/322,348, Examiner Interview Summary mailed 10-21-09", 3 pgs	
	"Application Serial No. 10/322,348, Final Office Action mailed 10-18-06", 14 pgs	
	"Application Serial No. 10/322,348, Final Office Action mailed 12-29-05", 11 pgs	
	"Application Serial No. 10/322,348, Non Final Office Action mailed 06-17-05", 26 pgs	
	"Application Serial No. 10/322,348, Non Final Office Action mailed 06-19-06", 18 pgs	

EXAMINER /Lena Najarian/ **DATE CONSIDERED** 05/30/2013

* 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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /L.N./

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/592,202	05/20/2014	8731963	101.031US9	5805

107632 7590 04/30/2014

Schwegman Lundberg & Woessner/Jazz Pharmaceutical
P.O. Box 2938
Minneapolis, MN 55402

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

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 Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

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

IN UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.:	8,731,963 B1	Docket No:	101.031US9
Issue Date:	May 20, 2014	Patentee:	Reardan et al.
Customer No.:	107632	Confirmation No.:	5805
Title	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD		

REQUEST FOR CERTIFICATE OF CORRECTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
ATTN: CERTIFICATE OF CORRECTION BRANCH

It is requested that a Certificate of Correction be issued correcting printing errors appearing in the above-identified United States patent. A copy of the text of the Certificate in the suggested form is enclosed.

Authorization to charge Deposit Account No. 19-0743 in the amount of $100.00 to cover the Certificate of Correction Fee.

Issuance of the Certificate of Correction would neither expand nor contract the scope of the claims as properly allowed, and re-examination is not required.

The Examiner is authorized to 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 : September 3, 2014

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

PTO/SB/44 (02-01)
Approved for use through 01/31/2004. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO : 8,731,963 B1 Page (1) of 2

DATED : May 20, 2014

INVENTOR(S) : 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:

On page 2, in column 2, under "Other Publications", line 1, delete "mailed" and insert --filed--, therefor

On page 2, in column 2, under "Other Publications", line 24, delete "mailed" and insert --filed--, therefor

On page 2, in column 2, under "Other Publications", line 42, delete "mailed" and insert --filed--, therefor

On page 2, in column 2, under "Other Publications", line 54, delete "mailed" and insert --filed--, therefor

On page 3, in column 2, under "Other Publications", line 54, delete "Sodiium" and insert --Sodium--, therefor

On page 3, in column 2, under "Other Publications", line 57, delete "Sodiium" and insert --Sodium--, therefor

In the drawings, Sheet 9 of 16, Fig. 6, delete "236" and insert --610--, therefor

On sheet 9 of 16, Fig. 6, delete "236" and insert --612--, therefor

On sheet 9 of 16, Fig. 6, delete "236" and insert --630--, therefor

MAILING ADDRESS OF SENDER:

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

Atty Docket No: 101.031US9

PATENT NO. _____8,731,963_____

No. of additional copies

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PTO/SB/44 (02-01)
Approved for use through 01/31/2004. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO : 8,731,963 B1

DATED : May 20, 2014

INVENTOR(S) : 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:

On sheet 9 of 16, Fig. 6, delete "350" and insert --640--, therefor

On sheet 12 of 16, Fig. 11, delete "XYREEM" and insert --XYREM--, therefor

In column 4, line 21, delete "RX/enrollment" and insert --Rx/enrollment--, therefor

In column 6, line 16, delete "302" and insert --402--, therefor

In column 6, line 25, after "pre-delivery", delete "30", therefor

In column 11, line 14, in Claim 24, after "drug,", insert --and--, therefor

MAILING ADDRESS OF SENDER:

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

Atty Docket No: 101.031US9

PATENT NO. _____8,731,963_____

No. of additional copies

⇨ _____

Electronic Patent Application Fee Transmittal

Application Number:	13592202
Filing Date:	22-Aug-2012
Title of Invention:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
First Named Inventor/Applicant Name:	Dayton T. Reardan
Filer:	Mark Victor Muller/Melissa Cuff
Attorney Docket Number:	101.031US9

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Certificate of Correction	1811	1	100	100
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**100**

Electronic Acknowledgement Receipt

EFS ID:	20037046
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:	107632
Filer:	Mark Victor Muller/Melissa Cuff
Filer Authorized By:	Mark Victor Muller
Attorney Docket Number:	101.031US9
Receipt Date:	03-SEP-2014
Filing Date:	22-AUG-2012
Time Stamp:	16:54:16
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$100
RAM confirmation Number	3435
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)	

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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		8731963COC1.pdf	74572 223e4d5bff9581a2aa1a1ea03ede36a008db5e90	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	Start	End
	Transmittal Letter	1	1
	Request for Certificate of Correction	2	2
	Miscellaneous Incoming Letter	3	4

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	29861 2024bd6e488c5553812ae8b2f3ca3f25b8b1bc1d	no	2

Warnings:

Information:

Total Files Size (in bytes):	104433

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: Reardan et al.

Examiner: Lena Najarian

Patent No.: 8,731,963 B1

Group Art Unit: 3686

Issue Date: May 20, 2014

Docket No: 101.031US9

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
ATTN: CERTIFICATE OF CORRECTION BRANCH

We are transmitting herewith the attached:

X Request for Certificate of Correction. (1 pg.)
X Certificate of Correction Form - PTO-1050 (2 pg.)
X Authorization to charge Deposit Account No. 19-0743 in the amount of $100.00 to cover the Certificate of Correction Fee.

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

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
Customer No: 107632

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

CERTIFICATE UNDER 37 CFR § 1.8: The undersigned hereby certifies that this correspondence is filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313-1450, on this 3rd day of September 2014.

Melissa Cuff
Name

/Melissa Cuff/
Signature

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
2:14–cv–05139–KM–MAH	8/15/2014	NEWARK, NJ

PLAINTIFF	DEFENDANT
JAZZ PHARMACEUTICALS, INC.	PAR PHARMACEUTICAL, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,731,963	5/20/2014	
2		
3		
4		
5		

In the above–entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	**DATE OF PATENT OR TRADEMARK**	**HOLDER OF PATENT OR TRADEMARK**
1		
2		
3		
4		
5		

In the above–entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Christine Melillo	8/15/2014

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy