Time Point	Total Patients at Time Point	Number of Patients With Abnormality (%)
<= 3 months	12	3 (25.0%)
> 3 - <= 6 months	42	2 (4.8%)
> 6 - <= 12 months	82	13 (31.0%)
> 1 - <= 2 years	37	13 (35.1%)
> 2 - <= 5 years	39	17 (43.6%)
> 5 - <=10 years	38	16 (42.1%)
>10 years	22	9 (40.9%)

- The individual patient listings for abnormal laboratory results do not indicate any items of concern.
  - The abnormalities of bicarbonate were all elevations ranging from 31 to 38 mEq/L with only 9 individual readings being > 34 mEq/L; in all 9 instances the values subsequently fell to ≤ 34 mEq/L
  - Abnormalities of random blood glucose consisted of elevations in the vast majority of instances; in many of those instances serial blood glucose estimations were consistently elevated such that these individuals could have had diabetes mellitus. 4 patients had random blood glucose readings that were considered low and ranged from 38 – 48 mg/dL; at least 1 of these patients had elevated blood glucose readings subsequently.
  - There are no clinical details available for these patients and it appears unlikely that these abnormalities were attributable to GHB. Similar elevations in serum bicarbonate were not seen in the Integrated Clinical Trials

8.6.3.3.3 LABORATORY ADVERSE EVENTS

There were no laboratory adverse events that had a frequency ≥ 5%. There were no adverse event discontinuations on account of abnormal standard laboratory tests (positive antinuclear antibody tests which led to treatment discontinuation in 2 patients are discussed in Section)

8.7 Vital Signs

8.7.1 Extent of Vital Sign Testing During Development

The data below refer only to post-treatment vital sign testing

8.7.1.1 Integrated Clinical Trials

Vital signs recorded and analyzed included sitting and standing blood pressure, heart rate, respiration, body temperature and body weight.

The frequency at which vital signs were intended to be checked (as per protocol) in these studies is indicated in the following table

Study #	Frequency of vital sign testing
OMC-GHB-2	Screening, end-of washout period, baseline, weekly during the 4 weeks of study drug administration and 3-5 days after completion of study drug

Study #	Frequency of vital sign testing
OMC-GHB-3	Baseline, 2 weeks and Months 1, 2, 4, 5, 6, 8, 10, 12, 14, 16, 18, 21 and 24
OMC-SXB-6	Screening, Week 2 and Months 2 and 6
OMC-SXB-7	Baseline and Months 6, 12, 18 and 24
Scrima	No provision for checking vital signs

8.7.1.2 Lammers Trial

There was no provision for recording vital signs during this trial

8.7.1.3 Integrated Pharmacokinetic Trials

Vital signs recorded and analyzed, when specified, included sitting and standing blood pressure, heart rate, respiration, body temperature and body weight.

Vital signs were to be checked in each of the single-dose pharmacokinetic trials as follows.

Study #	Frequency of Vital Sign Checks
OMC-GHB-4	Baseline and 60 hours after dosing
OMC-SXB-8	Baseline and 2, 4 and 8 hours after dosing
OMC-SXB-9	Baseline and 2, 6 and 10 hours after dosing
OMC-SXB-10	Baseline and 1, 3, and 8 hours after dosing
OMC-SXB-11	Baseline and 2, 6 and 10 hours after dosing
OMC-SXB-12	Baseline and 1, 2, 6 and 10 hours after dosing
OMC-SXB-14	Baseline and 2, 6, 10 and 24 hours after dosing
OMC-SXB-17	Baseline and 1, 2, 6 and 10 hours after dosing

8.7.1.4 Scharf Trial

There was no provision for checking vital signs in the protocol or Case Report Form.

8.7.2 Selection of Studies for Overall Drug-Control Comparisons And Other Analyses

3 study groupings have been selected

- Controlled Clinical trial: OMC-GHB-2 (this was the only controlled clinical trial in which vital signs were checked after administration of study drug)
- Integrated Clinical Trials
- Integrated Pharmacokinetic Trials

8.7.3 Standard Analyses and Explorations of Vital Sign Data

8.7.3.1 Controlled Clinical Trial OMC-GHB-2

The sponsor has provided a table that displays descriptive statistics for changes in vital signs across dose groups from baseline to Visit 6 (end of period of double-blind treatment). The mean changes seen were not clinically significant. The data suggested a dose-related decrease in weight and sitting diastolic blood pressure. An abbreviated form of the sponsor's main table, including only mean changes is reproduced below

Changes from baseline to Visit 6 in vital signs

Changes in vital signs	Placebo	GHB dose (g) 3	6	9
Weight (kg) - mean	0.69	-0.09	-0.34	-0.8
Sitting systolic blood pressure (mm Hg) - mean	1.41	3.56	-1.10	-0.31
Sitting diastolic blood pressure (mm Hg) - mean	2.09	0.53	0.77	-1.83
Standing systolic blood pressure (mm Hg) - mean	4.26	5.47	-1.55	0.00
Standing diastolic blood pressure (mm Hg) - mean	1.74	0.63	-0.55	-2.79
Pulse rate (bpm) - mean	-0.94	1.0	3.16	-1.76
Respiration (breaths per minute) - mean	-0.24	-0.87	-0.2	-0.19

The sponsor's main table also indicates that there were no clinically significant differences between the placebo group and the individual GHB dose groups in minimum and maximum changes for the above adverse events.

8.7.3.2 Integrated Clinical Trials

The sponsor has presented a table containing descriptive statistics for the change from baseline to last observation in vital signs. The tables indicate that mean changes for all parameters were very small and similar across all treatment groups. I have not reproduced these vital signs.

8.7.3.3 Integrated Pharmacokinetic Trials

Individual data listings have been made available for all pharmacokinetic trials except OMC-GHB-4; for the latter trial descriptive statistics have been made available for vital signs.

These data do not reveal any changes that could be considered clinically significant.

8.8 ECG

8.8.1 Extent of Electrocardiogram Testing During Development

The data below refer only to post-treatment electrocardiograms

8.8.1.1 Integrated Clinical Trials

Standard 12-lead resting electrocardiograms were performed.

The frequency at which electrocardiogram testing were intended to be checked (as per protocol) in these studies is indicated in the following table

Study #	Frequency of electrocardiogram testing
OMC-GHB-2	Screening and end of period of study drug administration
OMC-GHB-3	Baseline and Months 6, 12 and 18
OMC-SXB-6	Screening, and Month 6 (if medically indicated)
OMC-SXB-7	No provision for checking electrocardiograms
Scrima	No provision for checking electrocardiograms

8.8.1.2 Lammers Trial

There was no provision for checking electrocardiograms during this trial

8.8.1.3 Integrated Pharmacokinetic Trials

No post-treatment electrocardiograms were checked during these trials

8.8.1.4 Scharf Trial

A standard 12-lead electrocardiogram was to be checked at or prior to study entry, and annually thereafter

8.8.2 Selection of Studies for Overall Drug-Control Comparisons And Other Analyses

3 study groupings have been selected

- Controlled clinical trial: OMC-GHB-2
- Integrated Clinical Trials
- Scharf trial

8.8.3 Standard Analyses and Explorations of Electrocardiogram Data

8.8.3.1 Controlled Clinical Trial: OMC-GHB-2

The number and percentage of patients in each treatment group whose values went from normal to abnormal in each treatment group between the baseline and Week 6 (end of double-blind period) visits is summarized in the following table

Treatment Group	Number	Patient ID #s
Placebo	2 (6 %)	512, 818
GHB 3 g	2 (6 %)	407, 1610
GHB 6 g	1 (3.5 %)	105
GHB 9 g	3 (11.5 %)	206, 217, 1309

Details of all 8 patients are summarized in the following table

Abnormal ECGs at Visit 6

Patient number	Visit 1 Interpretation	Visit 6 Comments on abnormality	Follow-up (for ECGs not labeled NCS at V6)
105	Within normal limits	Sinus bradycardia – not clinically significant	
206	Within normal limits	Consider left atrial enlargement	Not clinically significant as determined by site
217	Within normal limits	Sinus arrythmia, vertical axis	Not clinically significant as determined by site
407	Within normal limits	Normal sinus rhythm, nonspecific T wave abnormality	Not clinically significant as determined by site No Change from baseline, CRF incorrectly reported
512	Within normal limits	QRS axis range 0 to 14 horizontal axis- not clinically significant	
818	Within normal limits	Sinus tachycardia - not clinically significant	
1309	Within normal limits	OCL unifocal ventricular extra beat (VPC), RR complex V1-V2 indicate primary right bundle branch block with QRS 0.10-0.11 seconds	ECG was repeated on 12/30/97 and read by Dr. Froeb. It was interpreted as Borderline ECG Within normal limits
1610	Within normal limits	Nonspecific T-wave abnormality in anterior-lateral leads when compared with ECG 08/08/97 per Dr Kathawalla - change possibly due to hypokalemia - not clinically significant	

None of the above electrocardiogram abnormalities was felt to be clinically significant.

8.8.3.2 Integrated Clinical Trials

The sponsor has presented shift tables for the categorical change from baseline to last observation in vital signs. The shift categories were:

Abnormal to abnormal	Within normal limits to abnormal
Abnormal to within normal limits	Within normal limits to within normal limits
Abnormal to not done	Within normal limits to not done

The tables indicate that no shifts of > 10% were seen for the entire population or for the "normal to abnormal" category in any single electrocardiogram parameter.

For the within normal limits to abnormal category the distribution was as follows

Dose Group	Placebo	3 g/day	4.5 g/day	6 g/day	7.5 g/day	9 g/day	Total
Number With Change	o	0	2	3	1	3	9
Total number in dose group	3	26	88	141	61	83	402

Note that all patients in each dose group did not have electrocardiograms done both at baseline and subsequently, the last row cannot therefore be used as a denominator to calculate percentages for the second row

8.8.3.3 Scharf Trial

All electrocardiograms in the study were categorized as being normal or abnormal and a shift table generated which demonstrates categorical change by dose group from baseline. This table is reproduced below.

ECG Shift	GHB dose (g) n (%) All Patients	3	4.5	6	7.5	9
Norm to Norm	9 (6.3)	0 (0.0)	3 (6.1)	4 (6.5)	2 (11.1)	0 (0.0)
Norm to Abn[1]	36 (25.2)	1 (20.0)	11 (22.4)	16 (25.8)	4 (22.2)	4 (44.4)
Abn to Norm[2]	5 (3.5)	0 (0.0)	3 (6.1)	2 (3.2)	0 (0.0)	0 (0.0)
Abn to Abn	39 (27.3)	0 (0.0)	13 (26.5)	19 (30.6)	5 (27.8)	2 (22.2)

[1]Patients included if they had a normal baseline ECG and had an abnormal ECG anytime while receiving GHB.
[2]Patients included if they had an abnormal baseline ECG and had a normal ECG anytime while receiving GHB.

Source: Section 15~Table 8

Note that of those patients who had baseline electrocardiograms, some had a single repeat recording whether others had multiple recordings done. The interval between recordings was highly variable.

Of the 36 patients who had electrocardiograms that were normal at baseline but abnormal later

- 28 patients had abnormalities that were considered “non-specific, benign and highly unlikely to be clinically significant”
- In the remaining 8 patients the abnormalities were considered to possibly be clinically significant, but probably not related to study medication. The sponsor has provided short descriptions of the conclusions(diagnoses) drawn for the electrocardiograms for these 8 patients. The diagnoses reached in these 8 patients were distributed in the following 4 categories: except for 1 patient each who were considered to have acute pericarditis and ischemic heart disease, the remainder had multiple electrocardiograms. No additional information is available for these patients and there is no evidence that an attempt was made to correlate electrocardiogram abnormalities with symptoms, physical signs or other cardiac tests in these patients.

Left ventricular hypertrophy	1 patient
Ischemic heart disease	3 patient
Conduction system disease	3 patient
Acute pericarditis	1 patient

8.9 Withdrawal Phenomenon and Abuse Potential

An separate review of this subject is being performed by the Controlled Substances Staff of this Agency

8.9.1 Background

As indicated earlier in this review, for many years GHB was distributed in this country as a health food product under a variety of trade names; in 1990 it was removed from the market by this Agency after a number of reports of adverse reactions.

Public Law 106-172 (passed by the United State Congress on February 18, 2000) has allowed for the designation of GHB as a Schedule I agent, with exemption from the security requirements of that schedule for the GHB drug product studied under an FDA-approved IND. Upon marketing approval from the FDA being received, the GHB drug product would become a Schedule III agent with Schedule I penalties for illicit use. All other forms and uses of GHB-containing products would remain under Schedule I, except that use under an FDA-approved IND would be exempted (as noted above).

There have been many reports in the media, over the last few years, of instances of overdose with illegally-manufactured GHB. A number of anecdotal single case reports/case series of a similar nature have also been published in the medical literature. There have also been similar reports linked to the use of related compounds such as gammabutyrolactone (GBL) and 1,4-butanediol (1,4-BD), both of which are converted to GHB in the body.

According to the sponsor, illicit GHB users in this country obtain the drug from the following sources

- Purchase from illegal vendors, including those selling the drug over the Internet
- By home manufacture: both recipes and starting materials are easily available

8.9.2 Purposes For Which GHB Is Misused Or Abused

These are listed by the sponsor as follows:

- As a steroid replacement in the body building community
- As a sleep aid
- As an intoxicant
- As an aphrodisiac
- As a means of enhancing the effects of alcohol and stimulants
- As a “date-rape” drug (related to its sedative and alcohol-enhancing properties)

8.9.3 Clinical Psychological And Physical Dependence In Humans

The sponsor states the following.

- Sodium oxybate does not appear to produce strong psychological or physical dependence

- No formal studies have been conducted to assess dependence with GHB
- A few case reports have suggested that chronic high-dose GHB use outside a clinical setting can, when the drug is withdrawn, lead to an abstinence syndrome comprising insomnia, anxiety, tremors and hallucinations. In the same setting dose-escalation to maintain a clinical effect has also been described. Several case reports also suggest that users outside a clinical setting may sometimes increase their dose to maintain a clinical effect.
- However
  - When GHB was discontinued after 3- and 6-month clinical trials for the treatment of alcohol withdrawal, no abstinence syndrome was seen. However during the 6-month trial an escalation of GHB consumption and craving for that drug was reported in about 10% of patients
  - In a clinical study of GHB in 48 narcoleptic patients, lasting 9 years, no tolerance to the effects of GHB was observed.
- Anecdotal reports and controlled trials suggest a potential cross-tolerance or dependence with alcohol. In alcoholics GHB may not only reduce the symptoms of alcohol withdrawal but may also decrease the consumption of and craving for alcohol
- GHB also relieves the abstinence syndrome that follows spontaneous opiate withdrawal; a similar effect on precipitated opiate withdrawal is blocked by naloxone.

8.9.4 Rebound Symptoms With GHB Withdrawal

In the randomized, double-blind, placebo-controlled, parallel-arm trial OMC-GHB-2, the incidence of adverse events suggestive of REM rebound (sleep disturbance, hallucinations, abnormal dreaming), and the incidence of cataplexy was compared between the following 2 periods

- The period of up to 5 days prior to the completion of double-blind treatment
- A period of up to 5 days between the cessation of double-blind treatment and the post-treatment follow-up visit

The difference in the incidence of adverse events was reported by the sponsor not to be statistically significant. Comparative data are not provided by the sponsor.

The sponsor has however supplied listings of adverse events which might be suggestive of REM rebound during the withdrawal period. 6 patients experienced such adverse events (each patient experienced one adverse event). These are listed in the following table

GHB dose during double-blind phase	Adverse events during withdrawal phase
3 g/day	Abnormal dreaming (1 patient) Sleep disorder (1 patient)
6 g/day	Abnormal dreaming (1 patient) Sleep disorder (1 patient)
9 g/day	Hallucinations (1 patient) Sleep disorder (1 patient)

All adverse events were mild and, except for the instance of “sleep disorder” seen in a patient who received 3 g/day previously (in whom the adverse event

lasted 7 days), lasted 1-2 days only. It is unclear exactly what the term "sleep disorder" refers to.

The sponsor also states that there was no tendency to rebound cataplexy during the short period of withdrawal.

8.9.5 Extent Of GHB Abuse In The United States

According to the sponsor

- Sodium oxybate abuse is mentioned relatively infrequently in Drug Abuse Warning Network reports compared with other sedative/hypnotics that are abused such as benzodiazepines
- Currently sodium oxybate abuse is too rare to be listed in any database
  - In the Drug Enforcement Administration June 1998 Drug/Chemical Review it was stated that 1000 encounters with GHB had been documented over an unspecified period of time
  - Only 32 cases of GHB misuse or abuse had been reported over an 18-month period ending December 1997 in a report presented at a February 1998 American Academy of Pediatric Sciences meeting
  - The Mid-Year 1999 Preliminary Emergency Department Data from the Drug Abuse Warning Network had no mention of GHB
- Only one GHB-related death was reported to the Drug Abuse Warning Network by participating medical examiners between 1992 and 1995; in this instance the death occurred in an individual who had concurrently used alcohol and GHB.

8.9.6 Pre-Clinical Studies Of Drug Abuse Potential

The sponsor has outlined the results of a battery of animal studies that have been done with GHB. These consist of studies of drug discrimination, reinforcing effects, and tolerance and dependence.

A full review of these studies is beyond the competence of this reviewer.

Based on these studies the sponsor has made the following conclusions:

- Drug discrimination studies consistently fail to show cross-substitution with abused depressant drugs such as the benzodiazepines and barbiturates, although there is evidence for some cross-substitution with ethanol over a narrow dose range
- Self-administration studies fail to show evidence for strong reinforcing effects
- Repeated administration of sodium oxybate may result in the development of tolerance.
- Overall, "based on preclinical studies alone, there is no compelling evidence that sodium oxybate represents a significant drug abuse hazard."

8.10 Human Reproduction Data

A single patient is reported to have become pregnant while taking GHB. She is described briefly in Section 8.3.1.5

8.11 Overdose

8.11.1 Background

Descriptions of the clinical effects of GHB overdose are derived almost entirely from anecdotal reports related to illegal use of the drug

Section 8.9.2 describes the circumstances under which GHB is used or abused.

When the above anecdotal reports are reviewed, the identification of the dose of GHB used and determining the causal relationship of the clinical syndrome described to GHB are both problematic for the following reasons.

- The sources of the drug are clandestine and varied, as are the starting materials used to manufacture the drug, and the dose ingested therefore unknown in most instances; in addition an evaluation of illegally manufactured sodium oxybate liquid samples has shown a high level of inconsistency of content.
- In a number anecdotal reports, precursor chemicals, i.e., gammabutyrolactone (GBL) and 1,4-butanediol have been ingested, rather than GHB to which the adverse events have been attributed. Although these precursor chemicals are converted to GHB in the body, their pharmacokinetics are different from GHB: for example, GBL is more lipid soluble and more rapidly absorbed
- Other drugs of abuse are frequently used concurrently including alcohol, methamphetamine, and MDMA. In such instances the adverse event has been attributed to GHB based, in most instances, on the clinical history alone; blood and tissue levels of GHB have been measured only rarely. Thus in those instances it has been difficult to know to what extent GHB contributed to the patient's clinical syndrome.

Of the 5 deaths reported in the medical literature and attributed to GHB consumption, only one was clearly linked to GHB use alone.

8.11.2 Clinical Presentation

According to the sponsor the clinical presentation of GHB overdose is influenced by the dose and frequency of ingestion, and most importantly, concurrent use of other drugs.

Patients presenting in a conscious state may be agitated, combative, anxious and confused, and may exhibit hallucinations. Varying degrees of obtundation may also be seen extending to deep coma that is unresponsive even to pain; deep coma has been associated with doses ranging from 2.5 g to 30 g. With an increased depths of unconsciousness the following may also be observed: bradycardia, hypotension, depressed respiration/Cheyne-Stokes breathing and hypothermia. Obtundation may be potentiated by the concurrent use of alcohol.

Other symptoms and signs may include dizziness, nausea, vomiting, myoclonus, blurred vision, visual field abnormalities, sluggish pupillary reactions, amnesia and hypotonia.

Symptoms may appear as early as 15 minutes after ingestion and may persist for 2 to 96 hours

Note that in the NDA safety database, 2 patients took, or are presumed to have taken overdoses. These patients are further described in Sections 8.3.1.1 and 8.3.2.2.

A further instance of Xyrem® overdose has been reported in the 120-Day Safety Update (see Section 13.10.4)

8.11.3 Treatment

According to the sponsor the treatment of GHB overdose is primarily symptomatic and supportive. The measures to be instituted include

- care of the airway, with intubation and artificial ventilation as needed
- consideration of gastric aspiration and lavage with activated charcoal
- measurement of blood levels of GHB.

While flumazenil and naloxone are ineffective for the treatment of GHB intoxication, intravenous physostigmine has been reported anecdotally to produce rapid reversal of obtundation.

9. Study OMC-SXB-20

This was an open-label study that was intended to evaluate the effects of 4 doses of Xyrem® on sleep architecture. The study report was submitted on 12/16/00, i.e., after the original NDA submission. The sponsor desires that the results of this study be included in labeling.

A brief outline of the study protocol and safety data from this study are presented below.

9.1 Objectives

9.1.1 Primary

The primary objective of this study was to characterize the polysomnographic sleep architecture in narcoleptic patients at 4 GHB doses: 4.5 g, 6.0 g, 7.5 g and 9 g daily

9.1.2 Secondary

The secondary objectives of the study were to

- Assess the effect of Xyrem® on sleep as measured by the Epworth Sleepiness Scale
- Assess the effects of Xyrem® on common symptoms of narcolepsy as measured by the Narcolepsy Symptoms Assessment

- Assess EEG measures of wakefulness under soporific conditions using the Maintenance of Wakefulness Test
- Assess the safety of Xyrem®

9.2 Design/Summary of Investigational Plan

This was an open-label uncontrolled study divided into 2 phases. Stimulant medication was maintained at a constant level during the trial

9.2.1 Phase I

This phase lasted 4 weeks

- In the initial 2 weeks of this phase patients were withdrawn from tricyclic antidepressants, selective serotonin re-uptake inhibitors and hypnotics
- In the last 2 weeks of this phase patients remained free of tricyclics

An overnight polysomnogram was performed at the beginning and end of this phase. The Epworth Sleepiness Scale questionnaire was administered at about the time of each polysomnogram

9.2.2 Phase II

This phase began with the patient receiving 4.5 g of GHB nightly for the initial 4 weeks. At the end of this period the dose was increased to 6.0 g nightly and further to 7.5 g nightly and 9 g nightly at 2 week intervals

Overnight polysomnograms on the night of the first dose of Xyrem® and on the last night of each dose. The Epworth Sleepiness Scale was administered at the end of each dosing period

9.3 Duration

10 weeks

9.4 Sample Size

20-30 planned

9.5 Key Inclusion Criteria

- Informed consent
- Age ≥ 18 years
- American Sleep Disorders Association criteria for narcolepsy
- Use of stable doses of tricyclic antidepressants or selective serotonin re-uptake inhibitors for narcolepsy for at least 3 weeks. If taking stimulants must have been on a stable dose for at least 3 weeks
- If female must be
  - Surgically sterile OR
  - 2 years post-menopausal OR
  - If of child-bearing potential must be using effective contraception and must continue this treatment during the study
- Adequate support for duration of trial

9.6 Key Exclusion Criteria

- Unstable diseases in any body system, other than narcolepsy, which would place the patient at risk or compromise the trial objectives
- Use of tricyclic antidepressants or selective serotonin re-uptake inhibitors for depression or for any indication other than narcolepsy
- History of substance abuse, as defined by DSM-IV, currently or within the past year
- History of psychiatric disorders that would preclude study participation
- Serum creatinine > 2 mg/dl; AST or ALT > 2 x upper limit of normal; serum bilirubin > 1,5 x upper limit of normal; pre-trial electrocardiogram results demonstrating a clinically significant arrhythmia or 2nd or 3rd degree A-V block; history of myocardial infarction within the past 6 months
- Any untreated disorder other than narcolepsy that could be considered a primary cause of excessive daytime sleepiness, including sleep apnea syndrome (criteria specified)
- Occupation requiring variable shift or routine night shift work
- Use of sodium oxybate within the preceding 30 days
- Use of any investigational drug within the preceding 30 days
- No clinically significant history of head trauma, seizure disorder or previous intracranial surgery
- Willing to not operate a car or heavy machinery if the clinical investigator feels such a restriction is warranted
- Use of medication for narcolepsy during baseline period, other than a stable dose of stimulant medication ("stable dose" defined as one without any significant change in dose for the 5 - day period just prior to the baseline period)
- Use of hypnotics, tranquilizers, antihistamines (except for the non-sedating variety of such drugs) and clonidine at the start of the baseline period.

9.7 Dosage

See Section 9.2

9.8 Outcome Measures

9.8.1 Primary Efficacy Measures

The following objective overnight polysomnogram parameters

- Wake After Sleep Onset (WASO) in minutes following the first and second dose of Xyrem and the summation
- Total Sleep Time (TST) in minutes following the first and second dose of Xyrem and the summation
- Stage 1 sleep time in minutes following the first and second dose of Xyrem and the summation
- Stage 2 sleep time in minutes following the first and second dose of Xyrem and the summation
- Stage 3 & 4 sleep time in minutes following the first and second dose of Xyrem and the summation

- Rapid Eye Movement (REM) sleep time in minutes following the first and second dose of Xyrem and the summation
- Sleep latency in minutes following the first and second dose of Xyrem
- REM sleep latency in minutes following the first and second dose of Xyrem
- Stage shifts per hour following the first and second dose of Xyrem and an average
- Total awakenings following the first and second dose of Xyrem® and the summation
- Delta power in microvolts^2/Hz following the first and second dose of Xyrem and an average

9.8.2 Secondary Efficacy Measures

- Epworth Sleepiness Scale
- Narcolepsy Symptoms Assessment
- Maintenance of Wakefulness Test

9.8.3 Safety Measures

Adverse events, safety laboratory tests, vital signs, electrocardiograms and physical examinations

9.9 Analysis Plan

- Demographic variables at baseline were summarized as follows
  - Gender and race were summarized by the number of patients in each category
  - Age, height and weight were summarized by descriptive statistics
- Efficacy variables were analyzed as follows
  - Inferential statistics were performed for descriptive purposes only as per the sponsor
  - Quantitative polysomnogram variables and the Epworth Sleepiness Scale were analyzed using 2-way ANOVA with patient and dosage as the main effects
  - If a statistically significant difference was found among dose groups using ANOVA, pairwise comparisons using the least significant difference test were performed. If the assumptions for the above ANOVA were not satisfied the rank changes from baseline were analyzed using the ANOVA model. The significance of the mean change from baseline (end of Phase I) in each dose group was determined using a paired t-test or a Wilcoxon signed rank test
  - For the above analysis the level of statistical significance was 0.05 (two-sided)
  - Variables for the narcolepsy symptom questionnaire measured as a change from the beginning of Phase I were presented by number and percentage of patients
- Safety analyses were performed as follows
  - Adverse events were summarized by body system using COSTART term and by relationship to treatment, dose and severity
  - Changes from the beginning of Phase 1 to the end of the study in laboratory parameters were summarized using descriptive statistics
  - Changes from the end of Phase I to the end of the study in vital signs were summarized using descriptive statistics
  - Changes from the beginning of Phase I to the end of the study in electrocardiogram parameters were summarized

9.10 Results

9.10.1 Patient Disposition

- 27 patients were enrolled in the study
- 25 patients were treated with GHB
- 21 patients completed the study

9.10.2 Baseline And Demographic Characteristics

Baseline and demographic characteristics for all 25 treated patients are summarized below

Variable	Mean	Standard Deviation
Age (years)	52.6	8.77
Weight (kg)	84.2	16.36
Height (cm)	166.9	8.32

Gender: Males 28%; Females 72%
Race: Caucasian 92%; Black 8%

9.10.3 Tricyclic Antidepressants, Selective Serotonin Re-Uptake Inhibitors And Hypnotics At Baseline

These are summarized in the next table, copied from the submission.

Preferred Term	Total
Number of Patients	25 (100%)
Patients Receiving Medications	22 (88%)
Clomipramine	3 (12%)
Fluoxetine	5 (20%)
Fluvoxamine	1 (4%)
Paroxetine	2 (8%)
Protriptyline	1 (4%)
Sertraline	4 (16%)
Venlafaxine	6 (24%)

TCA = Tricyclic antidepressant. SSRI = Selective serotonin reuptake inhibitors.
All medications were completed prior to the start of treatment.

9.10.4 Protocol Deviations

These are summarized in the next table copied from the submission. The table applies to all 25 treated patients

Type of Protocol Deviation	No. of Protocol Deviations
Inclusion/exclusion criteria	6
Compliance	7
Concomitant medication	28
Study visit interval	17
Error in dosing medication	23
Efficacy measure	33
Safety measure	
Laboratory procedure	2
Other safety measure	2
Other	7
Total	125

9.10.5 Treatment Compliance

Treatment compliance at each dose level is summarized in the following table copied from the submission. Mean compliance at each dose level was high.

	Dose (g)				
Number of Patients	4.5	6.0	7.5	9.0	Total
	25	22	22	21	25
Compliance (%)					
N	25	22	22	21	25
Mean	95.9	95.5	92.7	93.3	94.9
SD	11.45	9.63	9.06	13.85	7.62
Median	100.0	95.0	95.5	93.0	96.7
Minimum	58.5	70.3	67.0	61.0	70.0
Maximum	107.0	113.0	105.0	129.0	105.5

9.10.6 Extent Of Exposure

The mean duration of treatment was 63.3 nights (standard deviation: 21.29)

9.10.7 Efficacy Results

See summary in NDA Efficacy Review

9.10.8 Safety Results

9.10.8.1 All Adverse Events

18 out of 25 (72% of) patients participating in the study reported at least 1 adverse event.

A summary of adverse events in several broad categories, by dose at onset, is provided in the next table, copied from the submission.

	Xyrem Dosage at Onset (grams)				
	4.5	6.0	7.5	9.0	Total
Number of Patients	25 (100%)	22 (100%)	22 (100%)	21 (100%)	25 (100%)
All Events					
Patients with At Least One Adverse Event	10 (40%)	9 (41%)	6 (27%)	10 (48%)	18 (72%)
Patients with Serious Adverse Events	0	0	0	0	0
Patients with Related Adverse Events	6 (24%)	6 (27%)	5 (23%)	7 (33%)	11 (44%)
Patients with Severe Adverse Events	0	1 (5%)	0	0	1 (4%)
Patients Discontinued Due to Adverse Event	1 (4%)	0	1 (5%)	0	2 (8%)

Note that the patient listed in the table as having a SERIOUS adverse event did not in fact have one, according to the sponsor. 4 days prior to beginning study drug the patient was diagnosed to have a yeast infection and was treated with miconazole nitrate suppositories 5 mg daily. Her white blood cell count was elevated at 11.43 K/microliter at screening. After a single dose of Xyrem® 4.5 g she withdrew her consent to participate in the study and was not available for further visits or telephone contacts. I have reviewed the Case Report Form for this patient

The next 2 tables list treatment-emergent adverse events, by dose at onset, that occurred in ≥ 5% of patients in any dose group

COSTART Preferred Term	Xyrem Dosage at Onset (grams)				
	4.5	6.0	7.5	9.0	Total(a)
Number of Patients	25 (100%)	22 (100%)	22 (100%)	21 (100%)	25 (100%)
Patients With Adverse Events	10(40%)	9 (41%)	6 (27%)	10(48%)	18 (72%)
Body as a Whole	3 (12%)	3 (14%)	1 (5%)	2 (10%)	9 (36%)
Accidental Injury	0	1 (5%)	0	0	1 (4%)
Back pain	1 (4%)	0	1 (5%)	1 (5%)	3 (12%)
Flu syndrome	0	1 (5%)	0	0	1 (4%)
Infection	0	1 (5%)	0	1 (5%)	2 (8%)
Cardiovascular System	0	0	1 (5%)	0	1 (4%)
Migraine	0	0	1 (5%)	0	1 (4%)
Digestive System	4 (16%)	2 (14%)	0	6 (26%)	8 (32%)
Anorexia	0	0	0	3 (14%)	3 (12%)
Nausea	1 (4%)	2 (9%)	0	2 (10%)	5 (20%)
Vomiting	1 (4%)	1 (5%)	0	1 (5%)	3 (12%)
Metabolic and Nutritional System	1 (4%)	2 (9%)	1 (5%)	0	4 (16%)
Edema	1 (4%)	2 (9%)	0	0	3 (12%)
Generalized edema	0	0	1 (5%)	0	1 (4%)
Musculoskeletal System	1 (4%)	0	0	1 (5%)	2 (8%)
Myasthenia	0	0	0	1 (5%)	1 (4%)
Nervous System	3 (12%)	2 (9%)	2 (9%)	3 (14%)	8 (32%)
Anxiety	0	0	1 (5%)	0	1 (4%)
Dizziness	0	0	0	1 (5%)	1 (4%)
Emotional lability	2 (8%)	0	0	0	2 (8%)
Paresthesia	0	0	0	1 (5%)	1 (4%)
Sleep disorder	0	0	1 (5%)	1 (5%)	2 (8%)
Somnolence	0	2 (9%)	0	0	2 (8%)

COSTART Preferred Term	Xyrem Dosage at Onset (grams)				
	4.5	6.0	7.5	9.0	Total(a)
Number of Patients	25 (100%)	22 (100%)	22 (100%)	21 (100%)	25 (100%)
Respiratory System	1 (4%)	1 (5%)	1 (5%)	0	3 (12%)
Bronchitis	0	1 (5%)	0	0	1 (4%)
Respiratory disorder	0	0	1 (5%)	0	1 (4%)
Sinusitis	0	1 (5%)	0	0	1 (4%)
Skin	1 (4%)	1 (5%)	0	0	2 (8%)
Contact dermatitis	0	1 (5%)	0	0	1 (4%)
Special Senses	1 (4%)	0	1 (5%)	0	2 (8%)
Taste perversion	0	0	1 (5%)	0	1 (4%)
Urogenital System	1 (4%)	0	2 (9%)	0	2 (8%)
Breast abscess	0	0	1 (5%)	0	1 (4%)
Urinary incontinence	1 (4%)	0	1 (5%)	0	2 (8%)

(a) Patients are counted only once in each category, and only once in each body system summary.

A dose response did appear to be present for some adverse events such as anorexia, nausea and dizziness

9.10.8.2 Deaths And Serious Adverse Events

There were no deaths or serious adverse events. As noted earlier, the sole serious adverse event listed in the table in Section 9.10.8.1 was not a serious adverse event at all.

9.10.8.3 Adverse Event Discontinuations

2 patients discontinued treatment on account of adverse events. They are described further below:

9.10.8.3.1 PATIENT # 17304

This 67 year old woman had a past history of a tonsillectomy and of lumpectomy and radiation therapy for right-sided breast cancer.

In Study OMC-SXB-20 she received Xyrem® in the following consecutive dosing regimes: 4.5 g/day for 35 days; 6 g/day for 14 days; and 7.5 g/day for 1 day. On Study Day 51, after receiving her first dose of Xyrem® 7.5 g/day she experienced an "increase" in obstructive sleep apnea (it is unclear if she had obstructive sleep apnea earlier, either

preceding or during the trial) at which time Xyrem® was discontinued. Her subsequent course is unknown.

9.10.8.3.2 PATIENT # 42305

This 56 year old woman had a past history of depression with onset > 3 years prior to participating in the study. On Study Day 10 while receiving Xyrem® 4.5 g/day the patient experienced a worsening of depression; this adverse event resulted in her discontinuing Xyrem® on Day 27. Her depression reportedly resolved by Day 35

9.10.8.4 Laboratory Data

Mean changes from baseline and isolated abnormal values that were noted in the hematology and clinical chemistry data did not appear to be clinically significant. I have reviewed the individual patient data listings.

9.10.8.5 Vital Signs

Based on the descriptive statistics and individual listings provided, changes in vital signs were minimal and not clearly dose-related. I have reviewed the individual patient data listings.

9.10.8.6 Electrocardiograms

Only 1 patient had an electrocardiogram that was considered normal at baseline and abnormal at the end of the study. This abnormality was eventually determined to represent an old inferior wall myocardial infarction.

5 patients had electrocardiograms that were abnormal both at baseline and at study end. Details of the abnormalities noted are not provided.

9.11 Reviewer's Comments

The spectrum of adverse events seen in this study are broadly similar to those seen in other clinical studies of Xyrem® and do not raise any special concerns.

10. Safety Data From Study OMC-SXB-21

This study was intended to assess the long-term efficacy of Xyrem® based on a randomized withdrawal paradigm. The study is of relevance to the safety of Xyrem® in that it evaluates the potential adverse consequences of the abrupt withdrawal of therapeutic doses of the drug, including the incidence of rebound cataplexy.

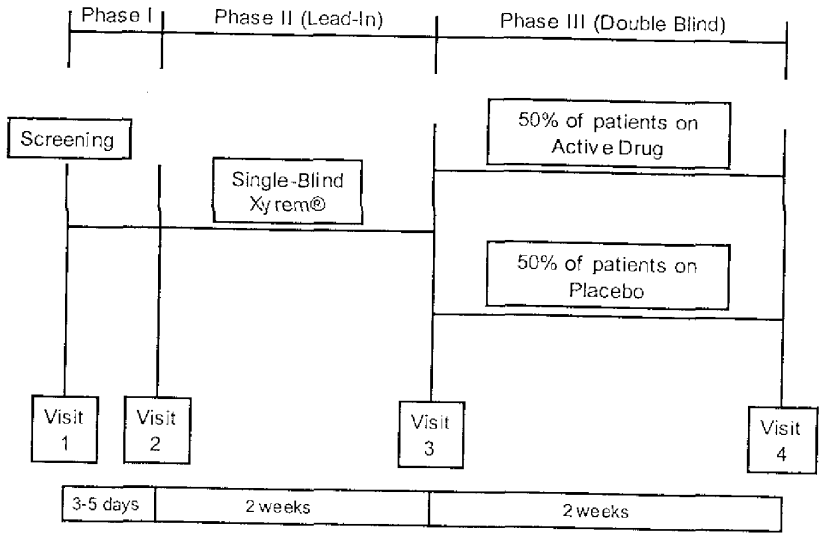
10.1 Brief Summary Of Study Protocol

10.1.1 Objective

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

10.1.2 Design

The design of the study is schematically summarized below



10.1.3 Duration

4 weeks (2 weeks of a double-blind withdrawal phase)

10.1.4 Sample Size

60 patients, with 30 in each treatment group in Phase 3, of the study will be included in the trial

10.1.5 Key Inclusion Criteria

- Informed consent
- Age ≥ 16 years
- Willing and able to complete the entire trial
- At least 5 cataplexy attacks per week prior to receiving any treatment (tricyclic antidepressants, selective serotonin uptake inhibitors, or Xyrem®) for cataplexy
- If female must be
  - Surgically sterile OR
  - 2 years post-menopausal OR
  - If of child bearing potential must be using a medically accepted means of birth control and must agree to continue such treatment for the duration of the study
- Treated continuously for the symptoms of narcolepsy with Xyrem® for at least 6 months, and not more than 3.5 years
- Willing to not operate a car or heavy machinery if the clinical investigator feels such a restriction is warranted
- Adequate support for the duration of the trial

10.1.6 Key Exclusion Criteria

- Unstable diseases in any body system, other than narcolepsy, which would place the patient at risk or compromise the trial objectives
- Psychiatric disorders that would preclude participation in, or completion of, the trial
- History of substance abuse, as defined by DSM-IV, currently or within the past year
- Serum creatinine > 2 mg/dl; AST or ALT > 2 x upper limit of normal; serum bilirubin > 1.5 x upper limit of normal; pre-trial electrocardiogram results demonstrating a clinically significant arrhythmia or 2nd or 3rd degree A-V block; history of myocardial infarction within the past 6 months
- Any untreated disorder other than narcolepsy that could be considered a primary cause of excessive daytime sleepiness, including sleep apnea syndrome (criteria specified)
- Occupation requiring variable shift or routine night shift work
- Use of tricyclic antidepressants, selective serotonin uptake inhibitors or medications for cataplexy other than Xyrem® in the 30 days prior to Visit 1 of the study
- Clinically significant history of head trauma; previous invasive cranial surgery; seizure disorder; use of anticonvulsant medication

10.1.7 Concomitant Medications

- The following medications were prohibited during the trial: selective serotonin uptake inhibitors and tricyclic antidepressants.
- Patients were to be cautioned regarding the use of opioid analgesics and skeletal muscle relaxants
- Alcohol was prohibited during the trial
- Over-the-counter medications needed careful review by the clinical investigator prior to use; non-sedating alternatives were to be used wherever possible
- Stable doses of stimulant medication could be used to treat excessive daytime sleepiness as clinically indicated

10.1.8 Dosage

Previously established dose of Xyrem® ranging from 3 to 9 grams daily

10.1.9 Schedule

- The visit schedule was as in the schematic above.
- The following were to be checked at Visit 1 alone: informed consent; selection criteria, medical history, cataplexy history prior to use of any medications, and “support systems”.
- Physical examinations, including neurological examinations were to be performed at Visits 1 and 4
- Daily diaries were to be provided and/or checked at visits 2, 3, and 4. Diaries were to record cataplexy and adverse events.

- Concurrent medications, vital signs and adverse events were to be checked at every visit
- A pregnancy test were to be checked if applicable at Visit 1
- Routine hematology and chemistry were to be checked at Visits 1 and 4

10.1.10 Outcome Measures

10.1.10.1 Efficacy Measure

Frequency of cataplexy attacks

10.1.10.2 Safety

Adverse events, laboratory data

10.1.11 Analysis Plan

10.1.11.1 Demographic And Baseline Variables

- The 2 double-blind period treatment groups were to be compared in regard to demographic and baseline variables
- Quantitative variables were to be analyzed using either a t-test or a Wilcoxon rank sum test as appropriate
- Qualitative variables were to be analyzed using Fisher's exact test

10.1.11.2 Primary Efficacy Parameter

- The primary efficacy parameter was the change in the number of cataplexy attacks per week in the 2-week period following Visit 3 (endpoint), compared with the 2-week period prior to Visit 3 (baseline). If a subject withdrew prior to Visit 4 the weekly average would be calculated based upon the data that were available
- The efficacy population was to consist of all those randomized at Visit 2 who had some post-baseline efficacy data
- The above change in the weekly number of cataplexy attacks was to be analyzed using a non-parametric ANCOVA as follows
  - The baseline number of cataplexy attacks and the change in the weekly number of cataplexy attacks were to be replaced by their corresponding ranks (mean ranks will be used when ties occur).
  - The ANCOVA would be constructed from the residuals derived from the ordinary least squares prediction of the change in the weekly number of cataplexy attacks based on a simple linear model
  - The treatment groups would then be compared with respect to these residuals using the Wilcoxon rank sum test.
  - Prior to completion of the analysis a test would be performed to compare the slopes for the 2 treatment groups.
- The significance of the mean change from baseline for each treatment group would be determined using the Wilcoxon signed rank test

10.1.11.3 Safety Parameters

- The safety population would consist of all those randomized to receive drug at Visit 3 who had some post-baseline safety data

- Adverse events would be summarized by treatment group and organized by preferred term and body system. Treatment groups would be compared to the incidence of each adverse event using Fisher's exact test
- Laboratory data would be summarized in tabular form as well as with the use of shift tables. Treatment groups would be compared in regard to the mean change from baseline using ANOVA. Within each treatment group the significance of the mean change from baseline was to be analyzed using a paired t-test

10.1.11.4 Sample Size Rationale

- The sample size calculation was based on the change in weekly cataplexy attacks comparing the 2 weeks prior to randomization and the 2 weeks after randomization
- The assumptions for the sample size calculation were as follows
  - Power of 80 %
  - 2-sided α of 0.05
  - A 50 % increase in the total number of cataplexy attacks in the placebo group, and a 10 % increase in a Xyrem® group
  - A standard deviation, based on a log transformation, of about 0.30 for the change in total number of cataplexy attacks (based on a previous study)
- Based on the above, a sample size of 22 patients would be required per treatment group to detect a treatment difference.
- To allow for a minor departure from the above assumptions a total of 30 patients would be randomized to each treatment group

10.2 Protocol Amendments

These have been incorporated into the above protocol outline.

10.3 Actual Analyses Performed

The analyses were performed according to the protocol

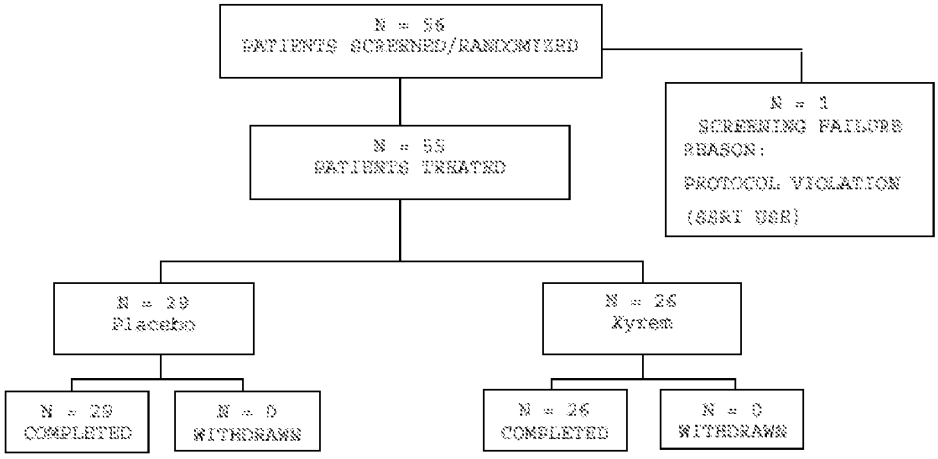
10.4 Efficacy Results

The full efficacy data are presented in this review as rebound cataplexy, which was seen in this study, is a manifestation of the abrupt withdrawal of GHB which is further described as part of this review.

The study was conducted at 14 centers. Each center enrolled between 1 and 7 patients

10.4.1 Patient Disposition

Patient disposition is summarized in the following schematic copied from the submission



Note that 1 randomized patient failed screening because of concomitant use of a selective serotonin re-uptake inhibitor (paroxetine). The blind was broken on 1 patient shortly after completion of the trial on account of a serious adverse event.

10.4.2 Protocol Deviations

- One patient was allowed into the trial despite having been treated with GHB for 3.7 years (the inclusion criteria specified that the duration of treatment should be from 0.5 to 3.5 years)
- One patient was allowed to continue in the trial despite receiving bupropion as a medication for cataplexy
- 3 patients overmedicated
- For "efficiency" 2 patients who were taking 3 g/day at study entry and continued to take that dose during the study were listed as taking 4.5 g/day
- For a number of patients Visits 1 and 2 were combined.

10.4.3 Medication Compliance

As the following table indicates medication compliance was comparable for the 2 Phase III treatment groups

Trial Medication Administration	Xyrem (N=26)			Placebo (N=29)		
	Phase II	Phase III	Total	Phase II[a]	Phase III	Total
Days Treated						
11	0	2		0	1	
12	1	1		0	0	
13	1	0		4	5	
14	16	13		20	13	
15	6	3		0	6	
16	1	0		0	0	
17	0	1		4	1	
18	1	0		1	1	
Duration of Treatment (Nights)						
Mean	14.7 ± 1.03	15.0 ± 1.46	28.8 ± 2.50	14.4 ± 1.35	14.0 ± 1.80	28.4 ± 1.99
Range	12-18	11-18	24-36	13-18	11-18	24-36
Compliance (%)						
Mean ± SD	105.9 ± 17.38	106.3 ± 18.85	106.0 ± 17.66	99.7 ± 8.07	102.4 ± 15.12	101.1 ± 9.28
Range	85-171	88-166	90-178	85-119	72-167	88-139

[a] Placebo group patients received Xyrem during Phase II.
SD = Standard deviation.

10.4.4 Baseline And Other Demographic Characteristics

These characteristics are summarized in the next 2 tables copied from this submission. Although gender, and baseline frequency of cataplexy attacks were not entirely balanced between the treatment groups the sponsor describes the differences as not being statistically significant. Note that the daily dose of Xyrem® did appear balanced between the Phase III treatment groups.

Characteristics	Total (N=55)	Treatment Group		p-Value
		Xyrem (N=26)	Placebo (N=29)	
Age (years)				
Mean ± SD	47.7 ± 15.59	47.3 ± 17.06	47.8 ± 14.60	0.999
Range	16.3 - 82.6	19.1 - 83.6	16.3 - 76.8	
Sex (n, %)				
Male	23 (42%)	8 (31%)	15 (52%)	0.172
Female	32 (58%)	18 (69%)	14 (48%)	
Weight (kg)				
Mean ± SD	80.5 ± 20.09	83.8 ± 24.91	77.6 ± 15.22	0.209
Range	56.8 - 142.0	56.8 - 142.0	58.6 - 127.6	
Height (cm)				
Mean ± SD	170.1 ± 10.25	169.6 ± 10.42	170.6 ± 10.34	0.710
Range	152.5 - 188.0	152.5 - 188.0	155.0 - 188.0	
Race (n, %)				
Caucasian	52 (95%)	25 (96%)	28 (100%)	0.999
African-American	2 (4%)	2 (8%)	0	
Asian	0	0	0	
Hispanic	1 (2%)	1 (4%)	0	
Other	0	0	0	
Time on Xyrem (months)				
Mean ± SD	21.22 ± 12.38	23.27 ± 12.96	19.38 ± 11.53	ND
Range	7 - 44	8 - 38	7 - 44	

(continued)

Characteristics	Total (N=55)	Treatment Group		p-Value
		Xyrem (N=26)	Placebo (N=29)	
Cataplexy attacks (7-week baseline)				
N	55	26	29	0.436
Mean	12.6	9.0	15.7	
SD	31.75	13.25	39.88	
Median	3.0	1.9	4.0	
Minimum	0.0	0.0	0.0	
Maximum	187.0	66.6	187.0	
Daily Dosage of Xyrem at Screening (n, %)				
3.0 g/d	2 (4%)	1 (4%)	1 (3%)	ND
4.5 g/d	8 (15%)	4 (15%)	5 (17%)	
6.0 g/d	15 (27%)	7 (27%)	8 (28%)	
7.5 g/d	15 (27%)	7 (27%)	8 (28%)	
9.0 g/d	14 (25%)	7 (27%)	7 (24%)	

ND = Not determined. SD = Standard deviation.

10.4.5 Primary Efficacy Analysis

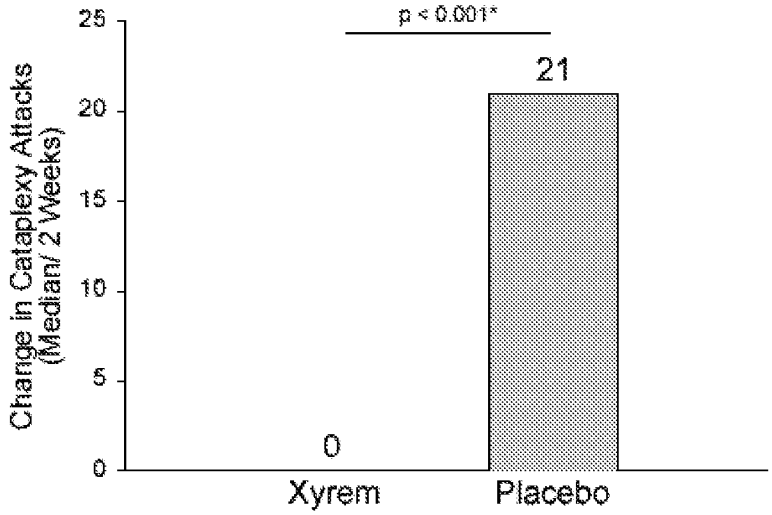
An intent-to-treat analysis was performed as specified in the protocol comprising all patients who received one or more doses of trial medication during the double blind withdrawal period and had recorded baseline and post-baseline efficacy measures

The results of the primary efficacy analysis are outlined in the table and figure below. For those receiving Xyrem® during the double-blind withdrawal phase there was no median change from baseline in the number of cataplexy attacks

over the 2 week period of withdrawal. For those receiving placebo during the withdrawal phase the median change in the number of cataplexy attacks during as compared with baseline showed an increase. The difference was statistically significant ($p < 0.001$). Note that the table and figure below depict median change

	Xyrem (N=26)			Placebo (N=29)		
	Phase II	Phase III	Change	Phase II'	Phase III	Change
Number of cataplexy attacks (per 2 weeks)						
Mean ± SD	9.0 ± 23.25	12.6 ± 30.34	3.6 ± 25.73	19.7 ± 33.88	58.4 ± 81.09	34.6 ± 68.72
Median	1.0	1.1	0.0	4.0	31.0	21.0
Minimum	0.0	0.0	-54.0	0.0	0.0	-15.0
Maximum	88.0	136.3	67.0	137.0	363.0	306.0
Rank change						
Mean ± SD			18.1 ± 12.65			36.9 ± 13.31*
Median			16.5			39.0
Minimum			1.0			3.0
Maximum			52.0			55.0

SD = standard deviation.
' Placebo group patients received Xyrem during Phase II.
* $p < 0.001$, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.

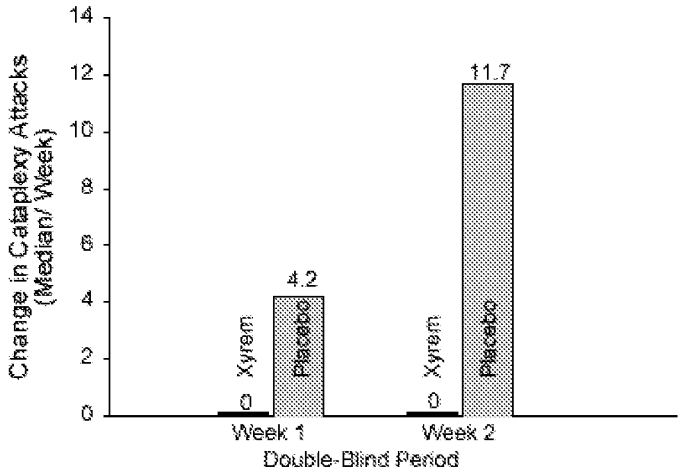


* $p < 0.001$, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.

As the next table and figure indicate the median change from baseline by week in the number of cataplexy attacks mirrors that for the primary efficacy analysis above

Number of Cataplexy Attacks	Xyrem			Placebo		
	Phase II*	Phase III	Change	Phase II*	Phase III	Change
Week 1						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	5.3 ± 11.84	0.8 ± 7.48	7.9 ± 19.84	21.1 ± 35.13	13.2 ± 22.62
Median	0.9	1.0	0.0	1.0	7.0	4.2
Minimum	0.0	0.0	-18.4	0.0	0.0	-7.5
Maximum	45.4	50.6	25.2	98.5	126.0	63.5
Week 2						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	7.2 ± 18.66	2.7 ± 13.74	7.9 ± 19.84	29.7 ± 47.36	21.8 ± 35.16
Median	0.9	0.5	0.0	1.0	13.0	11.7
Minimum	0.0	0.0	-19.7	0.0	0.0	-7.5
Maximum	45.4	87.0	62.0	98.5	168.0	143.5

* Baseline (Phase II) was determined by normalizing the total number of cataplexy attacks during the 2-week Phase II period to 7 days.



No formal analyses were carried out to evaluate differential effects at study sites, or to evaluate drug-drug or drug-disease interactions.

10.4.6 Analysis Of Secondary Efficacy Measures

This study had no secondary efficacy measures

10.5 Safety Results

10.5.1 Exposure

All 55 patients who received study medication were included in the safety analysis.

Information on the extent of medication compliance is described in the table in Section 10.4.3

Information on medication dose at study entry is further described in the table in Section 10.4.4.

26/55 (47%) of patients received their Xyrem® dose at study entry during the baseline and randomized withdrawal phases

29/55 (53%) of patients received their Xyrem® dose at study entry during the baseline phase of this study but received placebo during the randomized withdrawal phase

10.5.2 Deaths, Serious Adverse Events And Adverse Event Discontinuations

No deaths, serious adverse events or adverse event discontinuations are listed as having occurred during the study.

However a single patient (# 0232; Initials (b)(6developed an acute paranoid psychosis 3 days after participation in OMC-SXB-21 ended and after resuming GHB in OMC-SXB-7. A more detailed narrative for this patient is as follows:

This 44 year old woman with no previous history of psychiatric illness began taking Xyrem® on 4/1/99; from January 2000 onwards she took a stable dose of 9 g/day.

She entered OMC-SXB-21 from OMC-SXB-7. Concomitant medications at that time included modafinil, verapamil, ranitidine, aspirin and ibuprofen. She completed OMC-SXB-21 on 7/28/00 and re-entered OMC-SXB-7 taking 9 g/day again. After the blind for OMC-SXB-21 was broken it was confirmed that she had taken Xyrem® 9 g/day throughout that study as well.

On 8/1/00 she was hospitalized in an acutely paranoid state. She discharged herself from the hospital but was readmitted on 8/3/00. During her hospitalization she was treated with haloperidol, temazepam and clomipramine (clomipramine had been discontinued on 5/9/00). No GHB was administered after 7/30/00 and on 8/14/00 she told the investigator that she well. Clomipramine was apparently stopped and then resumed on 9/28/00 with a return of paranoia for a limited duration; this drug was however continued as apparently was modafinil. By 10/12/00 she had apparently returned to normal.

10.5.3 Other Adverse Events

The following tables copied from the submission display all adverse events that occurred during each phase of the study. The incidence of all adverse events during Phase III (the randomized withdrawal phase) are of particular interest; as the table indicates, the incidence of all adverse events in each treatment group was very low during this period. Of minor note is the presence of anxiety, dizziness, insomnia, “sleep disorder” and somnolence, each in 1-2 patients who received placebo during that phase, whereas none occurred in those receiving Xyrem®, which might suggest the infrequent presence of a mild withdrawal syndrome; however the total sample enrolled in this study and the number of those with these specific adverse events is too small to be conclusive.

Body System COSTART Term	Total* (N=55) n (%)	Treatment Group Xyrem (N=26) n (%)	 Placebo (N=29) n (%)
Phase I			
Patients with Adverse Events	**4 (7%)**	**1 (4%)**	**3 (10%)**
Body as a Whole	1 (2%)	0	1 (3%)
Accidental Injury	1 (2%)	0	1 (3%)
Metabolic & Nutritional System	2 (4%)	1 (4%)	1 (3%)
Alkaline phosphatase increased	1 (2%)	1 (4%)	0
BUN increased	1 (2%)	0	1 (3%)
Creatinine increased	1 (2%)	0	1 (3%)
Hyperglycemia	1 (2%)	0	1 (3%)
Hyperuricemia	1 (2%)	0	1 (3%)
Nervous System	1 (2%)	0	1 (3%)
Peripheral neuritis	1 (2%)	0	1 (3%)
Respiratory System	1 (2%)	0	1 (3%)
Pharyngitis	1 (2%)	0	1 (3%)
Phase II			
Patients with Adverse Events	**9 (16%)**	**4 (15%)**	**5 (17%)**
Body as a Whole	3 (5%)	1 (4%)	2 (7%)
Asthenia	1 (2%)	1 (4%)	0
Headache	3 (5%)	1 (4%)	2 (7%)
Digestive System	2 (4%)	2 (8%)	0
Diarrhea	1 (2%)	1 (4%)	0
Nausea	1 (2%)	1 (4%)	0
Metabolic & Nutritional System	1 (2%)	0	1 (3%)
Hyperglycemia	1 (2%)	0	1 (3%)
Respiratory System	1 (2%)	0	1 (3%)
Rhinitis	1 (2%)	0	1 (3%)

Body System COSTART Term	Total* (N=55) n (%)	Treatment Group Xyrem (N=26) n (%)	 Placebo (N=29) n (%)
Phase II (continued)			
Skin	3 (3%)	0	3 (3%)
Fungal dermatitis	3 (3%)	0	3 (3%)
Pruritus	2 (2%)	0	2 (2%)
Skin benign neoplasm	3 (3%)	0	3 (3%)
Skin nodule	2 (2%)	0	2 (3%)
Urogenital System	3 (3%)	2 (4%)	0
Vaginitis	3 (3%)	2 (4%)	0
Phase III			
Patients with Adverse Events	**12 (22%)**	**3 (12%)**	**9 (31%)**
Body as a Whole	4 (7%)	2 (4%)	2 (10%)
Accidental injury	2 (3%)	0	2 (3%)
Chest pain	2 (3%)	2 (4%)	0
Headache	2 (4%)	0	2 (7%)
Cardiovascular System	2 (3%)	0	2 (3%)
Migraine	3 (3%)	0	3 (3%)
Hemic-Lymphatic System	2 (3%)	0	2 (3%)
Lymphadenopathy	3 (3%)	0	3 (3%)
Metabolic & Nutritional System	2 (3%)	0	2 (3%)
SGOT increased	2 (3%)	0	2 (3%)
SGPT increased	3 (3%)	0	3 (3%)
Nervous System	5 (9%)	0	5 (17%)
Anxiety	2 (4%)	0	2 (7%)
Dizziness	2 (3%)	0	2 (3%)
Insomnia	2 (3%)	0	2 (3%)
Sleep disorder	3 (3%)	0	3 (3%)
Somnolence	2 (3%)	0	2 (3%)
Respiratory System	2 (4%)	3 (4%)	3 (3%)
Dyspnea	2 (3%)	2 (4%)	0
Pharyngitis	3 (3%)	0	3 (3%)
Skin	2 (4%)	3 (4%)	3 (3%)
Contact dermatitis	2 (3%)	2 (4%)	0
Rash	2 (4%)	3 (4%)	3 (3%)
Urogenital System	2 (3%)	2 (4%)	0
Urinary incontinence	3 (3%)	3 (4%)	0

* Patients are counted only once in each category.

10.5.4 Laboratory Data

The changes in hematology and clinical chemistry parameters may be summarized as follows

10.5.4.1 Mean Changes From Baseline To Last Observation

- Statistically significant changes from baseline were seen for
  - Monocytes (increase) and potassium (decrease) in the Xyrem® group
  - Total protein and albumin (decrease) and ALT (increase) in the placebo group
- Statistically significant differences between treatment groups for changes in baseline were seen for lymphocyte count and sodium
- Mean changes in each of the above categories were minor and inconsequential

10.5.4.2 Categorical Shifts From Baseline To Last Observation

All changes occurred in < 10% of patients in each treatment group and appeared to be of no consequence

10.5.4.3 Changes From Baseline In Individual Patients

No changes of clinical consequence were seen

10.5.5 Vital Signs

Descriptive statistics for changes in vital signs from baseline to last observation are summarized in the next table copied from the submission. As the table indicates these changes were inconsequential.

Parameter	Xyrem	Placebo
Number of Patients	28	28
Pulse (bpm)		
Mean	3.9	-0.3
SD	13.57	11.84
Median	5.5	0.0
Minimum	-31.0	-24.0
Maximum	32.0	22.0
Respiration (breaths/min)		
Mean	0.1	1.7
SD	3.66	3.32
Median	0.0	1.0
Minimum	-5.0	-2.0
Maximum	8.0	8.0
Diastolic Blood Pressure (mm Hg)		
Mean	1.8	0.2
SD	9.48	8.82
Median	0.0	0.0
Minimum	-20.0	-18.0
Maximum	18.0	20.0
Systolic Blood Pressure (mm Hg)		
Mean	3.1	-3.2
SD	11.65	13.15
Median	5.0	0.0
Minimum	-20.0	-32.0
Maximum	28.0	18.0
Body Temperature (°C)		
Mean	-0.0	-0.1
SD	0.55	0.76
Median	0.0	0.0
Minimum	-1.7	-1.9
Maximum	0.9	0.8
Body Weight (kg)		
Mean	-0.5	1.0
SD	2.06	2.78
Median	0.0	0.0
Minimum	-6.0	-2.0
Maximum	4.0	13.0

10.6 Sponsor's Conclusions Regarding Safety

These may be summarized as follows

- The incidence and severity of adverse events was low during this trial
- Withdrawal symptoms such as anxiety occur infrequently on abrupt withdrawal of chronic therapeutic doses of GHB

10.7 Reviewer's Comments

I concur with the sponsor's conclusions

11. Key Information From Integrated Summary Of Safety And OMC-SXB-21 Safety Data

11.1 All Adverse Events

The most common adverse events that appeared to be related to GHB use (based on a higher incidence in Xyrem® treated individuals in placebo-controlled trials), and were more frequent with higher doses of that drug, included headache, "pain" (unspecified), nausea, dizziness, and urinary incontinence. These appeared to be both reversible and infrequent.

In the Integrated Clinical Trials grouping the incidence of all the above adverse events, with the exception of headache, nausea and dizziness, was relatively low. In the Scharf trial the incidence of all the above common adverse events was considerably higher, presumably reflecting the duration of the trial, at least in part.

The issue of whether urinary incontinence in patients treated with GHB could be caused by unrecognized seizures has been explored further by the sponsor to a limited degree (see Section 8.5.5.1). Currently there is no strong evidence that GHB in the doses proposed for clinical use is epileptogenic or that urinary incontinence in patients treated with GHB is caused by unrecognized seizures. However the data provided so far that attempts to address these issues is very limited and either possibility cannot be ruled out.

11.2 Deaths

None of the deaths in the Xyrem® safety database could be causally linked to the drug; all 11 deaths occurred in the long-term, open-label, Scharf study and appeared to be due to intercurrent illnesses or accidents unrelated to Xyrem®.

Death occurred in 7.7% of patients participating in the Scharf study

11.3 Serious Adverse Events

Serious adverse events that could be causally linked to GHB use, at doses in the therapeutic range, included various combinations of the following: nausea, vomiting, dizziness, confusion, restlessness, agitation, somnolence and generalized weakness. There has been no comment by the investigator as to whether the reported "generalized weakness" represented true muscle weakness or not.

In 2 patients who may have or did take a drug overdose manifestations included coma, respiratory depression, incontinence and a flaccid tone.

Note that serious adverse events were seen in 4.5% of patients who participated in the Integrated Clinical Trials and 37.8% of those who participated in the Scharf trial; the much higher incidence in the Scharf trial is probably due to the duration of that study.

11.4 Adverse Event Discontinuations

Adverse event discontinuations that could be causally linked to GHB use, at doses in the therapeutic range, included varying combinations of the following: headache, nausea, vomiting, fatigue, reduced initiative and libido, dizziness, impaired memory, confusion, restlessness, agitation, paranoia, hallucinations, urinary and fecal incontinence, somnolence and generalized weakness (including difficulty maintaining an upright posture). Adverse events in that constellation of symptoms were seen in 5/102 patients receiving GHB in the randomized controlled trial OMC-GHB-2 but were not seen in any of 34 patients who received placebo. Such adverse events do appear more common at higher doses of GHB.

Particularly noteworthy was a single healthy 39 year-old subject participating in a pharmacokinetic trial who developed dizziness, nausea, vomiting, respiratory depression and fecal incontinence after a single (and initial) oral dose of 4.5 g of GHB, administered after an overnight fast.

One patient who may have taken a drug overdose manifest with coma, respiratory depression, incontinence and a flaccid tone (this patient is also listed as having a serious adverse event).

The proportion of patients discontinuing treatment on account of adverse events in the Integrated Clinical Trials, Scharf trial and Integrated Pharmacokinetic Trials were 10.9%, 8.4%, and 1.4%, respectively.

11.5 Laboratory Data

- No clinically relevant or clinically-correlated changes in routine safety laboratory tests-hematology, clinical chemistry and urinalysis-were seen
- As described in detail earlier (see Section 8.5.5.2), elevated antinuclear antibody titers were seen in a proportion of patients participating in the Scharf study. Further details are as follows
  - This test was not protocol-specified and was performed at a variable frequency only after the detection of the index case, a patient reported to have rheumatoid arthritis. Testing was performed in a variety of laboratories
  - Antinuclear antibody testing was not performed in patients participating in any other clinical trials of GHB
  - 87 patients participating in this study had antinuclear antibody titers tested on one or more occasions. 26 of these patients (29.9%) had one or more positive titers
  - 2 patients discontinued from the Scharf study on account of positive antinuclear antibody titers.
  - The *sine qua non* of drug-induced lupus is stated to be the presence of appropriate symptoms associated with the presence of antihistone antibodies. 15 patients with positive antinuclear antibody titers had antihistone antibodies tested for: one of these patients was borderline positive, the others were negative.
  - Only one patient who had positive antinuclear antibody titers is reported to have had symptoms suggestive of a systemic rheumatic disease (the index patient who was diagnosed to have rheumatoid arthritis; see Section 8.4.2.3). This patient did not have antihistone antibody testing done

11.6 Electrocardiograms

No clinically pertinent changes in electrocardiograms were seen that could be attributed to Xyrem®.

11.7 Vital Signs

A mild dose-related reduction in weight and sitting diastolic blood pressure was seen in GHB-treated patients in the randomized, controlled trial OMC-GHB-2.

No other clinically significant changes in vital signs were seen.

11.8 Withdrawal Phenomena

- The randomized withdrawal study OMC-SXB-21 was primarily intended to assess the long-term efficacy of Xyrem®. Spontaneous and elicited adverse event indicated the presence of anxiety, dizziness, insomnia, "sleep disorder" and somnolence, each in 3-7% of patients who received placebo during that phase, whereas none occurred in those receiving Xyrem®. These data might suggest the infrequent presence of a mild withdrawal syndrome; however the total sample enrolled in this study and the number of those with these specific adverse events is too small to be anywhere near conclusive.
- In OMC-SXB-21 the frequency of cataplexy attacks was increased to a statistically significant level in those who received placebo during the withdrawal phase relative to those who received GHB during that period.
- In the randomized, controlled, parallel-arm efficacy trial OMC-GHB-2, adverse events that were noted during a 5-day period following drug withdrawal included abnormal dreaming, hallucinations and an unspecified sleep disorder (a total of 3/102 patients who received GHB during this study had these adverse events and only 1 patient, who had previously received a Xyrem® dose of 9 g/day, had hallucinations). The sponsor reports that the frequency of cataplexy was not increased during the 5-day observation period following drug withdrawal.
- Thus, in the small number of patients formally studied there is very limited evidence that narcoleptic patients receiving therapeutic doses of GHB experience more than infrequent and mild withdrawal symptoms, other than an increased frequency of cataplexy

12. Literature Review

In this NDA the sponsor has provided full publications as well as synopses for clinical studies of GHB that have been reported in the medical literature, but are not otherwise included in this application. These studies fall into 2 categories

- Studies conducted in healthy individuals
- Studies conducted for a variety of medical indications

These studies are summarized in tabular form below

12.1 Published Studies Conducted In Healthy Individuals

These are summarized in the following table

Author	Purpose Of Study	Dose Of GHB	Number Of Subjects Exposed To GHB	Age Range	Adverse Events
Yamada	Effect of GHB on EEG	10-30 mg/kg Intravenous Single dose	12	20-33	None reported
Lee	Evaluation of metabolism of GBL	1 g Oral Single dose	4	Not available	None reported
Palatini	Pharmacokinetics of GHB	12.5 to 50 mg/kg Oral Single dose	8	22-26	Nausea, dizziness, drowsiness

The extent to which adverse events were systematically monitored for in these studies is unclear from the published reports ; the reports by Yamada and Lee do not specifically state that no adverse events occurred.

12.2 Published Studies Conducted For Specific Medical Indications

There are also 17 additional published reports supplied by the sponsor that describe studies done for several specific medical indications:

- These indications include alcohol withdrawal, alcohol dependence, opiate withdrawal, insomnia, sleep apnea, nocturnal myoclonus, neonatal startle disease, and as an anesthetic agent.
- Only 6 of these studies were controlled
- These studies have exposed a total of 152 subjects/patients to mainly single, oral or intravenous doses of GHB.
- The maximum individual doses used were as follows
  Oral: 50 mg/kg or 4.5 g
  Intravenous:150 mg/kg
- In a single open-label study for opiate withdrawal in 2 patients the dose used was 30 or 50 mg/kg every 4 hours for 7-8 days
- Adverse events that were reported across these studies include dizziness, vertigo, nausea, headache, gastric ulceration, drowsiness, pneumonia, semi-liquid stools and muscle pain. However in a number of publications the authors did not either list adverse events or specifically state that no adverse events occurred.

These studies are summarized in the next table

Author	Indication	Dose Of GHB	Number Of Subjects Exposed To GHB	Age Range (years)	Adverse Events
Gallimberti	Alcohol withdrawal syndrome	50 mg/kg Oral Single dose	11	28-63	Dizziness
Gallimberti	Reduction of alcohol consumption and alcohol craving	50mg/kg/day Oral 1 year	43	13-38	Vertigo, dizziness, nausea, headache and gastric ulceration
Gallimberti	Opiate withdrawal	25 mg/kg Oral Single dose	27	22-33	Dizziness
Oyama	Effects on fat and carbohydrate metabolism when used as an anesthetic	100-150 mg/kg Intravenous Single dose	10	14-48	None reported
Mamelak	Sleep induction in insomniacs	1-3 g/day Oral 3 nights	5	35-60	None reported
Mamelak	Insomnia	1-4.5 g/day Oral 3 nights	8	34-60	None reported
Van den	Anesthesia for	26.7 to 50 mg/kg	14	Not available	None reported

Author	Indication	Dose Of GHB	Number Of Subjects Exposed To GHB	Age Range (years)	Adverse Events
Bogaert	Cesarean section	Intravenous Single dose			
Mamelak	Narcolepsy and sleep apnea	60 mg/kg/day in 2 divided doses Oral 11 weeks	1	53	None reported
Strong	Reducing intracranial pressure in severe head injury	4 g Intravenous Multiple boluses	6	Not available	None reported
Hasenbos	Anesthesia for respiratory surgery	50 mg/kg Intravenous Single dose	1	64	Pneumonia
Scrima	Obstructive sleep apnea	50 mg/kg in 2 divided doses Oral 1 night	1	64	None reported
Scrima	Nocturnal myoclonus	50 mg/kg in 2 divided doses Oral 1 night	4	37-48	None reported
Bedard	Periodic leg movements in sleep in narcoleptic patients	2.25 g/day Oral 1 month	12	34-55	None reported
Ferrara	Pharmacokinetics in alcohol-dependent subjects	25 mg/kg b.i.d Oral Minimum of 7 days 50 mg/kg Oral Single-dose Day 10	10	34-56	Transient drowsiness
Series	Effects on slow-wave sleep in obstructive sleep apnea	60 mg/kg in 2 divided doses Oral 1 night	8	45 ± 2	None reported
Berthier	Neonatal startle disease	100 mg/kg (max) Intravenous Escalating doses (daily?) for 17 days	1	Newborn	None reported
Gallimberti	Opiate withdrawal syndrome	30-50 mg/kg every 4 hours for 7-8 days	2	24-30	Muscle pain; semi-liquid feces

The extent to which adverse events were systematically monitored for in these studies is unclear from the published reports ; except for the reports by Gallimberti (all), Hasenbos and Ferrara, the others do not specifically state that no adverse events occurred.

13. 120-Day Safety Update

13.1 Contents

This 120-Day Safety Update was submitted 2/1/01. It contains data from Study OMC-SXB-7 only. This was an open-label safety study conducted as part of Treatment IND # 57271, in patients previously exposed to GHB.

The data presented in this safety update consists of adverse events reported from study initiation (3/3/99) to data cut-off (9/30/00).

An earlier interim report for this study dated 8/9/00 was submitted with the main NDA application. That report contained safety data through a cut-off date of 12/31/99.

Adverse event data from 3/3/99 through 12/31/99 are therefore contained in both the interim report of 8/9/00 (submitted with the original NDA) and in the 120-Day Safety Update.

Data from 2 additional studies, OMC-SXB-20 and OMC-SXB-21, were not in the original NDA, but were submitted on 12/16/00. OMC-SXB-20 was a small open-label study of the effects of 4 doses of Xyrem® on sleep architecture. OMC-SXB-21 was a study of the long-term efficacy of Xyrem® using the randomized withdrawal paradigm. By agreement with this Division data from these studies are not included in the 120-Day Safety Update since they have already been submitted. Safety data from both these studies have been described elsewhere in this review.

13.2 Outline Of Protocol For OMC-SXB-7

The following protocol outline was submitted with the treatment IND

13.2.1 Objectives

- To evaluate the safety of sodium oxybate when used in patients with narcolepsy for upto 24 months or until the time of marketing approval at 5 specified doses
- To evaluate changes in the primary narcolepsy symptoms during the study including cataplexy attacks, daytime sleepiness, inadvertent naps during the day, awakenings during the night, hypnagogic hallucinations, and sleep paralysis

13.2.2 Design

Open-label, uncontrolled study

13.2.3 Inclusion Criteria

- Informed consent
- Age ≥ 12 years
- Previous use of GHB for narcolepsy under an approved IND application: the trials that will feed into this study include OMC-GHB-3, OMC-SXB-6 and the Scharf trial under IND # 21654, all of which are open-label studies: those in OMC-GHB-3 need to have completed at least 12 months of treatment; those in OMC-SXB-6 need to have completed at least 6 months of treatment; those in the Scharf trial could have received treatment for any length of time
- Willing and able to complete the entire trial
- Age ≥ 12 years
- If female must be
  - Surgically sterile OR
  - 2 years post-menopausal OR
  - If of child-bearing potential, not currently pregnant and using a medically accepted means of birth control

13.2.4 Exclusion Criteria

- Unstable diseases in any body system, other than narcolepsy, which would place the patient at risk or compromise the trial objectives
- Use of anticonvulsant medication
- History of substance abuse, as defined by DSM-IV, currently or within the past year
- Serum creatinine > 2 mg/dl; AST or ALT > 2 x upper limit of normal; serum bilirubin > 1.5 times normal; pre-trial electrocardiogram results demonstrating a clinically significant arrhythmia or 2nd or 3rd degree A-V block; history of myocardial infarction within the past 6 months
- Any untreated disorder other than narcolepsy that could be considered a primary cause of excessive daytime sleepiness
- Investigational therapy, other than GHB, within 30 days prior to screening visit
- History of porphyria

13.2.5 Sample Size

The study plans to enroll about 300 patients at 40 investigative centers

13.2.6 Duration

24 months or until marketing approval, whichever is sooner

13.2.7 Dosage

- The medication is to be taken twice each night, at bedtime and 2.5 - 4 hours later
- The dosage is to be titrated based on the diminution of symptoms (cataplexy, hypnagogic hallucinations, sleep paralysis and daytime sleepiness) during the day while awake, and adverse events
- The starting dose is that established in the previous trial
- If necessary, the dose may be increased upto 9.0 grams per day or decreased as far as 3.0 grams per day.
- If increments are made, it is suggested that they should consist of 0.75 grams per dose (1.5 grams per day)
- Allowing 2 to 4 weeks between dosage adjustments is recommended
- After an optimal dose of Xyrem^{TM} is reached that dose will be maintained throughout the trial but will be altered if clinically indicated

13.2.8 Concomitant Medication

- Stable doses of other agents may be used for the treatment of narcolepsy
- Alcoholic beverages should not be misused and should not be taken for 3 hours prior to bedtime
- Patients will be cautioned regarding the use of other drugs with central nervous system depressant actions.
- All concomitant medications will be documented in the Case Report Forms

13.2.9 Schedule

- Assessments will be at the following visits: baseline, and at months 3, 6, 9, 12, 15, 18, 21 and 24 ; these are also referred to as Visits 1 through 9, respectively.
- Written informed consent, medical history and a urinary pregnancy test will be obtained at baseline only; a baseline history may not be needed depending on which trial the patient is entering this protocol from
- Safety laboratory tests (hematology, clinical chemistry and urinalysis) will be checked at baseline and at Months 6, 12, 18 and 24
- Concomitant medication and adverse events will be checked at every visit.
- Vital signs will be checked at baseline and at Months 6, 12, 18 and 24
- Narcolepsy symptoms will be assessed at baseline and every subsequent visit by using a formal Narcolepsy Symptom Assessment Questionnaire (baseline and follow-up versions)

13.2.10 Statistical Considerations

- All patients who receive a single dose or more of medication will be included in the safety evaluation
- All patients who complete more than one assessment of the Narcolepsy Symptom Assessment Questionnaire will be included in the efficacy evaluation.

13.2.11 Safety Monitoring

This will be accomplished using vital signs, adverse events, concomitant medications, safety laboratory tests and electrocardiograms as outlined above under “Schedule”. A scheme for categorizing and reporting adverse events has been outlined.

13.3 Protocol Amendments

These have been incorporated into the above protocol description.

13.4 Patient Disposition

236 patients received treatment as part of this trial; they were at 26 study sites. Their disposition by last Xyrem® dose is illustrated in the following table, copied from the submission.

Patient Disposition		Last Xyrem Oral Solution Dosage (g/d)				
	Total	3.0	4.5	6.0	7.5	9.0
Treated	236 (100%)	5 (2%)	39 (17%)	76 (32%)	59 (25%)	57 (24%)
Discontinued	25 (11%)	0	3	7	5	10
Patient request	9 (4%)	0	1 (3%)	3 (4%)	2 (3%)	3 (5%)
Adverse event	10 (4%)	0	1 (3%)	2 (3%)	1 (2%)	6 (11%)
Protocol deviation	1 (<1%)	0	0	0	0	1 (2%)
Lost to follow-up	2 (<1%)	0	0	1 (1%)	1 (2%)	0
Other	2 (<1%)	0	0	1 (1%)	1 (2%)	0
Lack of efficacy	1 (<1%)	0	1 (3%)	0	0	0

13.5 Demographics

Demographics at study entry are as follows

Mean Age 48.3 years
Mean Weight 84.4 kg

Gender Males 45% Female 55%

13.6 Dosage

Patient distribution by dose during, and at the end of the trial is summarized in the next table which I have copied from the submission

Dosage	Total	Xyrem Oral Solution Dosage (g/d)				
		3.0	4.5	6.0	7.5	9.0
Last Dosage	236	5 (2%)	39 (17%)	78 (32%)	58 (25%)	57 (24%)
Patient Dosage*	236	7 (3%)	48 (20%)	106 (45%)	73 (31%)	59 (25%)

* Patient Dosage: the number of patients who took the specified dosage at any time during the trial. Patients may be counted multiple times, so the sum of patients exposed to specific dosages (293) exceeds the total number of patients treated in the trial (236).

13.7 Patient Exposure

As noted in the inclusion criteria, patients were enrolled in this study from 3 other sources

Study	Maximum Duration Of Exposure To GHB
OMC-GHB-3	24 months
OMC-SXB-6	6 months
Scharf	16 years

The next table summarizes duration of exposure by dose received during OMC-SXB-7 only.

Drug Administration	Total	Xyrem Oral Solution Dosage (g/d)				
		3.0	4.5	6.0	7.5	9.0
Exposure by Visit						
Visit 1	236 (100%)	4 (2%)	42 (18%)	98 (42%)	47 (20%)	45 (19%)
3 months (Visit 2)	223 (100%)	6 (3%)	37 (17%)	82 (37%)	56 (25%)	42 (19%)
6 months (Visit 3)	207 (100%)	6 (3%)	33 (16%)	68 (33%)	56 (27%)	44 (21%)
9 months (Visit 4)	133 (100%)	4 (3%)	18 (14%)	40 (30%)	39 (29%)	32 (24%)
12 months (Visit 5)	97 (100%)	2 (2%)	8 (8%)	29 (30%)	29 (30%)	29 (30%)
15 months (Visit 6)	48 (100%)	1 (2%)	4 (8%)	12 (25%)	16 (33%)	15 (31%)
18 months (Visit 7)	4 (100%)	0	0	1 (25%)	2 (50%)	1 (25%)
Last visit/end-of-trial	2 (100%)	0	0	2 (100%)	0	0
Duration of Treatment (days)						
N	236	7	48	106	73	59
Mean	284.0	246.9	198.7	230.0	239.2	235.8
SD	130.85	166.44	121.92	135.51	143.52	154.27
Median	272.5	292.0	187.5	187.0	188.0	207.0
Minimum	1.0	1.0	1.0	1.0	1.0	1.0
Maximum	568.0	454.0	464.0	541.0	555.0	568.0

Some patients were exposed to more than 1 dosage in the trial, so the sum of patients exposed to specific dosages (N= 293) exceeds the total number of patients in the trial (N= 236).

The mean duration of treatment in this updated study report was 284 days (0.78 years). Given that there were 236 patients enrolled in the study, the mean exposure to GHB for this study, based on this updated study report, was 184 patient-years.

In the earlier interim report for this study submitted with the original NDA, 145 patients had been exposed to the study drug for a mean duration of 104.4 days (0.29 years). The patient-exposure to GHB at that time was calculated as being 42.1 patient-years.

The additional exposure to GHB included in this safety update is therefore estimated at 141.5 patient-years

The 55 patients participating in the randomized withdrawal efficacy study, OMC-SXB-21, were drawn entirely from those participating in OMC-SXB-7. Patient exposure to GHB in OMC-SXB-21 is included in the above table, which takes into consideration those patients who were on placebo for 2 weeks during OMC-SXB-21.

13.8 Safety Results

13.8.1 All Adverse Events

The broad categories of adverse events and their distribution by dose are indicated in the following table, copied from the submission

As the table indicates serious adverse events, adverse event discontinuations and severe adverse events were all most common at the 9 g/day dose

		Xyrem Oral Solution Dosage (g/d) at Onset				
	Total	3.0	4.5	6.0	7.5	9.0
	236(100%)	7(100%)	48(100%)	106(100%)	73(100%)	59(100%)
Patients with at least 1 adverse event	146(62%)	4(57%)	26(54%)	56(53%)	37(51%)	33(56%)
Patients with serious adverse events	16(7%)	0	3(6%)	3(3%)	3(4%)	7(12%)
Patients with severe adverse events	24(10%)	0	5(10%)	8(8%)	2(3%)	10(17%)
Patients discontinued due to an adverse event	9(4%)	0	1(2%)	1(<1%)	1(1%)	6(10%)
Patient deaths	1(<1%)	0	0	1(<1%)	0	0

13.8.2 Adverse Event Tables

The following tables outline adverse events that occurred in ≥ 5 % of patients in any treatment group. The tables are copied from the submission

Body System COSTART Preferred Term	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset 3.0	4.5	6.0	7.5	9.0
Number of Patients	236(100%)[b]	7(100%)	48(100%)	106(100%)	73(100%)	59(100%)
Body as a Whole	72(31%)	3(43%)	11(23%)	24(23%)	23(32%)	17(31%)
Accidental injury	12(5%)	0	1(2%)	3(3%)	3(4%)	6(10%)
Allergic reaction[c]	4(2%)	1(14%)	0	2(2%)	1(1%)	0
Asthenia[c]	5(2%)	1(14%)	1(2%)	1(<1%)	1(1%)	1(2%)
Flu syndrome	11(5%)	2(29%)	0	2(2%)	5(7%)	2(3%)
Headache	15(7%)	2(29%)	3(6%)	5(5%)	2(3%)	4(7%)
Infection	17(7%)	0	1(2%)	8(8%)	5(7%)	3(5%)
Pain	14(6%)	1(14%)	1(2%)	3(3%)	4(5%)	5(8%)
Viral infection	6(3%)	0	2(4%)	1(<1%)	0	3(5%)
Cardiovascular System	15(6%)	0	3(6%)	4(4%)	3(4%)	1(2%)
Digestive System	37(16%)	1(14%)	10(21%)	12(11%)	4(5%)	10(17%)
Diarrhea	12(5%)	1(14%)	3(6%)	3(3%)	2(3%)	3(5%)
Nausea	15(6%)	0	2(4%)	4(4%)	2(3%)	7(12%)
Vomiting	10(4%)	0	3(6%)	3(3%)	1(1%)	3(5%)
Hemic-Lymphatic System	8(3%)	0	0	7(7%)	1(1%)	0
Metabolic and Nutritional System	20(8%)	2(29%)	1(2%)	5(5%)	6(8%)	6(10%)
Creatinine increased[c]	2(<1%)	1(14%)	0	1(<1%)	0	0
Hypercholesteremia[c]	3(1%)	1(14%)	0	2(2%)	0	0

Body System COSTART Preferred Term	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	236(100%)[b]	7(100%)	48(100%)	106(100%)	73(100%)	59(100%)
Musculoskeletal System	20(8%)	0	4(8%)	5(5%)	5(7%)	6(10%)
Nervous System	52(22%)	1(14%)	11(23%)	15(14%)	10(14%)	16(27%)
Depression[c]	3(<1%)	1(14%)	0	0	1(1%)	0
Insomnia	8(3%)	0	2(4%)	2(2%)	1(1%)	3(5%)
Sleep Disorder[d]	9(4%)	0	2(4%)	1(<1%)	2(3%)	4(7%)
Respiratory System	37(16%)	1(14%)	8(17%)	13(12%)	10(14%)	5(8%)
Rhinitis	8(3%)	0	2(4%)	1(<1%)	2(3%)	3(5%)
Sinusitis	13(6%)	1(14%)	3(6%)	6(6%)	2(3%)	1(2%)
Skin	14(6%)	0	1(2%)	6(6%)	2(3%)	6(10%)
Special Senses	6(3%)	0	1(2%)	1(<1%)	1(1%)	3(5%)
Urogenital System	29(12%)	3(43%)	4(8%)	11(10%)	4(5%)	7(12%)
Albuminuria[e]	3(1%)	1(14%)	0	1(1%)	0	1(2%)
Pyelonephritis[f]	2(<1%)	1(14%)	0	0	0	1(2%)
Urine Abnormality[g]	3(1%)	1 (14%)	0	1(<1%)	1(1%)	0

Some patients were exposed to more than 1 dosage in the trial, so the sum of patients exposed to specific dosages (N= 293) exceeds the total number of patients in the trial (N= 236).

The spectrum of adverse events seen is not greatly different from those in the Integrated Summary of Safety in the original NDA. The most common adverse events overall in descending order of frequency were infection, headache, nausea, pain, sinusitis, accidental injury, diarrhea and flu syndrome.

The percentages of adverse events that were classified as mild, moderate or severe, were 36%, 48% and 16%, respectively.

13.9 Deaths

A single patient died during the study. The cause of death was suicide. A narrative for this patient is below:

Patient # 0531 was a 47 year old woman who had earlier participated in the OMC-SXB-6 trial and had been taking Xyrem® 6 g/day since 6/3/99. Her past medical history that the investigator was aware of at screening was remarkable for a bipolar disorder, a previous head injury with coma and a morphine allergy. Concomitant medications included thyroxine, zolpidem, an albuterol inhaler, loratadine, risperidone and temazepam. Subsequently the investigator realized that she had previously made a suicide attempt

In May 2000 she began experiencing worsening insomnia. On 6/12/00 she underwent an elective surgical procedure for metrorrhagia.

On 7/4/00 she asked friends to leave a gathering at her home as she felt unwell. After a friend was unable to contact her, emergency personnel entered her home and found her dead the following day. A post-mortem toxicology screen was positive for opiates, acetaminophen and benzodiazepines. Quantitative testing showed toxic levels of multiple drugs including hydrocodone, oxycodone, morphine, hydromorphone, nordiazepam and zolpidem. It was presumed that she had committed suicide by taking an overdose of multiple drugs. The death certificate listed multiple drug toxicity as the cause of her death with atherosclerotic cardiovascular disease also being listed as a significant factor.

Post-mortem toxicology screening for GHB was not done, but the sponsor believes that this patient did not take an overdose of that drug for the following reasons

- At her last trial visit on 5/23/00 the patient received 6 bottles of Xyrem®, each containing 200 mL of the drug (each bottle contained 500 mg/mL)
- On 7/11/00 the patient's family returned to the investigator 5 bottles (4 full and 1 empty)
- The 6th bottle containing some drug was retained by the medical examiner but the quantity of drug in that bottle is not known
- The sponsor states that the although the patient's compliance with the drug could not be precisely estimated it was calculated as being between 39 and 78%

13.10 Serious Adverse Events

16 patients, including the patient who died, are stated to have had serious adverse events. All are summarized in the tables below

Patient No.	Xyrem Dosage at Onset (g/d)	COSTART Preferred Term	Relationship to Trial Drug	Led to Discontinuation
0214	9.0	Liver function tests abnormal	Unknown	Yes
0232	9.0	Paranoid reaction	Probably related	Yes
05020	9.0	Knee replacement with postoperative paralytic ileus[a]	Not related	No
0509	6.0	Chest tightness/diaphoresis[b]	Not related	No
05257	12.0	Gastroenteritis/ dehydration	Not related	No
	12.0	Urinary tract infection	Not related	No
0531	6.0	Death (Suicide)	Not related	Yes
0585	7.5	Chest pain	Not related	No
0933	4.5	Manic depressive reaction (bipolar affective disorder)	Not related	Yes
1131	9.0	Intentional overdose	Definitely related	Yes
14043	7.5	Suicide attempt[c]	Possibly related	Yes
1433	4.5	Breast carcinoma (suspected)	Not related	No
1509	6.0	Gastroenteritis	Not related	No
	6.0	Back pain	Not related	Yes
1630	7.5	Chest pain	Unknown	No
2030	9.0	Psychosis	Possibly related	Yes

Patient No.	Xyrem Dosage at Onset (g/d)	COSTART Preferred Term	Relationship to Trial Drug	Led to Discontinuation
23210[d]	4.5	Cardiospasm	Not related	No
	4.5	Chills and fever	Not related	No
2516	9.0	Fractured ankle[e]	Possibly related	Yes

Further descriptions have been provided for the following patients, based on a review of all patient narratives. Events in the other patient were felt by me not to be related to the study drug.

13.10.1 Patient # 0214

This patient has already been described in Section 8.3.1.6. His liver function abnormalities were attributed to Hepatitis C infection.

13.10.2 Patient # 0232

This patient has already been described in Section 10.5.2. The adverse event occurred shortly after she finished participating in Study OMC-SXB-21.

13.10.3 Patient # 0931

This 29 year old woman had taken Xyrem® from 7/5/99 until she developed the serious adverse event listed in the table above in April 2000. At screening, she did not disclose that she had a past history of depression.

Her dose of Xyrem® at the time of the adverse event was 4.5 g/day. She was also receiving modafinil 600 mg/day.

On 4/27/00 the study coordinator was informed that the patient had been hallucinating and had lost her job owing to a diminished ability to function at work. On 4/29/00 the patient was found to be unarousable in her car by emergency personnel: on being awakened she became violently agitated, but was also slow in responding to questions. She was hospitalized and treated with multiple medications for agitation. Her urine drug screen was positive for benzodiazepines. The patient later reported that on 4/29/00 she pulled off the road to sleep at which time she took both nightly doses of Xyrem® together without dilution. She was diagnosed to have a bipolar disorder.

She did not take any Xyrem® after 4/29/00 and at a follow-up visit on 6/14/00 appeared mentally well.

13.10.4 Patient # 1131

This 46 year old man was begun on Xyrem® on 4/30/99. At study entry he did not disclose that he had a past history of depression and a previous suicide attempt. Concomitant medications at study entry included modafinil 400 mg/day, ibuprofen, an aspirin-acetaminophen-caffeine combination pill, dextroamphetamine and bupropion (for smoking cessation).

His regular dose of Xyrem® at the time of the serious adverse event described below was 9 g/day.

He took an overdose of Xyrem® (subsequently estimated at 150 g) on 2/2/00. His wife found him unresponsive and incontinent of urine and feces that day. He was initially unresponsive with apneic spells, but with normal arterial blood gases. He later became combative and finally awoke, at which time he was observed to be depressed. He reported multiple major sources of stress. He required psychiatric hospitalization and did not resume Xyrem®.

13.10.5 Patient # 14043

This 26 year old woman had previously participated in the Scharf trial and had received GHB since 7/5/89. She entered the OMC-SXB-7 trial on 8/30/99. Her past medical history was remarkable for obsessive compulsive disorder. Concomitant medications during the OMC-SXB-7 trial include fluvoxamine, buspirone and methylphenidate.

On 4/2/00 she took her usual dose of Xyrem® (7.5 g/day) and then attempted suicide by taking 56 tablets of buspirone 5 mg. She immediately told her father what had happened, was taken to an emergency room where she was treated and released. She

reported being increasingly self-critical from January 2000 onward after beginning methylphenidate. After discontinuing Xyrem® (last dose on 4/4/00) she became more negative in outlook and noted an increase in cataplexy and in sleepiness.

13.10.6 Patient # 2030

This 18 year old man began taking Xyrem® on 5/28/99 and was maintained on a stable dose of 9 g/day thereafter. Concomitant medications included zolpidem, protriptyline, modafinil (200 mg/day), fluoxetine 20 mg/day, methylphenidate 40-45 mg/day. He reported no previous psychiatric history.

On 12/15/99 he began experiencing paranoia, confusion and hallucinations. He reported increasing his dose of methylphenidate earlier while preparing for examinations. He was hospitalized and treated with multiple medications. Xyrem® was stopped on 12/22/99. He improved and his psychosis was attributed to methylphenidate overuse and to sleep deprivation.

13.11 Adverse Event Discontinuations

10 patients, including the patient who died, discontinued treatment on account of an adverse event. They are summarized in the following table. With the exception of Patient 1305 all the others are listed under Deaths and Serious Adverse Events

Patient No. [a]	Xyrem Dosage at Onset (g/d)	COSTART Preferred Term	Relationship to Trial Drug	SAE (Y/N)
0214	9.0	Liver function tests abnormal[b]	Unknown	Y
0232	9.0	Paranoid reaction	Probably related	Y
0531	6.0	Death (Suicide)	Not related	Y
0931	4.5	Manic depressive reaction (bipolar affective disorder)	Not related	Y
1131	9.0	Intentional overdose	Definitely related	Y
1305	9.0	Movement disorder[c]	Unknown	N
14043	7.5	Suicide attempt[d]	Possibly related	Y
1509	6.0	Back pain	Not related	Y
2030	9.0	Psychosis	Possibly related	Y
2536	9.0	Fractured Ankle[e]	Possibly related	Y

13.11.1 Patient 1305

This 75 year old woman entered the OMC-SXB-7 trial after participating in the OMC-GHB-2 and OMC-GHB-3 trials. She had received Xyrem® since 8/5/97 and was on a stable dose of 9 g/day from 7/8/99. Her neurological history was unremarkable except for narcolepsy with cataplexy. Her concomitant medications included ibuprofen, conjugated estrogen, medroxyprogesterone, and long and short-acting methylphenidate.

On 2/12/00 she began experiencing an intermittent “movement disorder”. A nocturnal polysomnogram confirmed that she had periodic leg movements (it is unclear if the

"movement disorder" was considered to be the same as the periodic leg movements). She discontinued the study medication but her subsequent course is unclear.

13.12 Reviewer's Comments

- The spectrum of adverse events seen in this Safety Update is broadly similar to that in the Integrated Summary of Safety
- A causal relationship between GHB use and depression/suicide cannot be established from the deaths, serious adverse events and adverse event dropout reports reviewed above; the patients listed had a preceding history of depression or a psychiatric disorder.

14. Risk Management Program

14.1 Structure

In response to a concern that medically prescribed Xyrem® may be diverted for illegal use, or may be consumed accidentally (e.g., by small children), the sponsor has proposed a risk management program. The components of this program are as follows:

14.1.1 Closed-Loop Distribution System

14.1.1.1 Manufacture

The bulk drug will be manufactured at a single site:(b)(4)----------
(b)

The drug product will be manufactured by(b)(4)----------
(b)(4)---------- A secondary manufacturer will be (b)(4)----------
(b)(4)---------- Both these companies as ----------
(b)(4)---------- will perform drug substance release
----------ported to be FDA- and DEA-compliant, "fill-finish" facilities

Following manufacture the drug product will be stored at a facility compliant with Schedule III regulations, where a consignment inventory will be maintained. The inventory will be owned by Orphan Medical, Inc., and the facility will be managed by(b)(4)----------(see below) which will maintain the consignment inventory.

14.1.1.2 Distribution

The primary and exclusive distributor of Xyrem® to patients will be(b)(4)----------
(b)(4)---------- A back-up distributor, currently used for the sponsor's treatment IND # 57271, is(b)(4)---------- Xyrem® will NOT be placed in retail pharmacy outlets.

The functions of(b)(4)----------will be to

- Distribute Xyr----------
- Maintain inventory and distribution records
- Maintain a patient registry

(b)(4)----------will purchase its inventory at wholesale pricing from (b)(4)-----
(b)(4)----------that inventory will be maintained at a pre-set level. Pharmacy purchases from the manufacturer will be "recognized" by Orphan Medical.

(b)(4)----------will operate in the following manner

- ----------hysician to(b)(4)----------
- Upon receipt of a prescription this company will contact the prescribing physician and
  - Identify his/her name, license and DEA registration
  - Verify the prescription
  - (Obtain patient insurance information
- Nb)(4)--------will then verify that the physician is eligible to prescribe Xyrem® ---------- the National Practitioner Databank which contains current information about the authority of individual physicians to prescribe controlled substances. This stage of verification will include confirming that the physician has an active DEA number and will check on whether any actions are pending against the physician
- If the physician is a first-time prescriber of Xyrem® that pharmacy will then ship comprehensive printed and video materials to that physician: these materials (see Xyrem® Physician Success Program below) also contain information regarding the proper handling of the drug with an outline of precautions to be taken against diversion
- N(b)(4)-------will then contact the patient's insurance company to obtain ----------is will include obtaining a certificate of medical necessity from the physician and assignment of benefits from the insurance company. Subsequent reimbursement for prescription costs will be taken care of by a (b)(4)---------reimbursement specialist
- N----------will notify the patient of his/her approval status
- Once approval has been established, (b)(4)---------will verify the patient's home address and availability for ship----------ange shipment through (b)(4)----------or a similar carrier. The shipment will be accompanied by comprehensive printed and video materials (see Xyrem® Patient Success Program below) that also contain information regarding the proper handling of the drug with an outline of precautions to be taken against diversion
- Receipt of the drug by the patient will be ensured through the following
  - The courier service's own tracking system for shipments
  - A phone call by the pharmacy to the patient, no more than 24 hours after the shipment is delivered, to verify that the medication and educational materials have been received
- If the patient is unavailable to accept a shipment of Xyrem® and execute the required receipt, the package will be returned to the pharmacy.
- If a shipment is lost, an investigation will be launched to find it.
- All patient assignment of benefit forms and registry information will need to be signed and sent back to the pharmacy before the next scheduled refill can occur

- Every patient and prescribing physician will be registered with (b)(4)----------n a secure database. The database will contain the physician's name, address, telephone and facsimile numbers, DEA and state license numbers and prescribing frequency. The database will be made available for review by the DEA as well as other federal and state agencies upon request. From this database it will be possible to obtain the following information
  Prescriptions by physician specialty
  Prescriptions by patient name
  Prescriptions by volume (frequency)
  Prescriptions by dose
- If required by the patient's insurance company the product may be shipped by (b)(4)---------to another pharmacy for patient pick-up. The sponsor anticipates ----------be an unusual occurrence, and has a mechanism for verifying the second pharmacy's ability to protect against diversion of GHB before shipping the drug there.
- Prescription refills will be permitted in the number specified in the original prescription. In addition
  - If a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned by the pharmacist
  - A lost, stolen, destroyed, or spilled prescription/supply will be documented and the prescription replaced to the extent necessary to honor the original prescription (e.g., a destroyed or spilled bottle will reduce the prescription refill amount). The pharmacist has the discretion to grant or not grant refill requests under those circumstances and at a minimum will contact the prescribing physician to determine if the physician has any special concerns in regard to that refill request. New supplies of Xyrem® will be sent to the patient only if the pharmacist and physician are in agreement.
  - Repeat instances of lost, stolen, destroyed, or spilled prescriptions/supplies will be flagged for monitoring and future instances thoroughly questioned
- The quantity of medication to provided with each refill will be guided by the following
  - With the first prescription it is planned to provide the patient with only one month's supply of Xyrem®.
  - Following further contact between the pharmacy and patient, and verification that the patient understands the material in the Xyrem® Patient Success Program, supplies of Xyrem® that are intended to last longer than a month may be shipped
  - The quantity of drug shipped to the patient with each refill may also be regulated based on the requirements of the patient's health insurance plan and the terms of the prescription itself
  - It is anticipated that the majority of patients will receive only one month's shipment at a time and never more than 3 months' supply per shipment.

14.1.2 Drug Product Kit

The drug product kit will consist of

- The drug product, a clear solution, in a 240 mL amber bottle with a closure mechanism that is child-resistant
- The Press-In-Bottle-Adapter (PIBA Well) which will be inserted into the bottle by the pharmacist

- An Exacta-Med Dispenser which allows the patient to withdraw the appropriate dose of drug
- Two child-resistant dosing cups, one for each of 2 nightly doses. The first dose will be consumed just prior to lying down at bedtime and the second dose will be placed at the bedside, and sealed with a childproof lid until consumed by the patient 2.5 to 4 hours later.
- A package insert which includes a patient information sheet*

Every box of Xyrem® shipped to the patient will contain all the above items

*The patient information sheet includes the following information
- Dosing instructions
- Preparation of dose
  The steps involved in dose preparation and use are as follows
  - Remove bottle cap
  - Insert measuring device into bottle containing PIBA Well
  - Draw up prescribed dose
  - Remove measuring device from bottle
  - Empty dose into first dosing cup
  - Dilute with 60 mL of water
  - Repeat procedures with second dosing cup
  - Place second dosing cup at bedside after securing lid
  - Set alarm for no later than 4 hours after first dose
  - Drink first dose sitting up and immediately lay down
  - Awake for second dose.
  - Drink second dose sitting up
- Side-effects
- Special concerns: memory problems, dependence, withdrawal, changes in behavior and thinking, pregnancy
- Safe use of Xyrem®:
  - scheduling
  - self-observation for behavioral changes
  - cautions regarding concurrent use of medications and alcohol, driving, operating machinery, piloting an aircraft and pregnancy
  - caution against sharing Xyrem® with others
  - safe storage and disposal

14.1.3 Xyrem® Physician Success Program

This program consists of a videotape and printed material.

14.1.3.1 Distribution

This program will be distributed as follows
- "Customer targets." This phrase refers to a database of physicians who have prescribed modafinil more than 4 times (about 4000 physicians have done so at present but the data will be refreshed when Xyrem® is launched). When Xyrem® is launched the program will be mailed to the target physicians as well as handed to them by sales representatives. The mailing as well as the receipt from sales representatives will be documented. No physician samples will be provided by the sales representatives
- When a physician prescribes the drug for the first time, he/she will receive also be mailed the program: the mailing will be documented as will a follow-up phone call to the physician confirming receipt

14.1.3.2 Videotape

The draft video "story-board" prepared by the sponsor contains the following elements

- The identity and medical uses of Xyrem®
- A short history of the development of this drug
- The need for patients to follow the physician's instructions in their entirety. Among other instructions the physician will need to tell patients that
  - The optimal dose of Xyrem® will need to be reached by titration over a number of weeks
  - Improvements in symptoms may not be fully apparent until 60-90 days after the drug is first begun
- Instructions regarding the frequency of dosing, emphasizing the need to take the medication twice every night.
- Very detailed instructions regarding the preparation of individual doses
- The need to place the second nightly dosage cup in an area not accessible to children, to store the medication bottle in a secure location and to consume the entire content of both dosing cups, sitting up.
- Directions as to when the bottle is to be disposed of (i.e., when the solution can no longer be drawn out of the bottle with the dispensing device), and emphasis on the need to empty the bottle completely and deface the label with a marker pen before throwing it away
- Federal scheduling of Xyrem® for legal and illegal use, the latter for punitive purposes
- The need to follow all standard procedures used for prescribing controlled substances
- A listing of types of patient behavior that may indicate misuse or abuse of Xyrem®
- The need to make clear to the patient that he or she may be legally responsible for the careless use and/or illicit distribution of Xyrem®
- Penalties for misusing or abusing Xyrem®
- The provision of an optional Patient Consent ("Patient/Physician Responsibility Contract") form in the information package. The form is intended to have 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.

14.1.3.3 Printed Materials

These are provided in a binder and consist of the following items

- A medical record template that covers the history, physical examination, assessment, treatment plan, prescription record, and a checklist of questions for the patient at each visit that covers the following: what dosage the patient is taking, whether the patient is taking 2 nightly divided doses, whether the patient is experiencing any side effects and whether the patient's symptoms have improved.
- A tabular outline of how Schedules I and III apply to the dispensing, distribution, diversion potential, patient access, tracking ability and manufacturing of drugs, and how the same items apply to Xyrem®
- An outline of how to identify patients who may be abusing Xyrem®
- Adverse effects associated with the use of Xyrem®

- A "Patient Physician Responsibility Contract" to be signed by both the patient and physician
- A series of instruction cards (contain print and graphics) to be used for by a physician for educating patients about all aspects of Xyrem®

14.1.4 Xyrem® Patient Success Program

14.1.4.1 Videotape

The draft video "story-board" prepared by the sponsor contains the following elements (the patient is instructed to watch the videotape prior to reading the printed materials)

- The identity and medical uses of Xyrem®
- A short history of the development of this drug
- The need to follow the physician's instructions completely and precisely, and to contact the physician in the event of questions
- Instructions regarding the frequency of dosing, emphasizing the need to take the medication twice every night.
- Very detailed instructions regarding the preparation of individual doses
- The need to place the second nightly dosage cup in an area not accessible to children, to store the medication bottle in a secure location and to consume the entire content of both dosing cups
- Directions as to when the bottle is to be disposed of (i.e., when the solution can no longer be drawn out of the bottle with the dispensing device), and the need to empty the bottle completely and deface the label with a marker pen before throwing it away
- The patient's legal liability in relation to the use of Xyrem®
  - Federal scheduling for legal and illegal use
  - A statement that the patient may be legally responsible for the careless use and/or illicit distribution of Xyrem®
  - Penalties for misusing or abusing the drug

14.1.4.2 Printed Materials

These are provided in a binder and consist of the following items about Xyrem®

- The drug's identity, and the reason for its prescription
- Its most common side effects (dizziness, headache and nausea) and the less common ones (pain, sleep disorder, confusion, infection, vomiting and urinary incontinence)
- The mechanism for filling prescriptions
- The need to follow physician instructions and not to alter the dose of medication without consulting the doctor
- The contents of the drug product kit that will accompany every bottle of the drug
- Instructions regarding the frequency and variability of dosing, emphasizing the need to take the medication twice every night.
- The need to wait a period of weeks to months until titrated to the optimal dose and until the full therapeutic benefits of the drug are seen
- The lack of interactions with other medications
- Storage instructions
- Action to be taken in case of accidental ingestion
- Insurance coverage

- A brief statement about the scheduling of Xyrem®, the patient's legal liability for misuse, abuse and diversion of the prescribed drug and the penalties linked to that liability (it is clearly stated that the use of Xyrem® by an individual for whom it is not prescribed is illegal)
- A description of the Patient Success Program
- Resources for information (names, addresses, phone numbers and URLs) about Xyrem®, narcolepsy and sleep disorders in general
- A patient quiz about Xyrem®
- A patient registry application to be completed by the patient and is to contain the following information
  - Patient name, address, telephone number, fax number, e-mail address, date of birth gender, social security number, patient record number, and medical insurance details (company name, patient number and group number)
  - Physician name, specialty, clinic name and address
- At home storage and safety tips: these include the following
  - The method of shipping, and the need to sign the courier's receipt personally
  - To keep Xyrem® in its original container, in a secure location and away from children and pets
  - When mixing each nightly dose to always use the dosing cups with child-resistant caps,
  - to make certain the second nightly dose is kept in a secure place
  - To re-order the drug when a 7-day supply remains,
  - To report a missing or stolen supply of Xyrem® to the local police and the Xyrem® Patient Success Program
  - To call the prescribing physician or Xyrem® Patient Success Program in the event of questions
- Traveling tips: these include the following
  - To keep Xyrem® in its original container and to take only the number of bottles needed for the trip, making certain that what is not taken on the trip is in a secure place at home
  - To keep Xyrem® in a secure location at all times
  - To remember to take the dispensing device and dosing cups with child-resistant caps when traveling
  - Not to include Xyrem® in checked baggage
  - To return home with the Xyrem® taken on the trip
  - The need to be aware that, if traveling internationally, Xyrem® might be subject to different regulations in foreign countries
  - To contact the Patient Success Program in the event of traveling without Xyrem® or needing a fresh supply in the event of an extended stay.
- Reimbursement information

14.2 OPDRA Comments

The Office Of Post-Marketing Drug Risk Assessment reviewed the Risk Management Program proposed for Xyrem®. The opinion of that office was conveyed to this Division in a formal review and in a discussion held February 5, 2001.

The final recommendations of that Office were as follows:

- The verification process conducted by (b)(4)----------on receiving a formal prescription should include confirmatio----------nt's diagnosis
- 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

- The proposed consent form should be mandatory rather than optional so as to ensure that each patient fully understands the educational material provided
- The patient registry information and benefit forms should be received by Nova Factor prior to the initial dispensing of the drug.
- Since preparation of each dose is complex, and to avoid overdosage, dispensing in the form of unit dose packages should be considered
- In addition to the standard post-marketing adverse event reporting, post-marketing safety assessments should also focus on drug abuse and dependence, diversion and accidental overdosage (e.g., by small children)

14.3 Comments Of Controlled Substances Staff

Final comments from this Agency group are still pending but the risk management program has been extensively discussed with them at internal meetings and meetings with the sponsor. At these meetings the views of this group have been conveyed to us in several presentations.

14.4 Additional Risk Management Recommendations

At an internal meeting chaired by Dr R. Temple, Office Director, that was held on 4/26/01 it was decided to ask the sponsor to consider including the following additional elements in the risk management program.

- Obtaining physician agreement to use GHB only for cataplexy, at the time of the first prescription
- Obtaining a physician undertaking, at the time of the first prescription to report instances of misuse and overuse of GHB to the sponsor
- Requiring active post-marketing surveillance by the sponsor (e.g., through physician surveys) to look for specific adverse events
- Making certain that that the pharmacist carefully tracks all GHB prescriptions (even for cash-paying patients) to see if excessive quantities are being prescribed
- Obtaining the physician's signed confirmation that he/she fully understands how GHB is to be used prior to the first prescription being filled
- Obtaining the patient's signed confirmation that he/she fully understands how GHB is to be used prior to the first prescription being mailed

15. Labeling Review

This has been done in a separate document entitled "NDA 21196 Labeling Review"

16. Overall Comments

16.1 Clinical Safety

- When GHB is used to treat narcolepsy in doses of 3-9 g/day the most common, and seemingly drug and dose-related adverse events have included the following: headache, unspecified pain, nausea and dizziness. Urinary incontinence is slightly less common, but apparently dose and drug-related as well. More serious, but much less common, adverse events seen at the same dose range, and that could be attributed to Xyrem®, have included vomiting,

confusion, restlessness, agitation, paranoia, hallucinations, somnolence and generalized weakness. No deaths that could be attributed to study drug have been reported at therapeutic doses of GHB

- One healthy 39 year old woman participating in a pharmacokinetic trial developed dizziness, nausea, vomiting, respiratory depression and fecal incontinence, after a single (and initial) oral dose of 4.5 g of GHB, administered after an overnight fast.
- A single older narcoleptic patient who had been taking GHB for approximately 1 ½ years was hospitalized after an overdose of GHB 18 g. At the time of hospitalization, he was comatose and unresponsive. He needed intubation and artificial ventilation, and awoke 6 hours later. This incident suggests that the safety margin between therapeutic and toxic doses, even in narcoleptic patients maintained chronically on GHB, may not be very wide
- At therapeutic doses of GHB all adverse events appear to be reversible
- While currently there is no strong evidence that GHB in therapeutic doses is epileptogenic or that episodes of urinary and fecal incontinence due to GHB are due to seizures, there is insufficient data at present to rule out either possibility.
- "Recreational" use of GHB generally at doses presumed or known to be higher than the therapeutic has been associated with adverse events that included fatalities attributable to the depressant effects of this drug on the nervous system. However concurrent use of alcohol and of other drugs with effects on the central nervous system has been reported in many of these instances
- There is no evidence that GHB is toxic to any major organ other than the nervous system.

16.2 Clinical Efficacy

This may be summarized as follows (please see the NDA Efficacy Review for full details)

- Currently there are no drugs approved for the treatment of cataplexy. There are several drugs approved for the treatment of excessive daytime sleepiness accompanying narcolepsy, or for narcolepsy as a generic entity. These are modafinil, methylphenidate and dextroamphetamine.
- There appears to be adequate evidence in this application that GHB is superior to placebo in treating cataplexy. This evidence comes from at least two, and possibly three randomized, double-blind, placebo-controlled trials.
- The efficacy of GHB in treating narcolepsy is most consistently seen at a dose of 9 g/day. It does not appear that doses < 4.5 g/day are effective
- There is currently inadequate evidence that GHB is effective in treating daytime sleepiness accompanying narcolepsy

16.3 Withdrawal Phenomena And Abuse Potential

- There is no evidence from a small formal study with a randomized withdrawal paradigm (OMC-SXB-21) that the abrupt discontinuation of <u>therapeutic doses</u> of GHB used for 6 months to 3 ½ years leads to more than mild and

infrequent withdrawal symptoms, except for a significantly increased frequency of cataplexy.

- There are however a number of anecdotal reports of an actual withdrawal syndrome and, possibly, addiction in illicit "recreational" users of GHB, GBL or 1-4 BD. In all these individuals high doses of GHB or related drugs were believed to have been used at frequent intervals around-the-clock.

16.4 Risk Management Program

The proposed risk management program may be adequate once the additional measures to be proposed by the Agency are incorporated (see Section 14.4)

16.5 Additional Comments

See Section 20 for additional comments based on a review of an Amendment submitted on 3/23/01

17. Study Site Inspections

At the request of this Division the Division of Scientific Investigations carried out an inspection of the Scharf long-term safety study. This inspection was requested after the Agency was informed that the Institutional Review Board for Dr Martin Scharf's sponsor-investigator IND # 21654 had withdrawn approval for that IND; the approval was stated to have been withdrawn based on protocol violations in a study conducted under that IND in patients with fibromyalgia.

In the FDA Form 483 issued to Dr Martin Scharf on 2/23/01 which was based on an inspection conducted from 2/6/01 to 2/23/01, the following deficiencies that are relevant to this application (and to the Scharf study in narcolepsy/cataplexy) were noted. These deficiencies were based on a review of records for 13 patients which was apparently all that could be accomplished over the inspection period given the disorganized state in which the study records were maintained

- Records of subjects were not adequately maintained by the investigator to assure accurate reporting of the subjects' data with respect to adverse events, test article accountability, informed consent and patient diaries
- Serious adverse events for 6 patients were not reported to the appropriate Institutional Review Board
- 2 separate diaries were noted for the same subject for the same period of time (November 1999): the handwriting in the diaries was different as was the data which was conflicting
- In each of 5 patients, a number of adverse events in source documents were not reported to Orphan Medical, Inc.
- In 2 patients diaries covering periods of 1-2 years could not be found
- In a number of patients drug dispensing records were not available (the absent records were for periods from 1 to 7 years). When dispensing logs were actually available, they were incomplete

In an effort to ensure that major adverse events in this study were captured the Division made a number of recommendations to the sponsor during meetings and teleconferences held in February-March 2001.

- Obtaining as much information as possible about the status of the 80 patients in the Scharf study who did not enter the OMC-SXB-7 (treatment IND) study; if their current status was not known their health at the time of discontinuation from the Scharf study (which the majority of the 80 patients did leave) and for 1-2 months afterward needed to be ascertained.
- Obtaining as much information as possible about all patients listed as having convulsions during the study.
- Obtaining as much information as possible about all patients whose adverse events were listed as "unevaluable"
- Obtaining as much information as possible about patients with the following adverse events: confusion and other neuropsychiatric symptoms, and urinary and fecal incontinence
- Tracing drug dispensing records

A further inspection of the study site is planned, which is to intended to be mainly focussed on data submitted with the Major Amendment of 3/23/01

18. Financial Disclosure Certification

Financial disclosure certification has been submitted with this application.

18.1 Components Of Certification

This certification has 2 components

18.1.1 Certification Pertinent To Dr Lawrence Scrima

The sponsor has supplied required financial disclosure information for Dr Scrima.

Orphan Medical, Inc, entered into a financial contract with Dr Scrima on 11/10/99. The contract allowed Orphan Medical to access documentation associated with the double-blind, placebo-controlled, cross-over trial in 20 narcoleptic patients. The trial was conducted from April 5, 1986 to December 14, 1987.

The sponsor states that payments to Dr Scrima were made over 10 years after completion of the trial. While the payment was financially disclosable it did not have any impact on data collection, interpretation or analysis

18.1.2 Certification Pertinent To Other Investigators

The sponsor has supplied a list of 32 Investigators who conducted clinical trials on behalf of Orphan Medical, Inc. In regard to this list the sponsor has

- Certified that it has not entered into any financial agreement with the clinical investigators listed in the application whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)
- Certified that each listed clinical investigator required to disclose to the sponsor that whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements

- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)

18.2 Reviewer's Comment

It appears unlikely that the financial arrangement disclosed above introduced significant bias into the results of studies carried out with Xyrem®, and submitted with this NDA.

19. Major Amendment

On March 23, 2001, the sponsor submitted a major amendment to this NDA

The purpose of the amendment was to address the following

- The deficiencies in the Scharf study outlined previously
- A number of questions pertaining to the safety data for clinical trials conducted by Orphan Medical
- Several related issues.

In submitting the major amendment the sponsor requested a 90-day extension to the original Prescription Drug User Fee Act deadline of April 2, 2001.

This major amendment is reviewed in a separate document. Please refer to that review for full details

20. Additional Comments Based On Review Of Major Amendment

My comments are summarized below. In order to understand the context of the comments further, the reader will need to refer to the review of the Amendment itself which is in a separate document.

- The manner in which data for the Scharf study have been collected, recorded, and presented in this submission cannot be said to be ideal.
- Of the 80 patients who participated in the Scharf study and did not enter the currently ongoing Orphan Medical Treatment IND study OMC-SXB-7, 64 patients might be stated to have be "accounted for" although the basis for doing so is less-than-optimal in a significant number. Further efforts need to be made by the sponsor to account fully for 11 of the remaining 16 (unsuccessful recent efforts have been made to contact 5 patients out of those 16). The 11 patients are listed below. Adverse events that were ongoing at the time of discontinuation are reasons for obtaining further follow-up in at least some of these 11 patients

01-004/(b)
01-027/(6)
01-054/-----
01-065/------
01-228/----
01-240/-----
01-262/------
01-269/-----

01-283(b)(
01-2686)---
01-256-------

- None of the "adverse events" in the "unevaluable" category that occurred in the Scharf study appear to be attributable to GHB
- Urinary and fecal incontinence both appear to be unusually common adverse events in patients taking GHB and the key issues are whether such episodes are accompaniments of unrecognized convulsions, and whether GHB is capable of causing convulsions at therapeutic doses. Currently the evidence that the vast majority of episodes of incontinence in the entire NDA are related to unrecognized convulsions is weak. There does appear to be at least 1 patient in the Scharf study in whom incontinence clearly accompanied a true convulsion.
- While there are clearly a few patients (n = 2) in the entire NDA safety database who experienced, or may have experienced, convulsions while taking GHB, the presence of confounding factors (e.g., possible benzodiazepine withdrawal) makes it difficult to link the convulsions causally to GHB. Whether GHB is capable of causing other types of seizures, e.g., absence or partial complex, is even less clear
- 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. Detailed clinical descriptions of such episodes are not available for the majority of patients and their mechanism has not been delineated. A separate analysis of these episodes has not been performed by the sponsor and it is not clear how common they are in the Integrated Clinical Trials grouping, but such episodes have been associated with serious consequences (e.g., overdose, pyrogenesis, consuming toxic chemicals) in patients enrolled in the Scharf study
- The information available in this NDA does suggest that GHB is capable, at therapeutic doses, of causing a confusional state (which may be accompanied by psychotic symptoms). The incidence and seriousness of such adverse events may be slightly more pronounced at higher doses, and especially if higher doses are administered without titration. However a confusional state also appears to be capable of occurring at lower and even sub-therapeutic doses of GHB, and after maintenance treatment for several months. The presence of true confusion in patients taking GHB could lead to their taking GHB in a manner other than as prescribed. The symptoms that have been subsumed under the COSTART term "confusion" are not unusual for a sedative-hypnotic drug.
- In the majority of patients who developed "neuropsychiatric" adverse events (e.g., paranoia, hallucinations, anxiety, stupor, etc) while taking GHB in Integrated Clinical Trials it is not possible to attribute causality for the adverse event to GHB. Pre-existing psychiatric illness, and concomitant medications such as stimulants, as well as other factors, could be contributory. Even in patients in whom there was no recorded premorbid history of psychiatric illness the extent to which they were screened for such illness is not clear.

However the occurrence of neuropsychiatric adverse events in patients taking GHB, even if not directly caused by the drug, could place them at risk of intentional or accidental overdose, as is suggested by the narratives in this review

- There is no firm evidence that any patients participating in the Integrated Clinical Trials had drug-induced lupus. However antinuclear antibody and antihistone antibody testing was not performed for patients participating in this study
- There is no evidence suggesting a causal link to GHB for the small number of hypoglycemic an hyperglycemic blood test readings in the NDA; several of the apparently hypoglycemic readings could in fact have represented laboratory errors. Neither is there firm evidence in AERS or in the medical literature that GHB is capable of causing hypoglycemia.
- GHB is unlikely to have been the cause of transaminase elevations seen in a few patients in the Integrated Clinical Trials.
- The total number of patients exposed to GHB in the NDA Safety Database minus the Scharf study appears sufficient to meet ICH guidelines at the 6-month and 1-year levels but not in regard to the total number of patients exposed; however allowance can be given for GHB being designated as an orphan drug and the total number exposed may therefore be acceptable.

  However, the extent of exposure to GHB in patient-years is reduced by about 79% once the Scharf study data are eliminated. Admittedly, the ICH guidelines do not specifically address the issue of desirable exposure in patient-years.

  Further if one concludes (from the efficacy studies) that the 9 g/day dose is the only effective dose and is that to be recommended for general use the number of those exposed to Xyrem® for ≥ 12 months does not meet ICH guidelines

  Note that ICH guideline E1A (July 1997) states the following: "100 patients exposed for a minimum of 1 year is considered to be acceptable to include as part of the safety database. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use."

21. Conclusions

Deferred

22. Recommendations

Deferred

Ranjit B. Mani, M.D.
Medical Reviewer

J. Feeney, M.D. _____

rbm 5/3/01
cc:
HFD-120
NDA 21196
Homonnay

Electronic Acknowledgement Receipt

EFS ID:	15112941
Application Number:	13592202
International Application Number:	
Confirmation Number:	5805
Title of Invention:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
First Named Inventor/Applicant Name:	Dayton T. Reardan
Customer Number:	21186
Filer:	Eric B. Andersland/Valerie Murphy
Filer Authorized By:	Eric B. Andersland
Attorney Docket Number:	101.031US9
Receipt Date:	04-MAR-2013
Filing Date:	22-AUG-2012
Time Stamp:	18:42:16
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13592202_SIDS_3-4-13.pdf	223390 a69b1cac88477cce34bc6328d6695eab95021aa2	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Miscellaneous Incoming Letter	1	1
	Transmittal Letter	2	3
	Information Disclosure Statement (IDS) Form (SB08)	4	4

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Information:					
2	Non Patent Literature	0001_advisory_committee__briefing_information.pdf	9276770 1d647695f47c0f3f7a073e960a7080bc42350650	no	353
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Information:					
			Total Files Size (in bytes):	86338915	

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.

TABLE 23-C-continued

USA

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. LOT: MCH1064-3
(28 DAYS CHALLENGE TEST) CODE:
PROTOCOL 98126 REQUISITION: 1741
ORPHAN MEDICAL

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	258 mg/ml (103%)	NPLC-793-D
Impurities total	≦2.0%	0.045%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.45: 0.016%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.79: 0.009%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 2: 250 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328845

TABLE 23-D

ORPHAN MEDICAL INC. DATE: Jan. 21, 1999
13911, Ridgedale Drive NO.: 331346
Minnetonka, (MN) 55305
USA

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID LOT: MCH1064-3
FORMULATION CODE:
PROTOCOL 98126 REQUISITION: 1741
ORPHAN MEDICAL

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	256 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.18%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.46: 0.13%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.31: 0.03%	
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)

Formulation 2: 250 mg/cc; Malic acid; pH 7.5

*A: RRT 1.29: 0.007% RRT 3.93: 0.008%

TABLE 23-E

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Jan. 26, 1999
NO.: 333196

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	360 mg/ml (103%)	NPLC-793
Impurities total	≦2.0%	0.050%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.45: 0.017%	NPLC-793D
GBL-RRT 1.6	Impurity A (RRT 4.3): ≦0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.006% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.7	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 3: 350 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328847

TABLE 23-F

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Jan. 21, 1999
NO.: 331345

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	363 mg/ml (104%)	NPLC-793-D
Impurities total	≦2.0%	0.21%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.46: 0.14%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.31: 0.05%	
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	8.0	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 3: 350 mg/cc; Malic acid; pH 7.5
*A: RRT 1.29: 0.009% RRT 3.93: 0.008%

TABLE 23-G

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Jan. 26, 1999
NO.: 333195

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126

LOT: MCH1064-4
CODE: 1741
REQUISITION: 1741

TABLE 23-G-continued

ORPHAN MEDICAL TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	461 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.065%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.45: 0.018%	NPLC-793D
GBL-RRT 1.6	Impurity A (RRT 4.3): ≦0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.02% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 4: 450 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328875

TABLE 23-H

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Jan. 21, 1999
NO.: 331343

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	454 mg/ml (101%)	NPLC-793-D
Impurities total	≦2.0%	0.40%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.46: 0.26%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.31: 0.1%	
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 4: 450 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.03% RRT 3.93: 0.008%

TABLE 23-I

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Jan. 26, 1999
NO.: 333194

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	563 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.077%	NPLC-793D
Impurities specified	Gamma-	RRT 1.45: 0.020%	NPLC-793D

TABLE 23-I-continued

GBL-RRT 1.6	Butyrolactone (RRT = 1.6): ≦0.5%		
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.29: 0.03% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 5: 550 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328883

TABLE 23-J

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Jan. 21, 1999
NO.: 331341

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	561 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.56%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.46: 0.31%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.31: 0.2%	
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)

Formulation 5: 550 mg/cc; Malic acid; pH 7.5

*A: RRT 1.30: 0.04% RRT 3.93: 0.007%

TABLE 23-K

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Jan. 26, 1999
NO.: 333193

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	666 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.10%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.45: 0.025%	NPLC-793D
GBL-RRT 1.6	Impurity A (RRT 4.3): ≦0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.05% RRT 328: 0.007%	NPLC-793D

TABLE 23-K-continued

PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 6: 650 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328885

TABLE 23-L

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Jan. 21, 1999
NO.: 331336

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	660 mg/ml (102%)	NPLC-764
Impurities total	≦2.0%	0.81%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.46: 0.43%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.31: 0.3%	
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)

Formulation 6: 650 mg/cc; Malic acid; pH 7.5

*A: RRT 1.30: 0.07%

RRT 3.93: 0.007%

TABLE 23-M

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Jan. 26, 1999
NO.: 333192

CERTIFICATE OF ANALYSIS

QXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	518 mg/ml (104%)	NPLC-793
Impurities total	≦2.0%	0.065%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.45: 0.018%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.79: 0.007% RRT 5.99: 0.02%	NPLC-793D

TABLE 23-M-continued

PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 7: 500 mg/cc; Citric acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 329033

TABLE 23-N

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Jan. 21, 1999
NO.: 331335

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	515 mg/ml (103%)	NPLC-793-D
Impurities total	≦2.0%	0.38%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.46: 0.27%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.31: 0.1%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.93: 0.007%	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)

Formulation 7: 500 mg/cc; Citric acid; pH 7.5

TABLE 23-O

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Sep. 09, 1999
NO.: 330721

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM LIQUID FORM. (28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Challenge Test	Conforms to USP (0, 1, 7, 14, 21 and 28 days)	Conforms	USP 23 <51> S.8
Potency	Report	501 mg/ml (100%)	NPLC-793
Impurities total	≦2.0%	1.2%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.013%	NPLC-793D

TABLE 23-O-continued

	Report:		
PH	Report	7.3	USP <791>
Solubility study	Report	*B	PR 98126 IIA

COMMENTS:
Initial test
500 mg/ml cc; Malic acid; pH 7.5
*A: RRT 1.31: 0.02% RRT 1.67: 0.008%
RRT 1.91: Interference with peak of dilution solvent cannot calculate.
RRT 3.47: 0.1% RRT 3.79: 0.009% RRT 3.84: 0.01%
RRT 4.18: 0.06% RRT 5.10: 0.008% RRT 5.35: 0.02%
RRT 6.74: 0.9% RRT 6.90: 0.08% RRT 7.41: 0.006%
*B: Maximum solubility: 700 mg/ml no pH adjustment.

TABLE 23-P

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Feb. 26, 1999
NO.: 331307

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM LIQUID FORM.
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	508 mg/ml (102%)	NPLC-793
Impurities total	≤2.0%	0.70%	NPLC-793D
Impurities unspecified	Ind. imp. ≤0.1%	*A	NPLC-793D
Impurities specified	Gamma-Butyrolactone Report:	RRT 1.37: 0.054%	NPLC-793D
PH	Report	7.6	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
500 mg/cc; Malic acid; pH 7.5
*A: RRT 1.17: 0.03% RRT 3.47: 0.2%
RRT 5.46: 0.01% RRT 6.87: 0.3%
RRT 7.04: 0.007%
RRT 1.78: Can not calculate because it interfere with a dilution solvant peak.

This report summarizes the results of the above described study and provides a summary of previous development work which evaluated conditions other than those evaluated in this study. The purposes of this information is to define the scope and limitations of the self-preserving properties of Xyrem® oral solution for completion of patent application.

II. Summary of Results:

A. Preparation of Various Formulations of Sodium Oxybate and Formulations Using an Alternative Salt of GHB.

1. Various formulations of sodium oxybate were prepared as directed in the above Protocol. Sodium oxybate, 500 mg/cc with Malic Acid was not soluble at pH 5.0, and further evaluation of this solution was discontinued. All other solutions were successfully prepared as described.
2. The preparation of an alternative salt of gamma-hydroxybutyrate was described as the calcium salt, prepared at 500 mg/cc (or maximum possible) with Malic Acid at pH 7.5.
   a. The calcium salt of gamma-hydroxybutyrate was prepared by Toronto Research and shipped to NeoPharm for determination of solubility and evaluation according to the Protocol. The absolute limit of solubility, without pH adjustment, was determined to be 700 mg/cc. The pH of this solution was 8.4. Solutions of lower pH were more difficult to prepare at 500 mg/cc using Malic acid as acidulant. When pH was adjusted to 6.0 with Malic acid, the solubility of the calcium oxybate was limited (longer stirring required to solubilize). The desired solution of 500 mg/cc, pH 7.5 was prepared with Malic acid as acidulant without difficulty. Appearance of the final solution was slightly yellow in color. Copies of the laboratory record for preparation of these solutions is available.

B. Microbial Challenge Testing of the Various Formulations Prepared by MDS NeoPharm.

The microbial challenge testing was carried as specified in the Protocol and the following table summarizes the results of microbial challenge testing of various formulations of sodium oxybate and the single calcium oxybate formulation prepared.

TABLE 24

Testing of Sodium and Calcium GHB Salts

Sodium Oxybate Concentration	pH of Solution	Microbial Challenge Result
1. 500 mg/cc	7.5 (Malic acid)	Pass
2. 250 mg/cc	7.5 (Malic acid)	Pass
3. 350 mg/cc	7.5 (Malic acid)	Pass

TABLE 24-continued

Testing of Sodium and Calcium GHB Salts

	pH of Solution	Microbial Challenge Result
4. 450 mg/cc	7.5 (Malic acid)	Pass
5. 550 mg/cc	7.5 (Malic acid)	Pass
6. 650 mg/cc	7.5 (Malic acid)	Pass
7. 500 mg/cc	7.5 (Citric acid)	Pass
Calcium Oxybate Concentration		
500 mg/cc	7.5	Pass

C. Short Term Stability Evaluation of Various Formulations of Sodium Oxybate and a Formulation of Calcium Oxybate.

Solutions were tested on day zero (preparation day) and day 28 according to the described Protocol. The results of the stability evaluation are summarized in Table 25 below:

TABLE 25

Sodium and Calcium GHB Evaluation

Sodium oxybate solution	Potency mg/cc (%)	Impurities (Total)	Impurities (Unspecified)	Impurities (Specified – GBL)	pH
500 mg/cc pH 7.5 Malic Acid Day 0	512 mg/cc (102%)	0.68%	0.041%	0.027%	7.6
Day 28	510 mg/cc (103%)	0.36%	0.33%	0.028%	7.9
250 mg/cc pH 7.5 Malic Acid Day 0	258 mg/cc (103%)	0.045%	0.009%	0.026%	7.6
Day 28	256 mg/cc (102%)	0.18%	0.015%	0.16%	7.9
350 mg/cc pH 7.5 Malic Acid Day 0	360 mg/cc (103%)	0.050%	0.013%	0.037%	7.7
Day 28	363 mg/cc (104%)	0.21%	0.017%	0.19%	8.0
450 mg/cc pH 7.5 Malic Acid Day 0	461 mg/cc (102%)	0.065%	0.027%	0.038%	7.5
Day 28	454 mg/cc (101%)	0.40%	0.038%	0.36%	7.8
550 mg/cc pH 7.5 Malic Acid Day 0	563 mg/cc (102%)	0.077%	0.037%	0.040%	7.6
Day 28	561 mg/cc (102%)	0.56%	0.047%	0.51%	7.9
650 mg/cc pH 7.5 Malic Acid Day 0	666 mg/cc (102%)	0.10%	0.057%	0.045%	7.6
Day 28	660 mg/cc (102%)	0.81%	0.077%	0.73%	7.8
500 mg/cc pH 7.5 Citric Acid Day 0	518 mg/cc (104%)	0.065%	0.027%	0.038%	7.5
Day 28	515 mg/cc (103%)	0.38%	0.007%	0.37%	7.9

TABLE 25-continued

Sodium and Calcium GHB Evaluation

Calcium oxybate solution	Potency	Impurities (Total)	Impurities (Specified)	Impurities (Unspecified)	pH
500 mg/cc pH 7.5 Malic Acid Day 0	501 mg/cc (100%)	1.2%	>0.1% (See C of A Attached)	0.013%	7.3
Day 28	508 mg/cc (102%	0.70%	>0.1% (See C of A)	0.054%	7.6

D. Summary of Pertinent Solubility and Microbial Challenge Data are shown in Tables 26 and 27.

TABLE 26

Limits of Solubility

	pH of Solution	Comment
Sodium oxybate Maximum Solubility		
450 mg/cc	pH 4 (HCl)	25°
500 mg/cc	pH 5 (HCl)	25°
600 mg/cc	pH 6 (HCl)	25°
750 mg/cc	pH 6.8 (HCl)	25°
750 mg/cc + 1000 mg/cc	pH 10.3 pH (unadjusted)	25° 65° Soluble, 25° Gel
Calcium oxybate Maximum Solubility		
700 mg/cc	pH 8.4 (unadjusted)	25°
500 mg/cc	pH 6.0	25°

TABLE 27

Microbial Challenge Results

	pH of Solution	Microbial Challenge Result
Sodium oxybate Concentration (Date)		
750 mg/cc (December '97)	7.5 (HCl)	pass
500 mg/cc (December '97)	6.0 (HCl)	pass
500 mg/cc + Excipients (Xylitol) (March '98)	6.0 (Malic Acid)	pass
500 mg/cc (March '98)	9.0 (HCl)	pass (Borderline *aspergillus*)
150 mg/cc (BDL 1995)	5.0 (HCl)	fail (*aspergillus* only)
150 mg/cc (BDL 1995)	7.0 (HCl)	fail (*aspergillus* and staph)
150 mg/cc (BDL 1995)	3.0 (HCl)	fail (*aspergillus* only)
150 mg/cc (BDL 1995)	10.3 (unadjusted)	fail (*aspergillus* and staph)
500 mg/cc (May '98)	6.0 (Malic Acid)	discontinued
500 mg/cc (May '98)	7.5 (Malic Acid)	pass
500 mg/cc (May '98)	9.0 (Malic Acid)	discontinued
500 mg/cc (May '98)	7.5 (HCl)	pass
500 mg/cc	7.5 (Malic Acid)	pass
250 mg/cc	7.5 (Malic Acid)	pass
350 mg/cc	7.5 (Malic Acid)	pass
450 mg/cc	7.5 (Malic Acid)	pass
550 mg/cc	7.5 (Malic Acid)	pass

TABLE 27-continued

Microbial Challenge Results		
	pH of Solution	Microbial Challenge Result
650 mg/cc	7.5 (Malic Acid)	pass
500 mg/cc	7.5 (Malic Acid)	pass
Calcium oxybate Concentration (Date)		
500 mg/cc	7.5 (Malic Acid)	pass

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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The invention claimed is:

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 cataplepsy.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,851,506 B2
APPLICATION NO. : 11/777877
DATED : December 14, 2010
INVENTOR(S) : Harry Cook et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page, Item (56)
On page 2, under "Other Publications", in column 1, line 10, delete ""Gamma-Hydroxybutric" and insert -- "Gamma-Hydroxybutyric --, therefor.

Title Page, Item (56)
On page 2, under "Other Publications", in column 2, line 36, delete "Obsturctive" and insert -- Obstructive --, therefor.

On Sheet 1 of 1, in Figure 1, line 9, delete "rresistant" and insert -- resistant --, therefor.

In column 1, line 58, delete "paralysis," and insert -- paralysis --, therefor.

In column 3, line 61, delete "3.6;" and insert -- 3.6, --, therefor.

In column 6, line 56, delete "taitrate," and insert -- tartrate, --, therefor.

In column 9, line 4, delete "1-9," and insert -- 1.9, --, therefor.

In column 10, line 8, delete "separately," and insert -- separately --, therefor.

In column 10, line 14, delete "comprising," and insert -- comprising --, therefor.

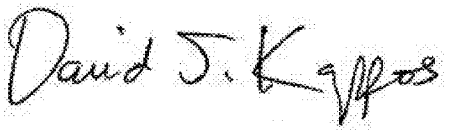
In column 12, line 8, delete "cout" and insert -- count --, therefor.

In column 12, line 60, delete "formulations-then" and insert -- formulations then --, therefor.

In column 14, line 61, delete "solutions," and insert -- solutions --, therefor.

In column 15, line 30, delete "thle" and insert -- the --, therefor.

Signed and Sealed this
Twenty-second Day of February, 2011



David J. Kappos
Director of the United States Patent and Trademark Office

In column 21, line 17, delete "GHB-content." and insert -- GHB content. --, therefor.

In column 24, line 31, delete "+5. %" and insert -- ±5% --, therefor.

In column 24, line 44, delete "25±20°" and insert -- 25±2° --, therefor.

In column 28, line 56, delete "Medical" and insert -- Medical. --, therefor.

In column 29, line 22, delete "(Coming" and insert -- (Corning --, therefor.

In column 29, lines 55-56, delete "Iansoprazole," and insert -- lansoprazole, --, therefor.

In column 30, line 4, delete "bad" and insert -- had --, therefor.

In column 31, line 63, delete "conditions," and insert -- conditions --, therefor.

In columns 33-34, line 6, above "TABLE 13" insert -- Formulation Study/PR98068
Results of Formulation Study - Time Zero determinations of Sodium Oxybate, GBL and Unspecified Impurities --.

In column 36, line 52, delete "HCL" and insert -- HCl --, therefor.

In column 36, line 53, delete "HCL," and insert -- HCl, --, therefor.

In column 36, line 53, delete "(250)" and insert -- (25°) --, therefor.

In column 38, line 61, delete "10"" and insert -- 10^5 --, therefor.

In column 40, line 15, delete "time," and insert -- time. --, therefor.

In columns 41-42, line 4, delete "Inoculu" and insert -- Inoculum --, therefor.

In column 43-44, line 4, delete "Inoculu" and insert -- Inoculum --, therefor.

In columns 47-48, line 33, delete "1C" and insert -- IC --, therefor.

In column 51, line 3, delete "show" and insert -- shown --, therefor.

In columns 59-60, line 64, delete "328:" and insert -- 3.78: --, therefor.

In columns 61-62, line 44, delete "QXYBATE" and insert -- OXYBATE --, therefor.

In columns 63-64, line 1, delete "Sep. 09," and insert -- Sep. 02, --, therefor.

In columns 65-66, line 7, delete "mg/ml cc;" and insert -- mg/cc; --, therefor.

In column 68, line 18, delete "(102%" and insert -- (102%) --, therefor.

In column 69, line 8, delete "(Malic" and insert -- (Citric --, therefor.

In column 70, lines 27-28, delete "Bouicicaut," and insert -- Boucicaut, --, therefor.

In column 71, line 5, delete "15:1333-11348," and insert -- 15:1333-1348, --, therefor.

In column 72, lines 36-37, in Claim 3, delete "catalepsy." and insert -- cataplexy. --, therefor.

EXHIBIT E

US007895059B2

(12) **United States Patent**
Reardan et al.

(10) **Patent No.: US 7,895,059 B2**
(45) **Date of Patent: *Feb. 22, 2011**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

(75) Inventors: **Dayton T. Reardan**, Shorewood, MN (US); **Patti A. Engel**, Eagan, MN (US); **Bob Gagne**, St. Paul, MN (US)

(73) Assignee: **Jazz Pharmaceuticals, Inc.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/704,097**

(22) Filed: **Feb. 11, 2010**

(65) **Prior Publication Data**

US 2010/0138237 A1 Jun. 3, 2010

Related U.S. Application Data

(63) Continuation of application No. 10/322,348, filed on Dec. 17, 2002, now Pat. No. 7,668,730.

(51) **Int. Cl.**
G06Q 10/00 (2006.01)

(52) **U.S. Cl.** **705/2**; 705/3; 600/300

(58) **Field of Classification Search** 705/2, 705/3; 600/300

See application file for complete search history.

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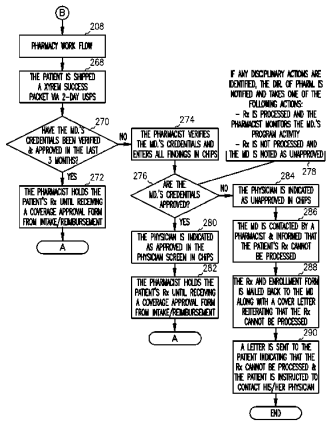
Primary Examiner—Jerry O'Connor
Assistant Examiner—Lena Najarian
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg & Woessner, P.A.

(57) **ABSTRACT**

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

16 Claims, 16 Drawing Sheets



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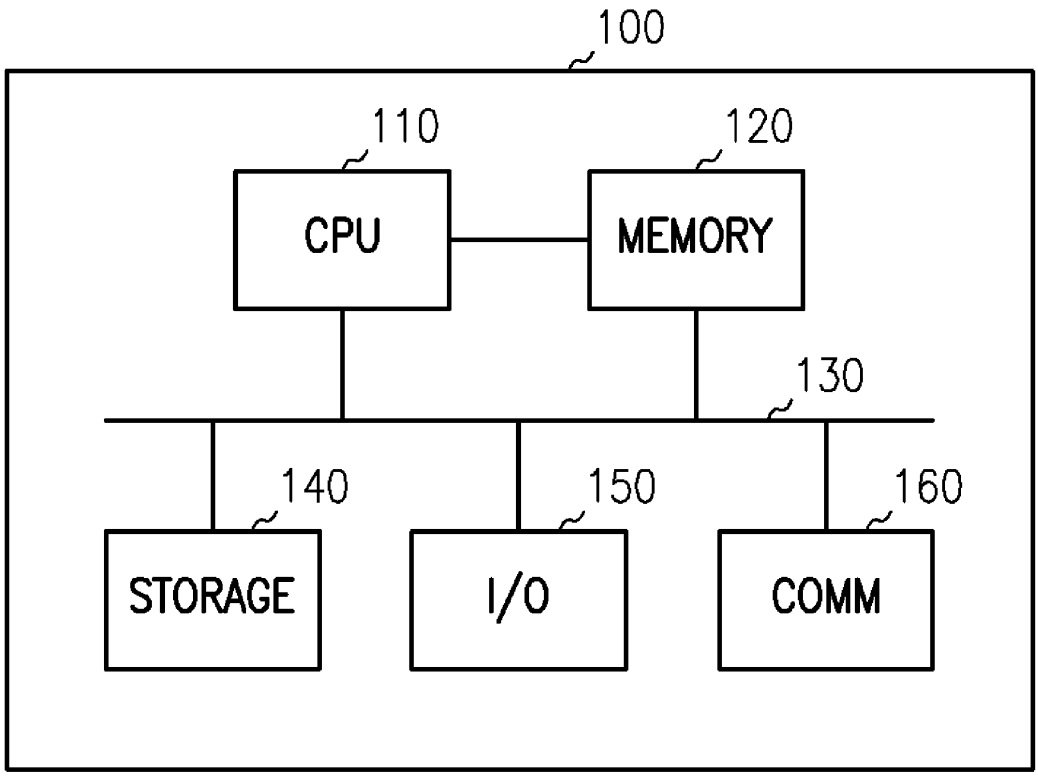

FIG. 1

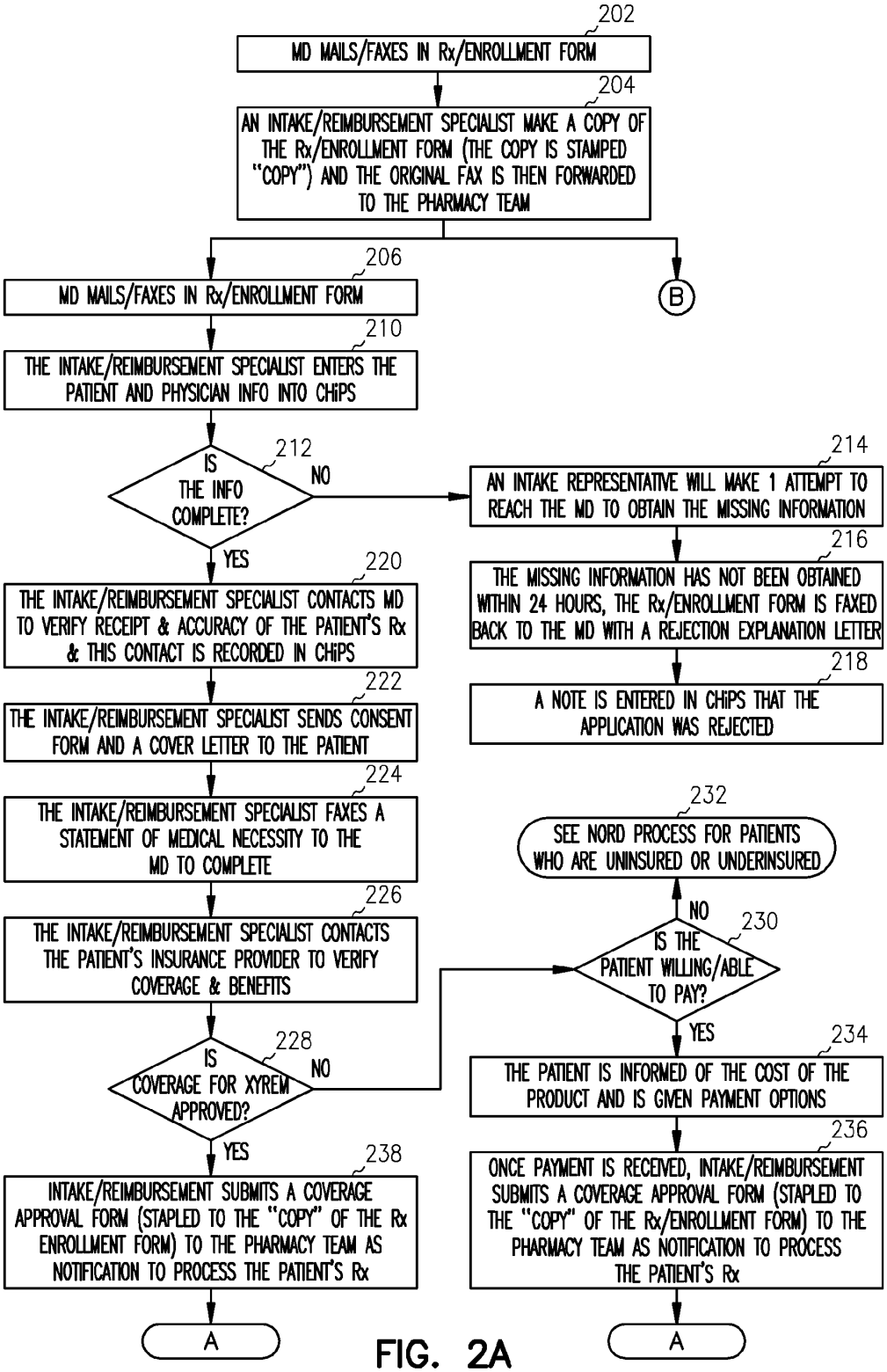
202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE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

FIG. 2A

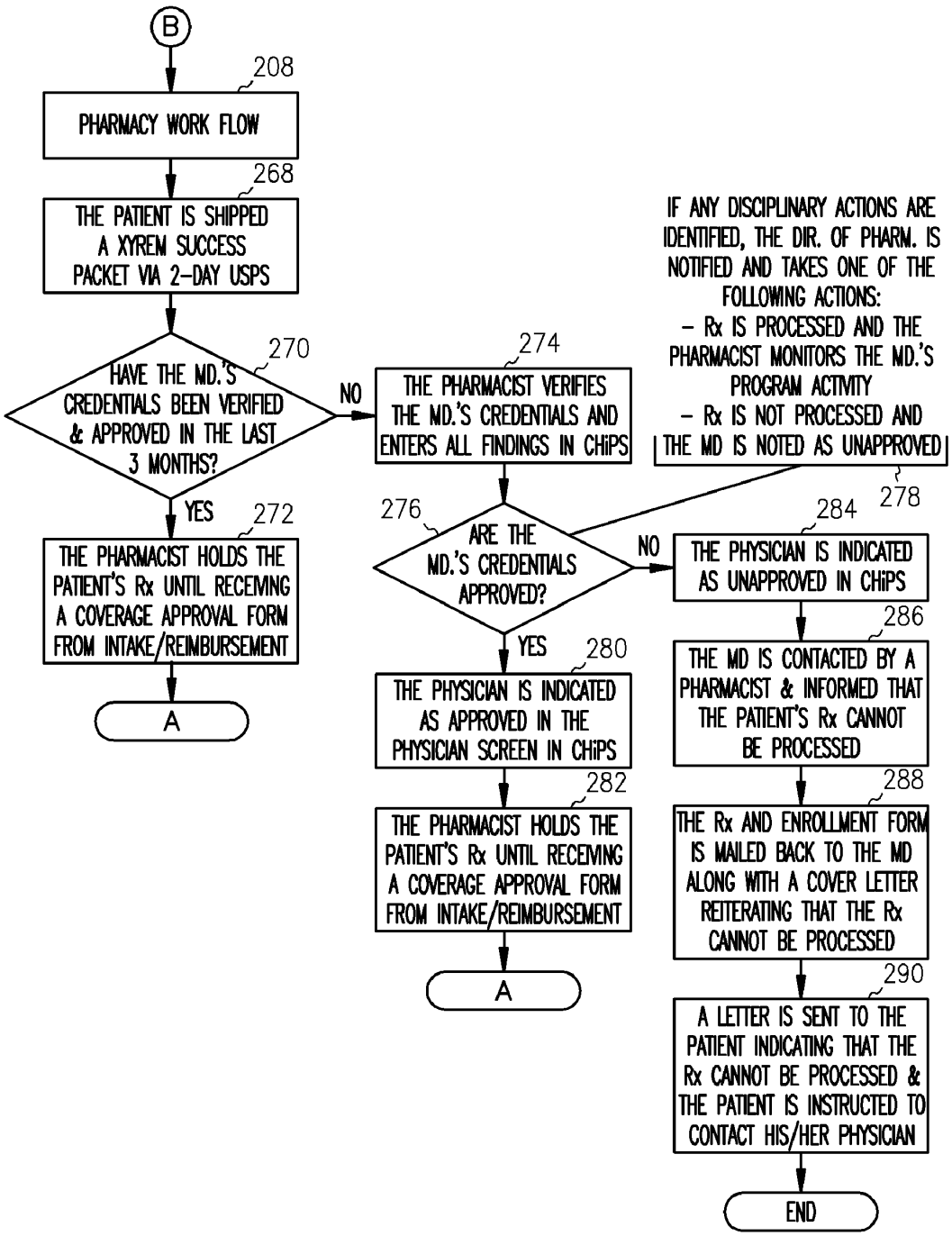
B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST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

FIG. 2B

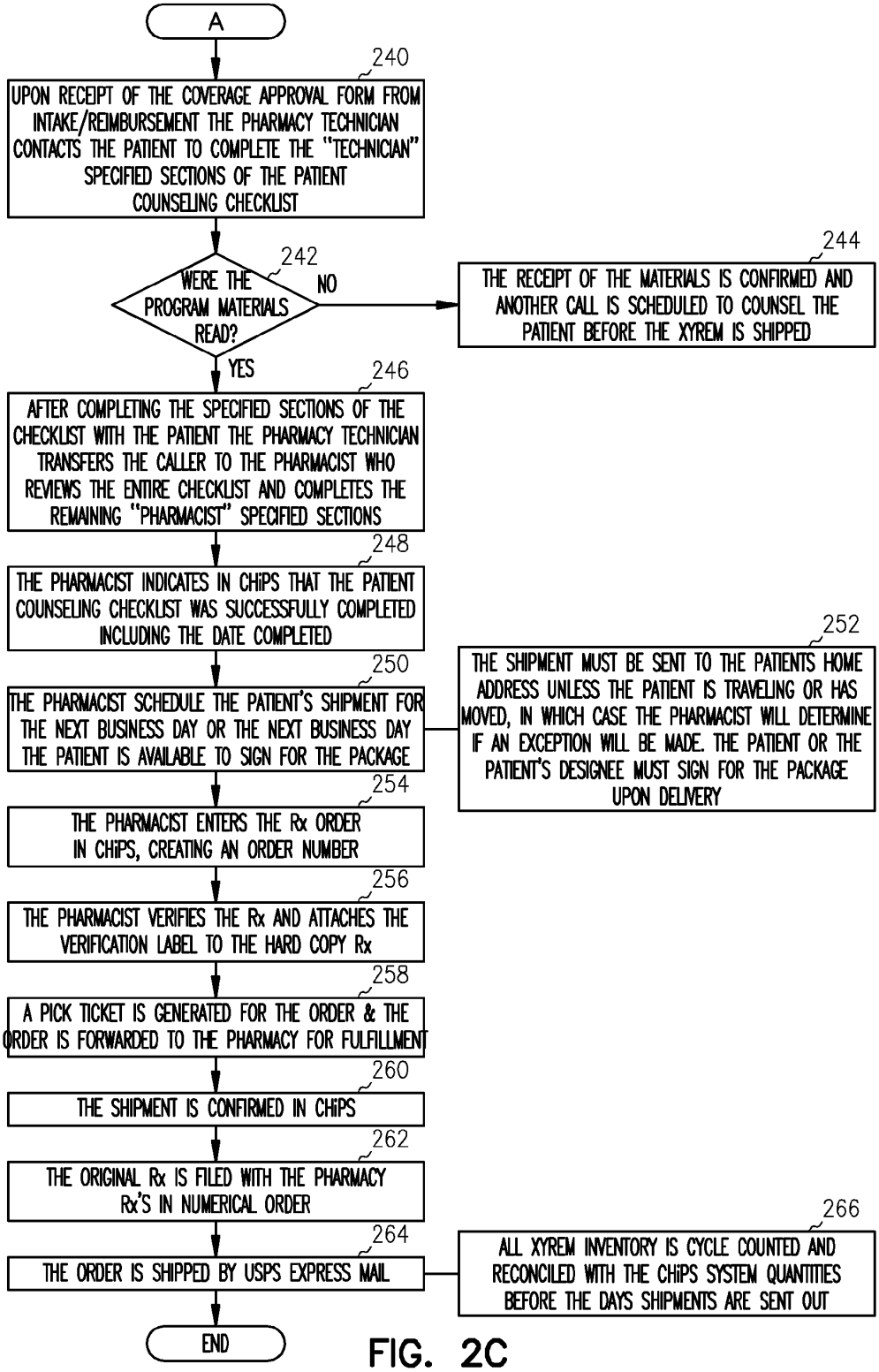
A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER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

FIG. 2C

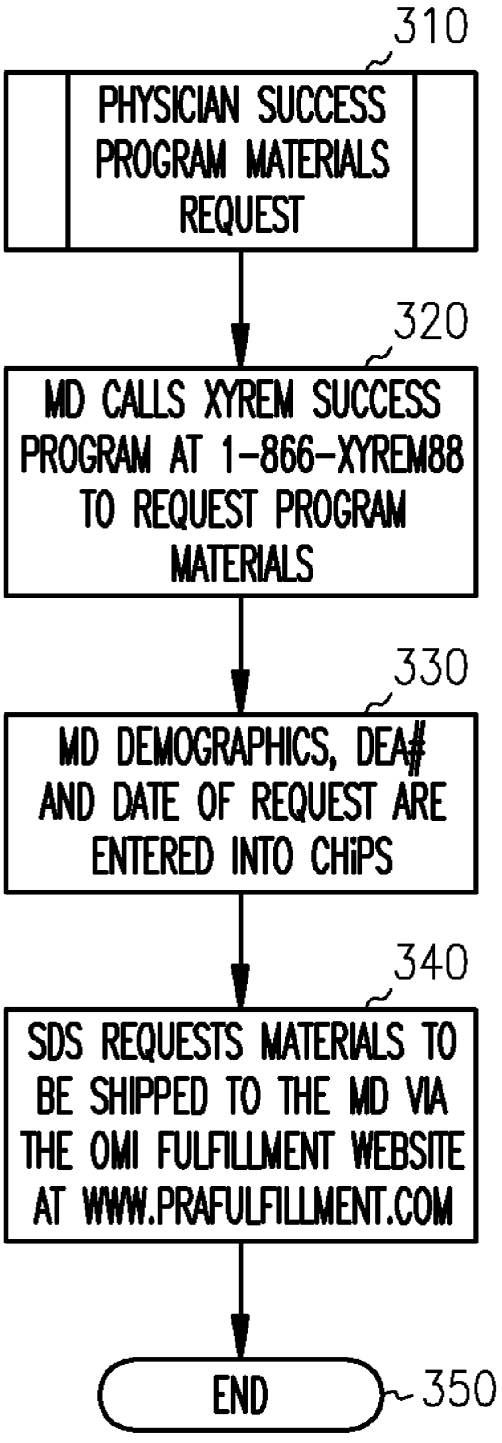
310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHIPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM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

FIG. 3

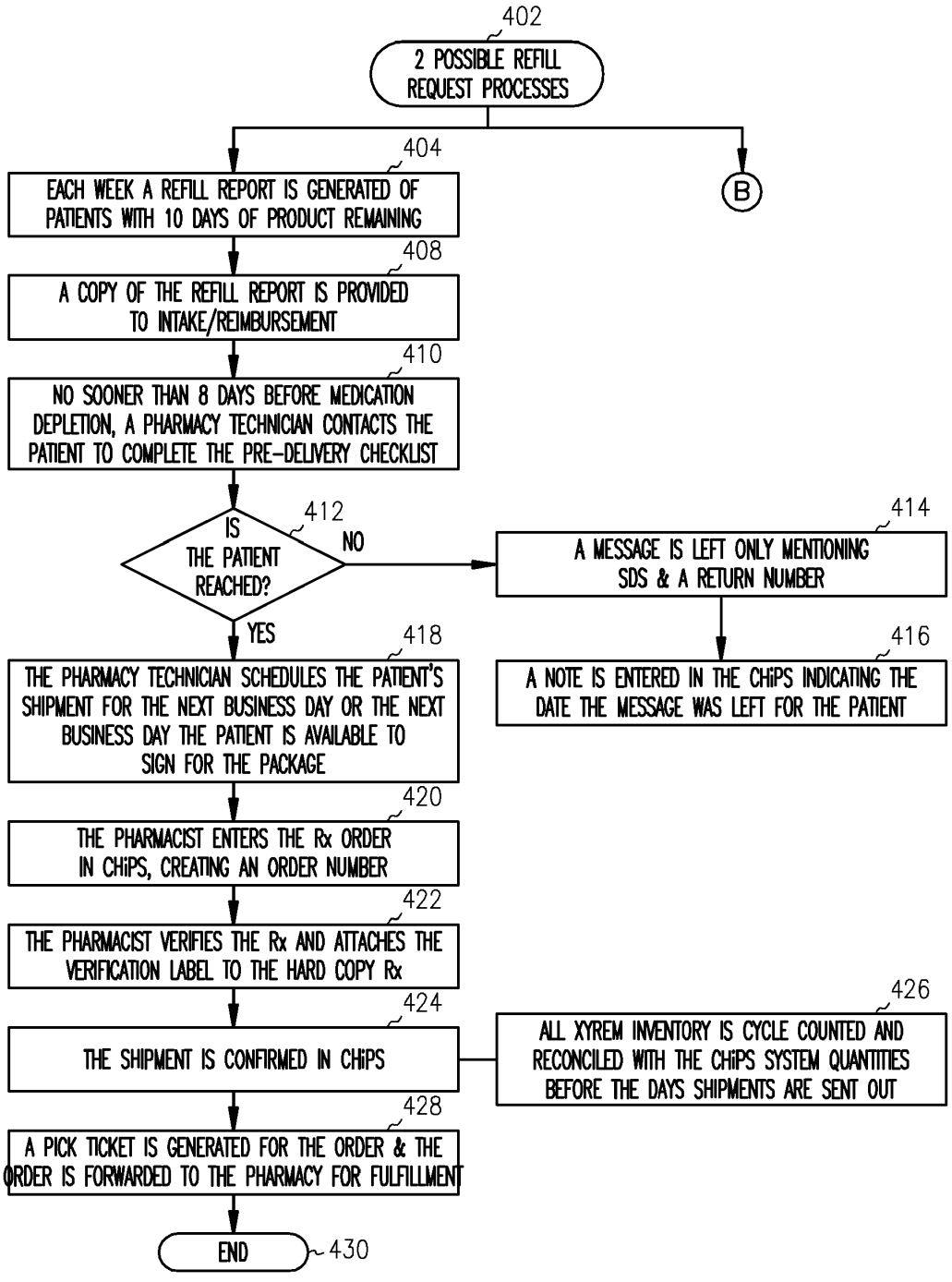
402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE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

FIG. 4A

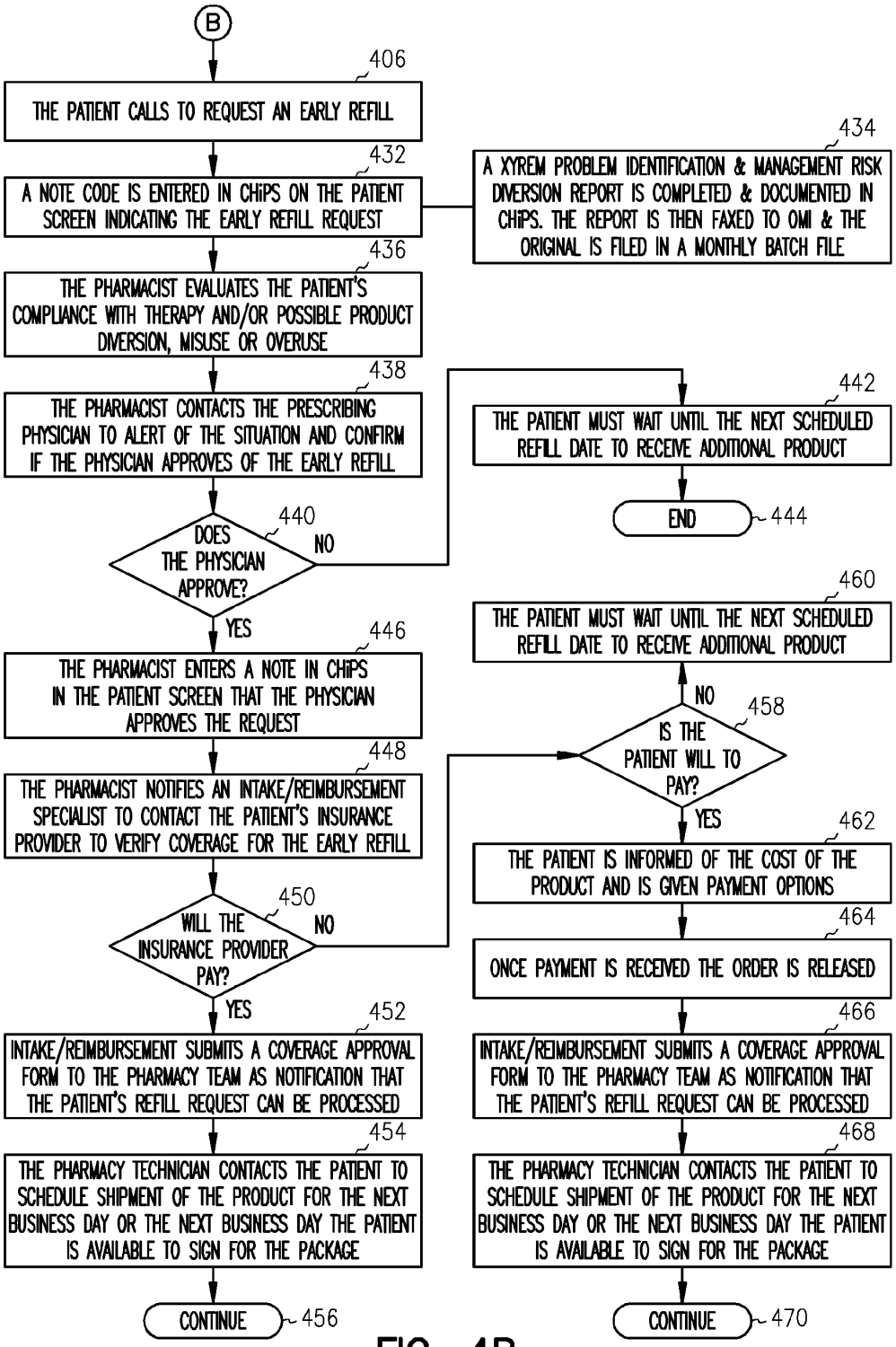
B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYREM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS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

FIG. 4B

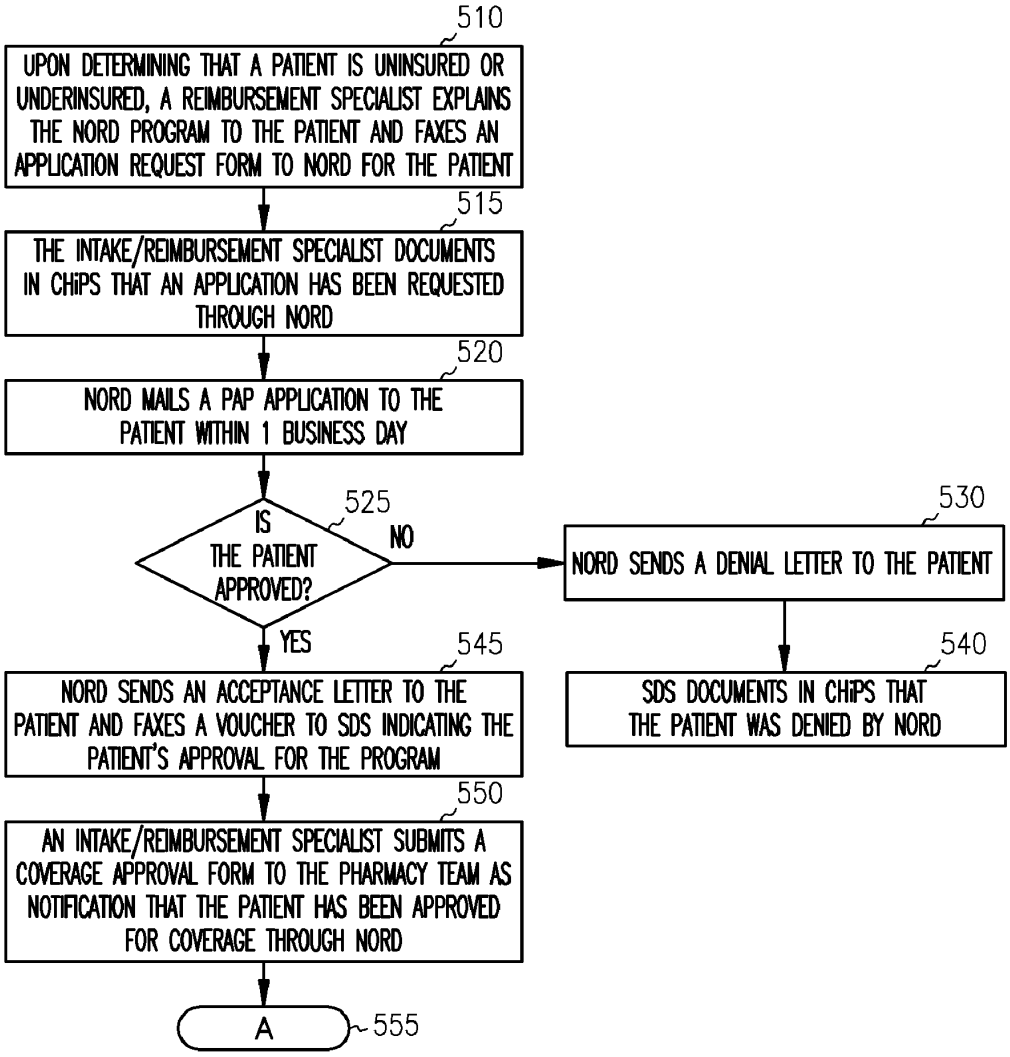
510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHIPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH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

FIG. 5

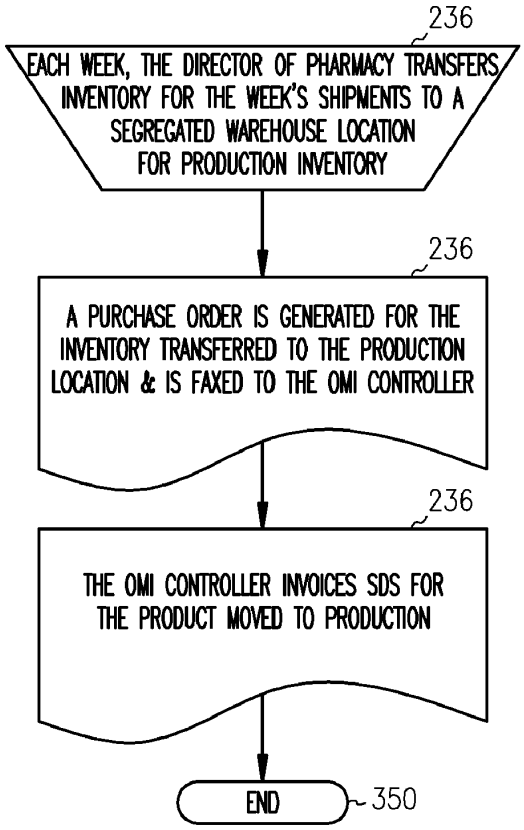

FIG. 6

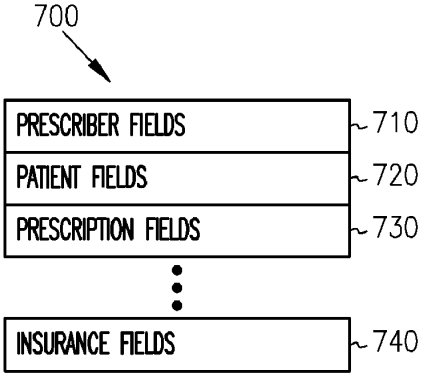

FIG. 7

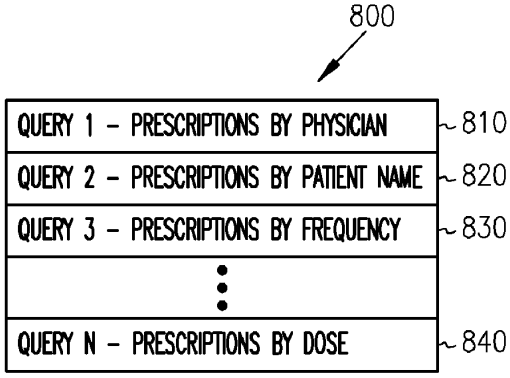

FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

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

PRESCRIPTION FORM

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

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

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

PATIENT INFORMATION

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

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

FIG. 9

PATIENT ASSISTANCE APPLICATION REQUEST FORM

DATE:

TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS

FAX #: 203-798-2291

PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:

PATIENT NAME _____

ADDRESS _____

_____

_____

TELEPHONE: ( ) _____

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

_____ BOTTLES (THREE MONTHS SUPPLY)

BACKGROUND INFORMATION:

_____

_____

_____

_____

_____

_____

FIG. 10

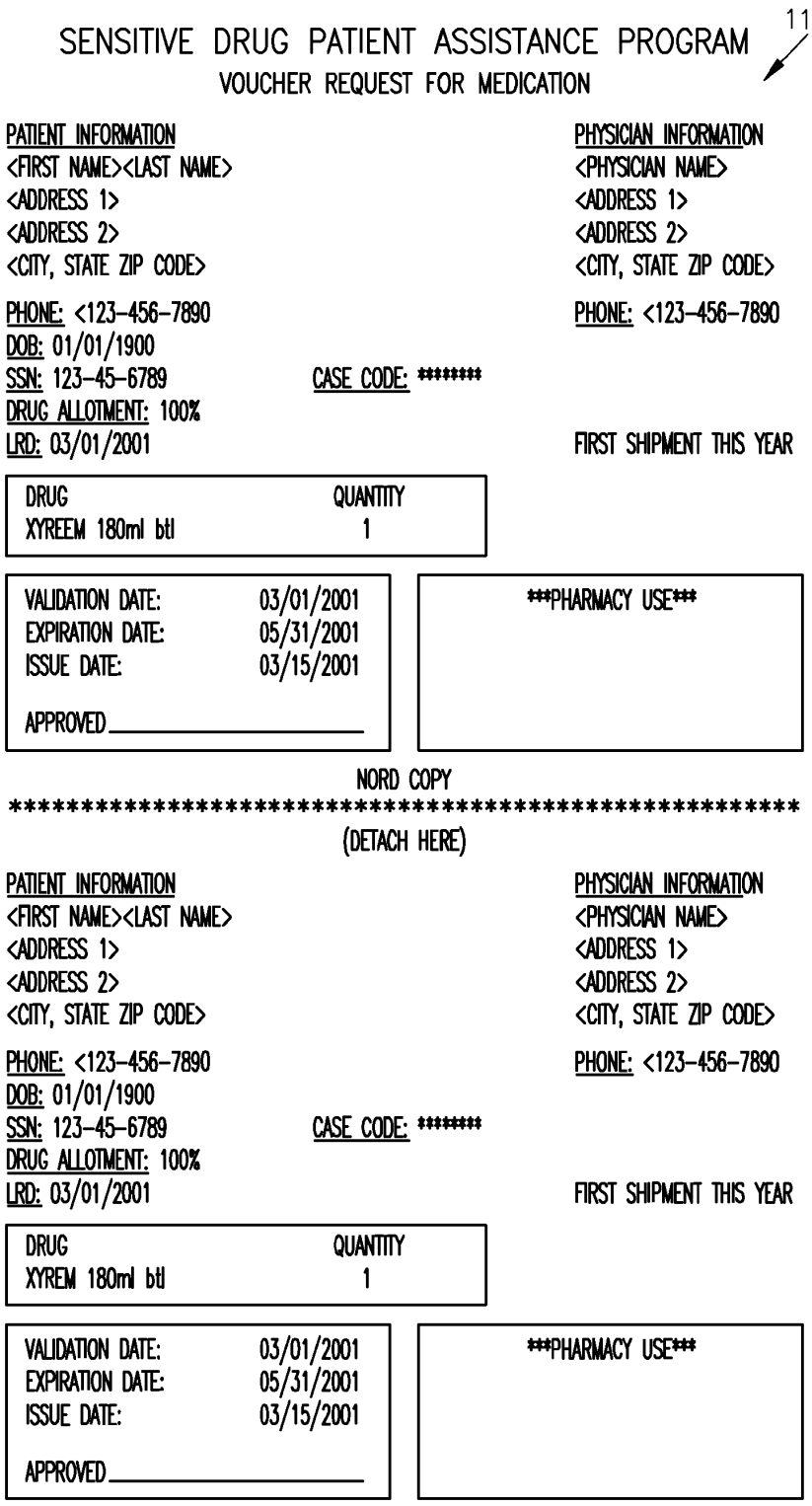
1100
SENSITIVE DRUG PATIENT ASSISTANCE PROGRAM
VOUCHER REQUEST FOR MEDICATION
PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>
PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
CASE CODE: ********
DRUG ALLOTMENT: 100%
LRD: 03/01/2001
PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>
PHONE: <123-456-7890
FIRST SHIPMENT THIS YEAR
DRUG
QUANTITY
XYREEM 180ml btl
1
VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001
APPROVED
PHARMACY USE
NORD COPY
****
(DETACH HERE)
PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>
PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
CASE CODE: ********
DRUG ALLOTMENT: 100%
LRD: 03/01/2001
PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>
PHONE: <123-456-7890
FIRST SHIPMENT THIS YEAR
DRUG
QUANTITY
XYREM 180ml btl
1
VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001
APPROVED
PHARMACY USE

FIG. 11

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE
OF MEDICAL NEED

PATIENT INFORMATION

DATE: _____

NAME: _____
LAST FIRST M

DATE OF BIRTH: _____

DRUG BEING PRESCRIBED: XYREM

DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: _____

ICD-9: _____

PHYSICIAN INFORMATION

PHYSICIAN'S NAME (PLEASE PRINT): _____

PHYSICIAN'S SIGNATURE: _____ DATE: _____

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

FIG. 12

ACTIVITY REPORTS

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

FIG. 13A

ACTIVITY REPORTS

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

FIG. 13B

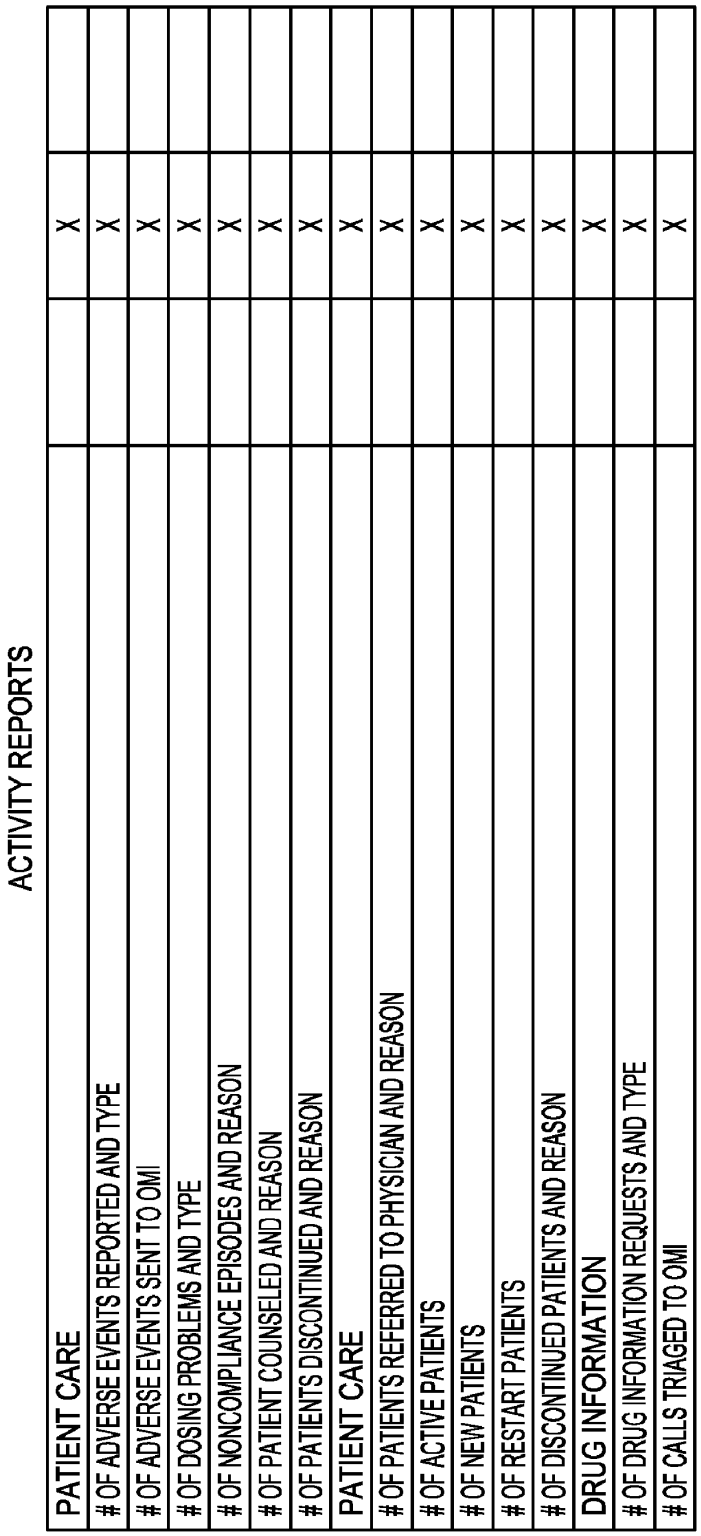
ACTIVITY REPORTS
PATIENT CARE
OF ADVERSE EVENTS REPORTED AND TYPE
OF ADVERSE EVENTS SENT TO OMI
OF DOSING PROBLEMS AND TYPE
OF NONCOMPLIANCE EPISODES AND REASON
OF PATIENT COUNSELED AND REASON
OF PATIENTS DISCONTINUED AND REASON
PATIENT CARE
OF PATIENTS REFERRED TO PHYSICIAN AND REASON
OF ACTIVE PATIENTS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

FIG. 13C

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

RELATED APPLICATION

This application is a continuation of U.S. Serial application Ser. No. 10/322,348, filed on Dec. 17, 2002, which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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

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

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

SUMMARY OF THE INVENTION

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

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

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

Prescription refills are permitted in the number specified in the original prescription. In addition, if a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned. A lost, stolen, destroyed or spilled prescription/supply is documented and replaced to the extent necessary to honor the prescription, and will also cause a review or full investigation.

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

FIG. **7** is a block diagram of database fields.

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

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

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

In the following description, reference is made to the accompanying drawings that form a part hereof, and in which is shown by way of illustration specific embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that other embodiments may be utilized and that structural, logical

and electrical changes may be made without departing from the scope of the present invention. The following description is, therefore, not to be taken in a limited sense, and the scope of the present invention is defined by the appended claims.

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

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

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

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

FIG. **1** is a simplified block diagram of a computer system **100**, such as a personal computer for implementing at least a portion of the methods described herein. A central processing unit (CPU) **110** executes computer programs stored on a memory **120**. Memory **120** in one embodiment comprises one or more levels of cache as desired to speed execution of the program and access to data on which the programs operate. The CPU is directly coupled to memory **120** in one embodiment. Both CPU **110** and memory **120** are coupled to a bus **130**. A storage **140**, I/O **150** and communications **160** are also coupled to the bus **130**. Storage **140** is usually a long term storage device, such as a disk drive, tape drive, DVD, CD or other type of storage device. In one embodiment, storage **140** is used to house a database for use with the present invention. I/O **150** comprises keyboards, sound devices, displays and other mechanisms by which a user interacts with the computer system **100**. Communications **160** comprises a network, phone connection, local area network, wide area network or other mechanism for communicating with external devices. Such external devices comprise servers, other peer computers and other devices. In one embodiment, such external device comprises a database server that is used in place of the database on storage **140**. Other computer system architectures capable of executing software and interacting with a database and users may also be used. Appropriate security measures such as encryption are used to ensure confidentiality. Further, data integrity and backup measures are also used to prevent data loss.

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

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

There are two workflows involved at the pharmacy team, intake reimbursement **206** and pharmacy workflow **208**, which may proceed in parallel or serially. The intake work flow **206** starts with an intake reimbursement specialist entering the patient and physician information into an application/database referred to as CHIPS, which is used to maintain a record of a client home infusion program (CHIP) for Xyrem®. A check is made to ensure the information is complete at **212**. If not, at **214**, an intake representative attempts to reach the MD or prescriber to obtain the missing information. If the missing information has not been obtained within a predetermined period of time, such as 24 hours at **216**, the Rx/Enrollment form is sent back to the MD with a rejection explanation. A note is entered in CHIPS that the application was rejected.

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

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

Upon receipt and initial processing of the prescription enrollment form and sending an original to the pharmacy work flow block **208**, the patient is shipped a Xyrem® success packet via mail. In one embodiment, the Xyrem® success packet contains educational material for a patient that advises of the proper use, care and handling of the drug and consequences of diversion at **268**. The medical doctor's credentials are checked to determine if the physician has a current DEA license to prescribe controlled substances and if he or she has had any actions related to misuse/misprescribing of controlled drugs against him or her, within a predetermined time, such as three months at **270**. If they have, a pharmacist holds the prescription until receiving a coverage approval form from the intake reimbursement specialist at **272**.

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

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

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

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

At **250**, the pharmacist schedules the patient's shipment for the next business day or the next business day that the patient or designee is able to sign for the package. Further, as indicated at **252**, the shipment must be sent to the patient's home address unless the patient is traveling or has moved. In that event, the pharmacist may determine that an exception may be made. The patient or the patient's designee who is at least 18 years old, must sign for the package upon delivery.

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

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

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

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

In the first path, a copy of the report is provided to an intake reimbursement specialist at **408**. No sooner than 8 days before the medication depletion, a pharmacy technician contacts the patient at **410** to complete the pre-delivery checklist. At **412**, if the patient is not reached, a message is left mentioning the depletion, and a return number at **414**. A note is also entered into the database indicating the date the message was left at **416**.

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

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

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

If the insurance provider will not pay at **450**, it is determined whether the patient is willing and/or able to pay at **458**. If not, the patient must wait until the next scheduled refill date to receive additional product at **460**. If it was determined at **458** that the patient was willing and able to pay, the patient is informed of the cost of the product and is given payment options at **462**. Once payment is received as indicated at **464**, the specialist submits a coverage approval form to the pharmacy team as notification that the refill request can be pro-

cessed at **466**. At **468**, the pharmacy technician contacts the patient to schedule shipment. The process of filling the order is continued at **470** by following the process beginning at **240**.

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

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

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

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

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

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

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

FIG. **11** is a copy of one example application **1100** for financial assistance as requested by form **1000**. The form requires both patient and physician information. Social security number information is also requested. The form provides information for approving the financial assistance and for tracking assistance provided.

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

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

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

The invention claimed is:

1. A 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;

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

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.

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:

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;

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.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,895,059 B2
APPLICATION NO. : 12/704097
DATED : February 22, 2011
INVENTOR(S) : Dayton T. Reardan et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On page 2, under "US Patent Documents", in column 1, line 1, delete "Reardon" and insert -- Reardan --, therefor.

On Sheet 9 of 16, above Box 1, Figure 6, delete reference numeral "236" and insert -- 610 --, therefor. (Drawing sheet attached.)

On Sheet 9 of 16, above Box 2, Figure 6, delete reference numeral "236" and insert -- 620 --, therefor. (Drawing sheet attached.)

On Sheet 9 of 16, above Box 3, Figure 6, delete reference numeral "236" and insert -- 630 --, therefor. (Drawing sheet attached.)

On Sheet 9 of 16, above Box 4, Figure 6, delete reference numeral "350" and insert -- 640 --, therefor. (Drawing sheet attached.)

On Sheet 12 of 16, Figure 11, line 14, delete "XYREEM" and insert -- XYREM® --, therefor.

On Sheet 14 of 16, Figure 13A, line 26, delete "Rx/ENROLLEMENT" and insert --Rx/ENROLLMENT --, therefor.

ln column 1, line 28, delete "buterate" and insert -- butyrate --, therefor.

ln column 3, line 33, delete "Xyrem," and insert -- Xyrem®, --, therefor.

ln column 4, line 14, delete "Xyrem." and insert -- Xyrem®. --, therefor.

ln column 6, line 1, delete "Xyrem," and insert -- Xyrem®, --, therefor.

Signed and Sealed this
Thirty-first Day of May, 2011

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

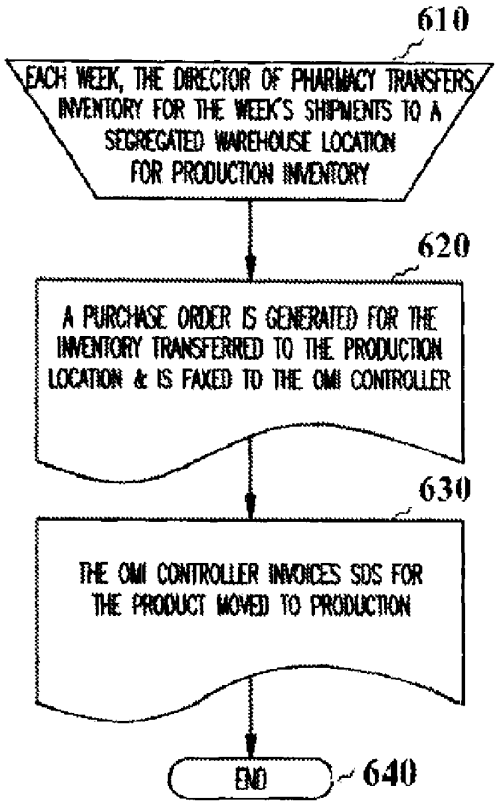

FIG. 6

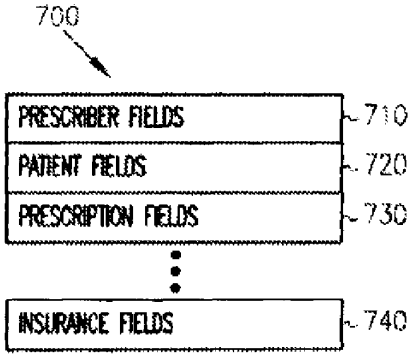

FIG. 7

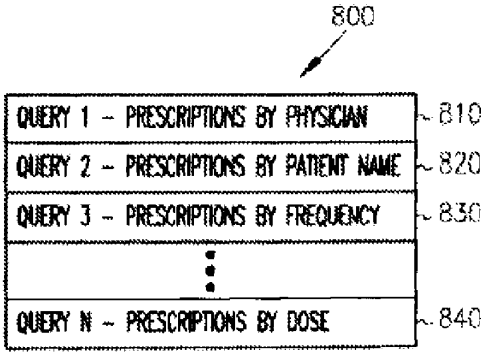

FIG. 8

EXHIBIT F

US008263650B2

(12) **United States Patent**
Cook et al.

(10) **Patent No.: US 8,263,650 B2**
(45) **Date of Patent: *Sep. 11, 2012**

(54) **MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY**

(75) Inventors: **Harry Cook**, Eden Prairie, MN (US); **Martha Hamilton**, St. Paul, MN (US); **Douglas Danielson**, Otsego, MI (US); **Colette Goderstad**, St. Paul, MN (US); **Dayton T. Reardan**, Shorewood, MN (US)

(73) Assignee: **Jazz Pharmaceuticals, Inc.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/446,940**

(22) Filed: **Apr. 13, 2012**

(65) **Prior Publication Data**

US 2012/0202880 A1 Aug. 9, 2012

Related U.S. Application Data

(60) Continuation of application No. 13/182,324, filed on Jul. 13, 2011, which is a continuation of application No. 12/913,644, filed on Oct. 27, 2010, which is a continuation of application No. 11/777,877, filed on Jul. 13, 2007, now Pat. No. 7,851,506, which is a division of application No. 10/841,709, filed on May 7, 2004, now Pat. No. 7,262,219, which is a division of application No. 10/194,021, filed on Jul. 11, 2002, now Pat. No. 6,780,889, which is a division of application No. 09/470,570, filed on Dec. 22, 1999, now Pat. No. 6,472,431.

(60) Provisional application No. 60/113,745, filed on Dec. 23, 1998.

(51) **Int. Cl.**

A61K 31/34	(2006.01)
A61K 31/215	(2006.01)
A61K 31/185	(2006.01)
A61K 31/19	(2006.01)

(52) **U.S. Cl.** **514/473**; 514/529; 514/553; 514/557

(58) **Field of Classification Search** 514/473, 514/529, 553, 557

See application file for complete search history.

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Primary Examiner — Raymond Henley, III

(74) *Attorney, Agent, or Firm* — Schwegman, Lundberg & Woessner, P.A.

(57) **ABSTRACT**

Disclosed are formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial growth. Also disclosed are formulations of gammahydroxybutyrate that are also resistant to the conversion into GBL. Disclosed are methods to treat sleep disorders, including narcolepsy, with these stable formulations of GHB. The present invention also provides methods to treat alcohol and opiate withdrawal, reduced levels of growth hormone, increased intracranial pressure, and physical pain in a patient.

18 Claims, 2 Drawing Sheets

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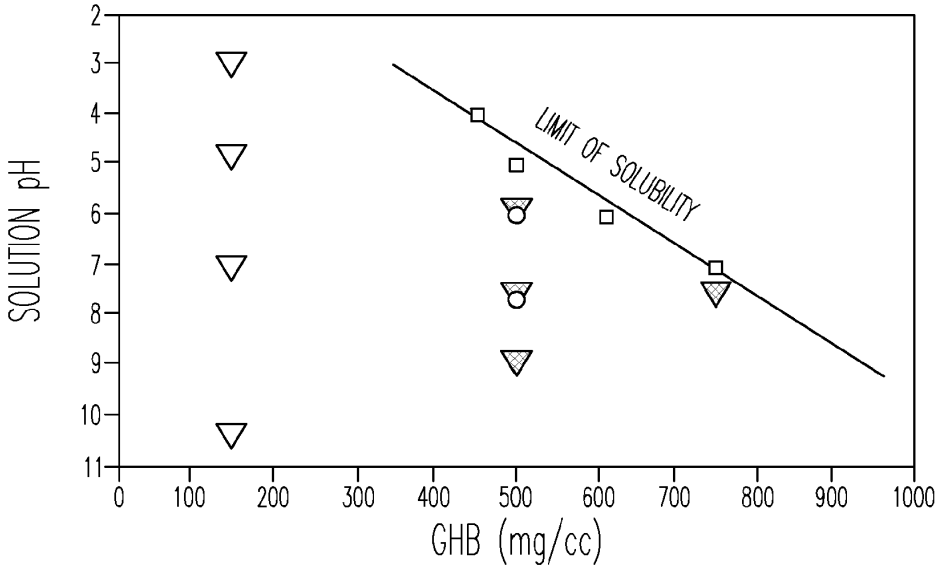

□ DATA POINTS INDICATING LIMIT OF SOLUBILITY OF GHB AS A FUNCTION OF CONCENTRATION AND pH, SEE TABLE 1.

▽ SOLUTIONS SUSCEPTIBLE TO MICROBIAL GROWTH, DESIGNATED "FAIL". (ALL SOLUTIONS DEMONSTRATED ACTIVITY AGAINST PSEUDOMONAS AERUGINOSA. SOME REDUCTION OF ASPERGILLUS NIGER MOLD OCCURRED IN 7 DAYS OF CONTACT TIME.)

▽ SOLUTIONS RESISTANT TO MICROBIAL GROWTH, DESIGNATED "PASS". RATE OF REDUTION OF MICROORGANISM COUNTS WAS SLIGHTLY HIGHER AT pH 7.5 AND 6.0 THAN pH 9.0. THE RATE OF REDUCTION OF FORMULATIONS AT 750mg/cc GHB WERE SLIGHTLY LOWER THAN FORMULATIONS AT 500 mg/cc GHB.)

○ SOLUTIONS RESISTANT TO MICROBIAL GROWTH, DESIGNATED "PASS". RESULTS WERE SIMILAR FOR MALIC ACID AND HCl. TASTE VARIATIONS HAS IMPLICATIONS FOR DEVELOPMENT OF FLAVOR SYSTEMS.

▽ ▽ INDICATES pH ADJUSTMENT WITH HCl.

○ INDICATES pH ADJUSTMENT WITH MALIC ACID.

NOTE: SOLUTIONS WITH pH AT 9.0 ARE NOT PALATABLE OR SAFE FOR ORAL CONSUMPTION.

Fig. 1

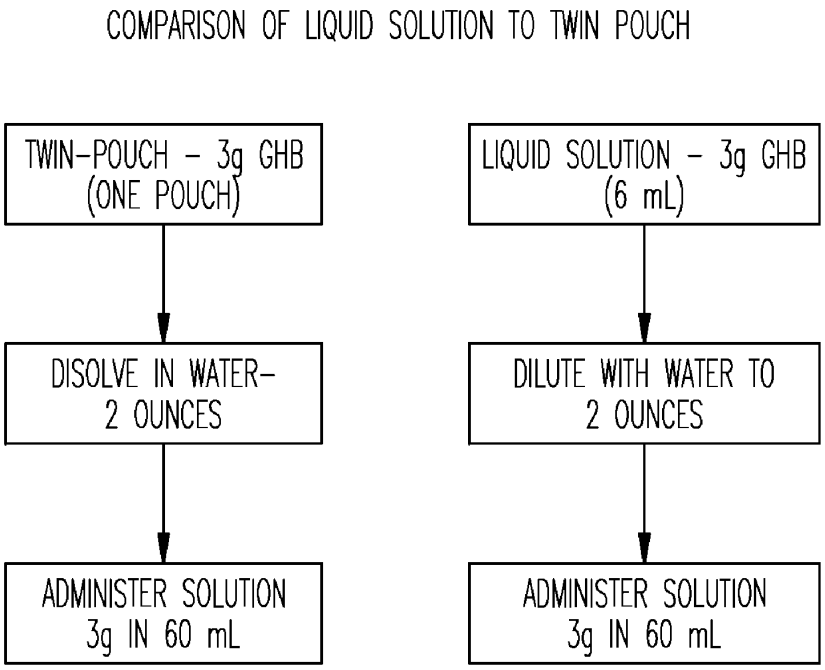
COMPARISON OF LIQUID SOLUTION TO TWIN POUCH
TWIN-POUCH - 3g GHB (ONE POUCH)
DISOLVE IN WATER- 2 OUNCES
ADMINISTER SOLUTION 3g IN 60 mL
LIQUID SOLUTION - 3g GHB (6 mL)
DILUTE WITH WATER TO 2 OUNCES
ADMINISTER SOLUTION 3g IN 60 mL

Fig. 2

MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY

RELATED APPLICATIONS

This patent application is a continuation of U.S. application Ser. No. 13/182,324, filed on Jul. 13, 2011 and is currently pending, which is a continuation of U.S. application Ser. No. 12/913,644, filed on Oct. 27, 2010 and is currently pending, which is a continuation of U.S. application Ser. No. 11/777,877 filed on Jul. 13, 2007 and issued on Dec. 14, 2010 as U.S. Pat. No. 7,851,506, which is a divisional of U.S. application Ser. No. 10/841,709, filed on May 7, 2004 and issued on Aug. 28, 2007 as U.S. Pat. No. 7,262,219, which is a divisional of U.S. application Ser. No. 10/194,021, filed Jul. 11, 2002 and issued on Aug. 24, 2004 as U.S. Pat. No. 6,780,889, which is a divisional of U.S. application Ser. No. 09/470,570, filed Dec. 22, 1999 and issued on Oct. 29, 2002 as U.S. Pat. No. 6,472,431, which claims priority from U.S. Provisional Patent Application Ser. No. 60/113,745, filed Dec. 23, 1998. These applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention relates generally to the fields of pharmaceutical compositions to be used in treatments, such as, sleeping disorders, such as, e.g., narcolepsy (particularly cataplexy), drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or for an increased level of intracranial pressure or the like. The present 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, e.g.

II. Description of Related Art

GHB is an endogenous compound with hypnotic properties that is found in many human body tissues. GHB is present, for example, in the mammalian brain and other tissues. In brain the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter (Snead and Morley, 1981). The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB is converted to succinate and then metabolized via the Krebs cycle. Clinical trials have shown that GHB increases delta sleep and improves the continuity of sleep (Ladinsky et al., 1983; Anden and Stock, 1973; Stock et al., 1973; Laborit, 1973; Lapierre et al., 1988; Lapierre et al., 1990; Yamda et al., 1967; Grove-White and Kelman, 1971; Scharf, 1985).

GHB has typically been administered in clinical trials as an oral solution (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993). GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e. daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency (Mamelak et al, 1973; Yamada et al., 1967; Bedard et al., 1989), reduces sleep apnea (Series et al, 1992; Scrima et al., 1987), and improves general anesthesia (Hasenbos and Gielen, 1985).

GHB has several clinical applications other than narcolepsy and sleep disorders. GHB has been reported to reduce alcohol craving, the number of daily drinks consumed, and the symptoms of alcohol withdrawal in patients (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992). GHB has been used to decrease the symptoms of opiate withdrawal, including both heroin and methadone withdrawal (Gallimberti et al., 1994; Gallimberti et al., 1993). It has analgesic effects that make it suitable as a pain reliever (U.S. Pat. No. 4,393,236). Intravenous administration of GHB has been reported to reduce intracranial pressure in patients (Strong, A. 1984). Also, administration of GHB was reported to increase growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970).

A good safety profile for GHB consumption, when used long term for treatment of narcolepsy has been reported. Patients have been safely treated for many years with GHB without development of tolerance (Scharf, 1985). Clinical laboratory tests carried out periodically on many patients have not indicated organ or other toxicities (Lammers, 1993; Scrima, 1990; Scharf, 1985; Mamelack, 1977; Mamelak, 1979; Gallimberti, 1989; Gallimberti, 1992; Gessa, 1992). The side effects of GHB treatment have been minimal in incidence and degree of severity, though they include sleepwalking, enuresis, headache, nausea and dizziness (Broughton and Mamelak, 1979; Mamelak et al., 1981; Mamelak et al., 1977; Scrima et al., 1989; Scrima et al., 1990; Scharf et al., 1985).

The pharmacokinetics of GHB have been investigated in alcohol dependent patients (Ferrara et al., 1992) and in normal healthy males (Palatini et al., 1993) after oral administration. GHB possesses a rapid onset and short pharmacological effect (Ferrara et al., 1992; Palatine et al., 1993; Lee, C., 1977; van der Bogert; Gallimberti, 1989; Gallimberti, 1992; Lettieri and Fung, 1978; Arena and Fung, 1980; Roth and Giarman, 1966; Vickers, 1969; Lee, 1977). In alcohol dependent patients, GHB absorption into and elimination from the systemic circulation were fast processes. Virtually no unchanged drug could be recovered in the urine. There were preliminary indications that the pharmacokinetics of GHB might be non-linear or dose-dependent (Ferrara et al., 1992). In the healthy volunteers study, the pharmacokinetics of three rising GHB doses (12.5, 25, and 50 mg/kg) were investigated. These findings indicate that both the oral absorption and elimination processes of GHB were capacity-limited though the degree of dose dependency was moderate (Palatini et al., 1993).

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). 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.

SUMMARY OF THE INVENTION

The present invention overcomes deficiencies in the prior art by providing compositions of GHB in an aqueous medium that are resistant to microbial growth. These compositions are also resistant to the uncontrolled degradation of GHB into GBL or other substances. The compositions of the present invention are stable compositions of GHB that improve shelf-life, and provide a titratable formulation of GHB for easy dose measurement. In addition, the concentrated solutions embodied in this invention reduce shipping and storage requirements and allow patients to carry more drugs for their convenience. The present invention provides methods to treat a number of conditions treatable by GHB, referred to herein as "therapeutic categories." Therapeutic categories for the present invention include, but are not limited to, sleeping disorders, drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders, such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or an increased level of intracranial pressure or other conditions treatable with GHB.

The invention first provides a pharmaceutical composition of GHB rendered chemically stable and/or resistant to microbial growth in an aqueous medium. Preferred GHB salts of the present invention include sodium, ammonium and calcium. As used herein in certain embodiments, "stable" may mean resistant to degradation of GHB into its known or unknown decomposition elements. The level of GBL that is acceptable can be up to 0.1% of the formulation as per the ICH guidelines for shelf-life determination. As used herein in certain embodiments, "resistant to microbial growth" or "resistant to microbial challenge" means that the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days. As used herein in certain embodiments, an "aqueous medium" may mean a liquid comprising more than about 50% water. In certain preferred embodiments, an "aqueous medium" may be a solution, suspension, gel or emulsion of GHB, with a solution of GHB being most preferred. Preferred gels are thixotropic gels. Compositions that are resistant to microbial growth are created by dissolving or mixing GHB in an aqueous medium to a concentration or content of greater than of about 150 mg/ml GHB to the maximal solubility of GHB. The solubility of GHB is up to about 750 mg/ml at room temperature (20° C. to about 25° C.), however, heating the aqueous medium during preparation up to 100° C. will increase GHB solubility to at least about 1000 mg/ml. A preferred concentration or content of GHB is about 500 mg/ml.

The amount of GHB that may be mixed or dissolved into an aqueous medium and still be resistant to microbial growth depends upon the pH of the aqueous medium. In certain embodiments the presence of a preservative may allow the amount of GHB contained in the compositions of the present invention to be increased and still maintain resistance to chemical degradation and/or microbial growth. In one embodiment of the present invention, the pH of the aqueous medium of the pharmaceutical composition is about 3 to about 10.

In a preferred embodiment, the pH of said aqueous medium is about 6 to about 7.5. The pH may be from about 3.0 to about 10.3, namely of about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0, about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, about 10.0, about 10.1, about 10.2, or about 10.3, and all pH values between each of the listed pH values, of the aqueous media. This will produce a GHB composition that is resistant to microbial growth as defined by the test described herein. As used herein, the term "about" generally means within about 10-20%.

These pH values will produce compositions resistant to microbial growth in an aqueous medium if the amount of GHB added, admixed, or dissolved is from above about 150 mg/ml to about 450 mg/ml, namely, above about 150 mg/ml, about 160 mg/ml, about 170 mg/ml, about 180 mg/ml, about 190 mg/ml, about 200 mg/ml, about 210 mg/ml, about 220 mg/ml, about 230 mg/ml, about 240 mg/ml, about 250 mg/ml, about 260 mg/ml, about 270 mg/ml, about 280 mg/ml, about 290 mg/ml, about 300 mg/ml, about 310 mg/ml, about 320 mg/ml, about 330 mg/ml, about 340 mg/ml, about 350 mg/ml, about 360 mg/ml, about 370 mg/ml, about 380 mg/ml, about 390 mg/ml, about 400 mg/ml, about 410 mg/ml, about 420 mg/ml, about 430 mg/ml, about 440 mg/ml, to about 450 mg/ml, and all amounts of GHB between the values listed.

At the medium to high end of the concentration or content of GHB that may be dissolved or mixed in the aqueous medium, the maximal pH that may be used is reduced at room temperature. This is shown in FIG. **1**, a graphical presentation of acceptable formulation ranges. At a concentration or content of about 450 mg/ml GHB, the pH may be of about 3.9 to about 10.3. At a concentration or content of about 500 mg/ml GHB, the pH may be of about 4.75 to about 10.3. At a concentration or content of about 600 mg/ml GHB, the pH may be of about 6.1 to about 10.3. At a concentration or content of about 750 mg/ml GHB, the pH may be of about 7.0 to about 10.3. Of course, all pH and concentration or content values in between each of the listed pH and concentration or content values are encompassed by the invention.

Certain embodiments may be selected as sub-ranges from these values of GHB content and aqueous medium pH. For example, a specific embodiment may be selected as a content of about 170 mg/ml to about 440 mg/ml GHB in an aqueous medium, at a pH range of about pH 5.5 to about pH 8.7. Another example of how a range may be selected in an embodiment would be the selection of a content of about 155 mg/ml of GHB, which is a value between the above listed values, to a content of about 350 mg/ml of GHB, and the selection of a pH range of the aqueous medium, such as a pH range of about 8.87, which is a value between the listed pH values, to a pH of about 8.93, which is another value between the listed values of pH. A third example of ranges that may be selected for a specific embodiment would be selection of a single content or concentration of GHB, such as about 200 mg/ml of GHB, and the selection of a pH range, such as a pH of about 3.5 to about 8.2. A fourth example of ranges that may be selected for a specific embodiment would be selection of a content or concentration of GHB over a range, such as about 300 mg/ml to about 400 mg/ml, and the selection of a single pH value for the aqueous medium, such as a pH of about 3. Another example of a range selected for an embodiment may

be the selection of a single content or concentration of GHB, such as 400 mg/ml GHB, and a single pH value of the aqueous medium, such as pH 7.7.

Other examples of how a range of an embodiment of GHB content or concentration may be selected include a range of GHB content or concentration from about 200 mg/ml to about 460 mg/ml GHB, encompassing the ranges for GHB described herein, and a range of pH for the aqueous medium may be from about pH 4.3 to about pH 7, encompassing ranges for GHB in an aqueous medium at room temperature described herein. Another example would be the selection of a range of GHB content or concentration from about 153 mg/ml to about 750 mg/ml, and a pH range of about 7 to about 9, encompassing ranges between the listed values of GHB content and pH described herein. An example may be the selection as a GHB concentration or content of about 170 mg/ml to about 640 mg/ml in an aqueous medium, at a pH range of about pH 6.5 to about pH 7.7. Another example of how a range may be selected in an embodiment would be a content or concentration of about 185 mg/ml of GHB, which is a value between the listed values, to a content or concentration of about 750 mg/ml of GHB, at a pH range of about 7.87, which is a value between the listed pH values, to a pH of about 8.91, which is another value between the listed values of pH. An additional example of ranges that may be selected for a specific embodiment would be a content or concentration of about 200 mg/ml of GHB at a pH of about 7 to about 8.2. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 750 mg/ml to about 400 mg/ml at a pH of about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 300 mg/ml to about 750 mg/ml at a pH of about 8.5 to about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 400 mg/ml to about 600 mg/ml at a pH of about 9 to about 5.8. And so forth. Thus, all ranges of pH and GHB concentration or content that can be selected from the values herein and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

The chemical stability of GHB is affected by pH, with compositions of GHB in an aqueous medium with a pH below about 6 being less effective in maintaining the chemical stability of GHB. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, all concentrations or content of GHB in an aqueous medium, as described herein, and as would be understood by those of ordinary skill in the art, may be selected to produce compositions of the present invention.

Additionally, the ranges described above are for a composition at room temperature, which is defined herein as from about 20° C. to about 25° C., namely, about 20° C. about 21° C., about 22° C., about 23° C., about 24° C., to about 25° C. Within the values and ranges of pH described above, the ranges of concentration or content of GHB may increase at temperatures greater than room temperature. Thus, the maximal content or concentration of GHB in an aqueous medium at a temperature of from about 26° C. about 100° C., namely about 26° C., about 27° C., about 28° C., about 29° C., about 30° C., about 31° C., about 32° C., about 33° C., about 34° C., about 35° C., about 36° C., about 37° C., about 38° C., about 39° C., about 40° C., about 41° C., about 42° C., about 43° C., about 44° C., about 45° C., about 46° C., about 47° C., about 48° C., about 49° C., about 50° C., about 51° C., about 52° C., about 53° C., about 54° C., about 55° C., about 56° C., about 57° C., about 58° C., about 59° C., about 60° C., about 61° C., about 62° C., about 63° C., about 64° C., about 65° C., about 66° C., about 67° C., about 68° C., about 69° C., about 70° C., about 71° C., about 72° C., about 73° C., about 74° C., about 75° C., about 76° C., about 77° C., about 78° C., about 79° C., about 80° C., about 81° C., about 82° C., about 83° C., about 84° C., about 85° C., about 86° C., about 87° C., about 88° C., about 89° C., about 90° C., about 91° C., about 92° C., about 93° C., about 94° C., about 95° C., about 96° C., about 97° C., about 98° C., about 99° C., to about 100° C. may be from about 750 to about 1 g/ml, namely to about 751 mg/ml, about 760 mg/ml, about 770 mg/ml, about 780 mg/ml, about 790 mg/ml, about 800 mg/ml, about 810 mg/ml, about 820 mg/ml, about 830 mg/ml, about 840 mg/ml, about 850 mg/ml, about 860 mg/ml, about 870 mg/ml, about 880 mg/ml, about 890 mg/ml, about 900 mg/ml, about 910 mg/ml, about 920 mg/ml, about 930 mg/ml, about 940 mg/ml, about 950 mg/ml, about 960 mg/ml, about 970 mg/ml, about 980 mg/ml, about 990 mg/ml, to about 1000 mg/ml. At temperatures below room temperature, the solubility of GHB may decrease, and compositions at lower temperature and solubility of GHB at the pH values and ranges described herein are also encompassed by the invention. Additionally, differences of atmospheric pressure may also increase or decrease the solubility of GHB within the ranges described, and embodiments of the invention with an increased or decreased content of GHB due to changes in pressure are also encompassed by the invention. Of course, it is understood that the present invention encompasses embodiments of GHB concentration or content in an aqueous medium at higher or lower temperature within the values described herein, such as about 980 mg/ml to about 200 mg/ml at 95° C. GHB at a pH of about 9 to about 7.5. Or about 150 mg/ml GHB at about 17° C. at about pH 6 to about pH 7. And so forth. Thus, all ranges of pH and GHB content that can be selected at various temperatures and pressures from the values above, and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

In certain other embodiments of the present invention, the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids, bases, or combinations thereof. In certain embodiments, the acid may be an organic acid, preferably a carboxylic acid or alphahydroxy carboxylic acid. In certain other embodiments, the acid is selected from the group including, but not limited to, acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like. In a preferred embodiment, the acid is malic or hydrochloric acid. In certain other embodiments, the pH adjusting agent may be a base selected from the group including, but not limited to, acetanilide, ammonia, apomorphine, atropine, benzocaine, caffeine, calcium hydroxide, cocaine, codeine, ephedrine, morphine, papaverine, physostigmine, pilocarpine, potassium bicarbonate, potassium hydroxide, procaine, quinine, reserpine, sodium bicarbonate, sodium dihydrogen phosphate, sodium citrate, sodium taitrate, sodium carbonate, sodium hydroxide, theobromine, thiourea or urea. 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.

In certain embodiments, the composition may contain one or more salts. A "salt" is understood herein to mean certain embodiments to mean a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base. Various salts, including salts of GHB, are also encompassed by ***the invention, particularly as pH adjusting or buffering agents. Pharmaceutically acceptable salts, include inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as malic, acetic, oxalic, tartaric, mandelic, and the like. Salts formed can also be derived from inorganic bases such as, for example, sodium, potassium, silicates, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropyamine, trimethylamine, histidine, procaine and the like. Alkali metal salts such as lithium, potassium, sodium, and the like may be used, preferably with an acid to form a pH adjusting agent. Other salts may comprise ammonium, calcium, magnesium and the like. In one embodiment, a salt of GHB comprising an alkali metal may be combined with an acid to create a composition that achieves the desired pH when admixed with an aqueous medium. In another embodiment, a weak base may be combined with GHB to create a composition that achieves the desired pH when admixed with an aqueous solution. Of course, other salts can be formed from compounds disclosed herein, or as would be known to one of ordinary skill in the art, and all such salts are encompassed by the invention.

In certain embodiments, excipients may be added to the invention. An "excipient" as used herein shall mean certain embodiments which are more or less inert substances added as diluents or vehicles or to give form or consistency when the remedy is in a solid form, though they may be contained in liquid form preparations, e.g. syrups, aromatic powders, honey, and various elixirs. Excipients may also enhance resistance to microbial growth, and thus act as a preservative. Such excipients include, but are not limited to, xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, cellulose derivatives, magnesium carbonate and the like.

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, propyl gallate BP, sorbic acid, chlorobutanol, dihydroacetic acid, monothioglycerol, potassium benzoate, propylparaben, benzoic acid, benzalkonium chloride, alcohol, benzoic acid, benzalkonium chloride, benzethonium chloride, benzyl alcohol, butylparaben, cetylpyridinium chloride, ethylenediamine, ethylparaben, ethyl vanillin, glycerin, hypophosphorus acid, methylparaben, phenol, phenylethyl alcohol, phenylmercuric nitrate, propylparaben, sassafras oil, sodium benzoate, sodium propionate, thimerosal and potassium sorbate. Preferred preservatives may be selected from the group comprising, but not limited to, xylitol, sodium benzoate, methylparaben, propylparaben and potassium sorbate. Xylitol is particularly preferred in certain compositions of the invention, because it acts as an preservative and a sweetener, is a caries preventative, is less laxative than other sweeteners, and is recommended for diabetics.

In certain embodiments, the pharmaceutical composition may also contain an antioxidant. An "antioxidant" is understood herein to mean certain embodiments which are substances that inhibits oxidation. Such antioxidants include, but are not limited to, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, potassium metabisulfite, sodium metabisulfite, anoxomer and maleic acid BP.

In certain embodiments, the pharmaceutical composition may also contain a flavoring agent. A "flavoring agent" is understood herein to mean certain embodiments which are substances that alters the flavor of the composition during oral consumption. A type of "flavoring agent" would be a sweetener. Preferred sweeteners or flavoring agents would be microbially non-metabolizable. Especially preferred sweeteners or flavoring agents would be carbohydrates such as xylitol and sorbitol. Such flavoring agents include, but are not limited to, acacia syrup, anethole, anise oil, aromatic elixir, benzaldehyde, benzaldehyde elixir-compound, caraway, caraway oil, cardamom oil, cardamom seed, cardamom spirit, cardamom tincture-compound, cherry juice, cherry syrup, cinnamon, cinnamon oil, cinnamon water, citric acid, citric acid syrup, clove oil, coca, coca syrup. coriander oil, dextrose, eriodictyon, eriodictyon fluidextract, eriodictyon syrup aromatic, ethyl acetate, ethyl, vanillin, fennel oil, ginger, ginger fluidextract, ginger oleoresin, glucose, glycerin, glycyrrhiza, glycyrrhiza elixir, glycyrrhiza extract, glycyrrhiza extract-pure, glycyrrhiza fluidextract, glycyrrhiza syrup, honey, non-alcoholic elixir, lavender oil, citrus extract or oil, lemon oil, lemon tincture, mannitol, methyl salicylate, nutmeg oil, orange-bitter-elixir, orange-bitter-oil, orange flower oil, orange flower water, orange oil, orange peel-bitter, orange-peel-sweet-tincture, orange spirit-compound, compound, orange syrup, peppermint, peppermint oil, peppermint spirit, peppermint water, phenylethyl alcohol, raspberry juice, raspberry syrup, rosemary oil, rose oil, rose water, saccharin, saccharin calcium, saccharin sodium, sarsaparilla syrup, sorbitol solution, spearmint, spearmint oil, sucrose, syrup, thyme oil, tolu balsam, tolu balsam syrup, vanilla, vanilla tincture, vanillin or wild cherry syrup.

Salts, excipients, pH adjusting agents such as acids, bases and buffering agents, flavoring agents, and other agents that may be combined with the compositions of the present invention, or may be used to prepare the compositions of the present invention, are well known in the art, (see for example, "Remington's Pharmaceutical Sciences" 8th and 15th Editions, and Nema et al., 1997, incorporated herein in their entirety), and are encompassed by the invention.

In certain other embodiments, the pharmaceutical composition comprises GHB, a pH adjusting or buffering agent, and an aqueous medium, wherein the components are admixed (sequentially or simultaneously) to prepare said pharmaceutical composition. The pH adjusting or buffering agent and aqueous medium may be any described herein.

The invention also provides a method of preparing a chemically stable and microbial growth-resistant pharmaceutical composition for the treatment of a condition responsive to GHB, comprising admixing GHB and a pH-adjusting or buffering agent in an aqueous medium. In certain embodiments, the method of preparing the pharmaceutical composition further comprises admixing a preservative with the pharmaceutical composition. Other components, such as flavoring agents, salts, and the like, may be added to the composition. The pH adjusting or buffering agent, aqueous medium, preservative, flavoring agents, salts, or other ingredient may be any described herein.

In certain other embodiments, the method of preparing the pharmaceutical composition comprises admixing GHB, a pH adjusting or buffering agent, and an aqueous medium soon before administration to a patient suspected of having a condition responsive to GHB.

The invention also provides a method of treating any therapeutic category of disorder responsive to GHB, comprising administering to a patient suspected of having such a condition a therapeutic amount of a pharmaceutical composition comprising chemically stable GHB (e.g. 1-10 gms.) in an aqueous medium resistant to microbial growth. In certain embodiments, the method of treating a condition responsive to GHB comprises a patient taking a first dosage of from about 0.1 g to about 10 g, namely about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1-9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0 about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, to about 10 grams of GHB, or as needed by the patient as would be recognized by one of skill in the art. Of course, it will be understood that all values in between those listed, such as 9.45 grams, 6.32 grams, etc. may be administered, and those values are encompassed well. In preferred embodiments, the first dose is administered within an hour of sleep. In preferred embodiments, a second dose of GHB within the values described above may be administered. This second dose is administered preferably within about 2.0 to about 5.0 hrs, namely about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, to about 5.0 hours after the first dose, though it may be administered at a time outside of the preferred range.

In certain embodiments, a second pharmaceutical may be administered with the composition of GHB. Such a second pharmaceutical may be e.g., a stimulant administered within the same 24 hour period as the first dose of GHB. The stimulant may be, e.g., but not limited to, methylphenidate or pemoline to counter the residual effects of GHB treatment during periods of wakefulness. In certain embodiments, the method of treating a sleep disorder may include the discontinuation of other second pharmaceuticals used to control a sleep disorder. Such second pharmaceuticals may include, but are not limited to, a tricyclic antidepressant.

In certain embodiments, the invention provides a method of treating any appropriate therapeutic category of disorder, by administration of GHB compositions of the present invention as described above for the treatment of sleep disorders. When GHB is used in methods of treating any therapeutic category of disorder, the GHB composition of the present invention may be mixed with the aqueous medium, and optionally pH adjusting or buffering agent or other additives, by the patient or administrator soon before consumption. The patient may prepare the composition within a few minutes to hours before administration. Alternatively, one or more of the components may be premixed for ready use. The components of the GHB composition of the present invention, GHB, an aqueous medium, pH adjusting or buffering agent, excipients, preservatives, flavoring agents, and/or other components or additives may be stored in a container means suitable to aid preservation. Preferably, the container means is in the form of a set. A "set" as used herein certain embodiments is one or more components of the composition packaged in a container or other suitable storage means.

The present invention also provides a set for the treatment of a condition responsive to GHB comprising, in suitable storage means, GHB and a pH adjusting or buffering agent. In certain embodiments, the GHB and the pH-adjusting or buffering agent are separately packaged. In certain other embodiments the GHB and the pH adjusting or buffering agent may be mixed. The set may contain an aqueous medium. In certain other embodiments, at least one component selected from the group including, but not limited to, GHB, the pH-adjusting or buffering agent and/or an aqueous medium is separately packaged. In certain other embodiments, at least two of the components selected from the group comprising GHB, a pH adjusting or buffering agent and an aqueous medium are mixed together. In some embodiments, the set further contains a preservative. Such a set may have one, two, or more components from the group comprising GHB, a pH-adjusting or buffering agent, an aqueous medium or a preservative packaged separately. Such a set may have two or more components mixed together. Thus, both liquid and dry formulations of GHB and other components may be packaged in a set for mixing before administration, or one or more components may be premixed and packaged together with other components, or all the components may be premixed and packaged in a set.

It is understood that the compositions of the present invention, including those in a set, may be dispersed in a pharmaceutically acceptable carrier solution as described below. Such a solution would be sterile or aseptic and may include water, co-solvent vehicle buffers, isotonic agents, pharmaceutical aids or other ingredients known to those of skill in the art that would cause no allergic or other harmful reaction when administered to an animal or human subject. Therefore, the present invention may also be described as a pharmaceutical composition of GHB with increased stability in a pharmaceutically acceptable carrier solution.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also as used herein, the term "a" "an" or "the" is understood to include the meaning "one or more". Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. **1**. The Range of Gamma-Hydroxybutyrate's Resistance to Microbial Growth and Chemical Stability in Aqueous Solution. The ordinate is the pH of solutions of GHB. The axis is the concentration (mg/ml) of GHB in aqueous solution. The region below the diagonal line [/] is the range of GHB solubility at room temperature. Greater solubility can be achieved, up to 1 g/ml, by heating the solution up to 100° C.

FIG. **2** illustrates the concentration and volume of GHB solution that a patient administers (see also Table 4).

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

I. Formulations of Gamma-Hydroxybutyrate

A. Microbial Growth and Gamma-butyrolactone Formation

The present invention arises from the discovery of chemically stable and microorganism resistant formulations of GHB in an aqueous medium, preferably a solution, and the efficacy of these formulations in the treatment of therapeutic categories of disorders, such as narcolepsy and other sleep disorders. Specifically, GHB is prepared at a concentration greater than about 150 mg/ml in an aqueous medium, up to the limits of GHB's solubility or retention in an aqueous medium, to produce the compositions of the present invention.

The maximum solubility of GHB is affected by the pH of the aqueous medium. At about pH 4, the maximum amount of sodium-GHB that can be dissolved is about 450 mg/ml. The value of pH that is conducive to GHB solubility increases, as is shown at FIG. **1**, so that the minimal pH that will dissolve 750 mg/ml GHB was found to be about pH 6.8. This is shown in Table 1.

TABLE 1

	Limits of Sodium Oxybate Solubility		
ID A	Sodium Oxybate Maximum Solubility	pH of Solution	Temperature
B	450 mg/cc	pH 4 (HCl)	25°
C	500 mg/cc	pH 5 (HCl)	25°
D	600 mg/cc	pH 6 (HCl)	25°
E	750 mg/cc	pH 6.8 (HCl)	25°
F	750 mg/cc+	pH 10.3	25°
G	1000 mg/cc	pH unadjusted	65° Soluble 25° Gel

The pH of the aqueous medium also affects the resistance of the composition to microbial growth at about 500 mg/ml GHB. GHB at this concentration in an aqueous medium that is between about pH 5 and pH 9 is resistant to microbial growth, with compositions at about pH 6 to about pH 7.5 being particularly resistant to microbial growth. However, at concentrations of GHB greater than about 750 mg/ml above about pH 7.5, the resistance to microbial growth is reduced. This is shown at Table 2.

TABLE 2

	Microbial Challenge Data Summary		
ID H	Sodium Oxybate Concentration	pH of Solution	Microbial Challenge Result
I	750 mg/cc	7.5 (HCl)	pass
J	500 mg/cc	6.0 (HCl)	pass
K	500 mg/cc + Excipients (Xylitol)	6.0 (Malic Acid)	pass
L	500 mg/cc	9.0 (HCl)	pass (borderline *aspergillus*)
M	150 mg/cc (BDL 1995)	5.0 (HCl)	fail (*aspergillus* only)
N	150 mg/cc (BDL 1995)	7.0 (HCl)	fail (*aspergillus & staph*)
O	150 mg/cc (BDL 1995)	3.0 (HCl)	fail (*aspergillus* only)
P	150 mg/cc (BDL 1995)	10.3 (unadjusted)	fail (*aspergillus & staph*)
Q	500 mg/cc	6.0 (Malic Acid)	discontinued
R	500 mg/cc	7.5 (Malic Acid)	pass

TABLE 2-continued

	Microbial Challenge Data Summary		
ID H	Sodium Oxybate Concentration	pH of Solution	Microbial Challenge Result
S	500 mg/cc (May 1998)	9.0 (Malic Acid)	discontinued
T	500 mg/cc (May 1998)	7.5 (HCl)	pass*
U	Others: 200 mg/cc-800 mg/cc	5.0-9.0	pending

*pass is generally defined as:
For Category 1C Products
Bacteria: Not less than 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days' count at 28 days.
Yeast and Molds: No increase from the initial calculated count at 14 and 28 days.

The data from Table 1 and Table 2 are graphically shown in FIG. **1**. The concentration of GHB in the composition, when evaluated in relationship to the pH, affects the resistance of the GHB composition to microbial challenge. Compositions of GHB at or below 150 mg/ml are poorly resistant to microbial challenge from a pH range of about pH 3 to about pH 9. However, concentrations of GHB of greater than about 150 mg/ml, up to about 1000 mg/ml of GHB, are believed to be suitably resistant to microbial contamination at these pH ranges.

The chemical stability of GHB is affected by pH. Accordingly, the method for preparing GHB, as described herein, particularly as disclosed in the specific examples, varies with pH. GBL begins to form if the pH is about 6 or less. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of 15 GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, any pH or range of pH values where a clinically acceptable amount of GBL is produced is also contemplated as being preferred, and is encompassed by the present invention. The range of GBL could be regulatorily broadened with availability of sufficient toxicological data.

In certain embodiments of the invention, a pH-adjusting agent may be added to the composition. The choice of a pH adjusting agent may affect the resistance to microbial challenge and/or the stability of GHB, as measured by the reduction in assayable GHB. Compositions of GHB, pH adjusted with malic acid are resistant to both microbial growth and chemical degradation of GHB, and are preferred. Other pH adjusting or buffering agents may be selected. Agents that adjust pH that are selected on this basis will undergo a taste testing study. However, any pH adjusting agent disclosed herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the invention. Of course, any salt, flavoring agent, excipient, or other pharmaceutically acceptable addition described herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the invention.

Any of the above formulations may be prepared and/or packaged as a powdered or dry form for mixing with an aqueous medium before oral administration, or they may be prepared in an aqueous medium and packaged. After mixing with an aqueous medium, preferably to prepare a solution, these formulations are resistant to both microbial growth and chemical conversion of GHB to GBL, thereby increasing the shelf-life of therapeutic formulations of GHB in an aqueous medium. These formulations-then provide an easily titratable liquid medium for measuring the dosage of GHB to be administered to a patient. Additional embodiments of the composition and methods of preparation are described below and in the examples.

B. Pharmaceutical Compositions

1. Pharmaceutically Acceptable Carriers

Aqueous compositions of the present invention comprise an effective amount of GHB dissolved or dispersed in a pharmaceutically acceptable carrier and/or an aqueous medium. The phrases "pharmaceutically or pharmacologically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is not appropriate. Supplementary compatible active ingredients can be incorporated into the compositions. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by the Food and Drug Administration (FDA).

The GHB may be lyophilized for more ready formulation into a desired vehicle where appropriate. The active compounds may be formulated for parenteral administration, e.g., formulated for injection via intravenous, intraarterial, intramuscular, sub-cutaneous, intralesional, intraperitoneal or other parenteral routes. The preparation of an aqueous composition that contains a GHB agent as an active component or ingredient will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for using to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including, e.g., aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

Solutions of the active compounds as free acid or pharmacologically acceptable salts can be prepared in water suitably mixed with hydroxypropylcellulose and/or a pharmacueutically acceptable surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof as well as in oils. Under ordinary conditions of storage and use, these preparation may best contain a preservative to further prevent the growth of microorganisms.

A GHB composition of the present invention can be formulated into a composition in a neutral or salt form. Such salts can be formed from any of the acids and bases described herein particularly depending on the particular GHB or GHB salt used, or as would be known to one of ordinary skill in the art.

The carrier can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, or the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a substance, such as lecithin (e.g. a coating), by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by any of the preservatives described herein, or as would be known to one of ordinary skill in the art, including various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The preparation of more, or highly, concentrated solutions for direct injection is also contemplated, where the use of DMSO as solvent (although DMSO may not now be a permitted human drug) is envisioned to result in extremely rapid penetration, delivering high concentrations of the active agents to a small area.

Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above, but drug release capsules and the like can also be employed.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences"15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The active GHB may be formulated within a therapeutic mixture to comprise about 100 to about 10,000 milligrams per dose. Multiple doses can also be administered.

In addition to the compounds formulated for parenteral administration, such as intravenous or intramuscular injection, other pharmaceutically acceptable forms include, e.g., tablets or other solids; liposomal formulations; time release capsules; and any other form currently used, including cremes, which then may be admixed with an aqueous medium for oral administration.

One may also use nasal solutions or sprays, aerosols or inhalants in the present invention. Nasal solutions are usually aqueous solutions designed to be administered to the nasal passages in drops or sprays. Nasal solutions are prepared so that they are similar in many respects to nasal secretions, so that normal ciliary action is maintained. Thus, the aqueous nasal solutions usually are isotonic and slightly buffered to maintain a pH of 5.5 to 6.5, though other pH ranges disclosed

herein the specific examples, such as pH 3 to about pH 9, or pH 6 to about 7.5, are contemplated. In addition, preservatives, similar to those used in ophthalmic preparations, and appropriate drug stabilizers, if required, may be included in the formulation. Various commercial nasal preparations are known and include, for example, antibiotics and antihistamines and are used for asthma prophylaxis.

The preferred oral formulations may include such normally employed excipients, as, for example, pharmaceutical grades of xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate and the like. These compositions can take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders to be admixed with an aqueous medium. In certain defined embodiments, oral pharmaceutical compositions will comprise an inert diluent or assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsule, or they may be compressed into tablets, or the GHB may be packaged separately from or in combination with the excipients, salts, flavorings or any other components described herein, to be admixed with an aqueous medium for oral or injectable formulations, or they may be incorporated directly with the food (i.e. a beverage) of the diet.

For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of tablets, buccal tablets or tabs, troches, capsules, elixirs, suspensions, syrups, wafers, and the like, to be admixed with an aqueous medium. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 75% of the weight of the unit, or preferably between 25-60%. The amount of active compounds in such therapeutically useful compositions is such that a suitable dosage will be obtained.

The tablets, troches, pills, capsules and the like may also contain the following: a binder, natural as gum tragacanth, acacia, cornstarch, or gelatin or synthetic as polyvinyl acetate; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a natural or synthetic flavoring agent. When the dosage unit form is a capsule for admixing with a specific volume of an aqueous medium, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with sugar, natural or synthetic polymers, or both. A syrup or elixir may contain the active compounds, sucrose as a sweetening agent, a preservative, a dye and/or a flavoring.

Additionally, any excipient, salt, acid, pH-mediating, adjusting or buffering compound or agent, flavoring, solution, solvent, dispersion, glycerol, glycol, oil, antibacterial and antifungal agents, antibiotics and antihistamines, binders, disintegrating agents, lubricants, sweetening agents, or any other additive or ingredient from those enumerated above or in the examples, or in any pharmaceutically acceptable composition or carrier described herein, or as would be known by one of skill in the art, is contemplated for use in aqueous mediums or solid forms of the GHB compositions of the invention. One or more of these compositions may be packaged with GHB or packaged separately from GHB prior to consumption. If packaged separately, useful compositions of GHB may be obtained by mixing GHB with the other components with an aqueous medium prior to consumption. Such components may be packaged in a set, described below.

2. Sets

Therapeutic sets of the present invention are sets comprising GHB. Such sets will generally contain, in suitable container, a pharmaceutically acceptable formulation of GHB. The set may have a single container, or it may have distinct container for each component, or distinct container for various combinations of components.

When the components of the set are provided in one or more liquid formulations, the liquid formulation is an aqueous medium, with a sterile aqueous solution being particularly preferred. The GHB compositions may also be formulated into a syringeable composition. In which case, the container means may itself be a syringe, pipette, vial, ampule or other such like apparatus, from which the formulation may be applied to an infected area of the body, injected into an animal, or even applied to and mixed with the other components of the set.

However, the components of the set may be provided as dried powder(s). When reagents or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent. It is envisioned that the solvent may also be provided in another container means.

The container means will generally include at least one vial, test tube, flask, bottle, pouch syringe or other container means, into which the GHB formulation or components thereof are placed, preferably, suitably allocated. The sets may also comprise a second container means for containing a sterile, pharmaceutically acceptable buffer or other diluent.

The sets of the present invention will also typically include a means for containing the vials in close confinement for commercial sale, such as, e.g., injection or blow-molded plastic containers into which the desired vials are retained.

Irrespective of the number or type of containers, the sets of the invention may also comprise, or be packaged with, an instrument for assisting with the injection/administration or placement of the GHB composition within the body of an animal. Such an instrument may be a drinking cup, syringe, pipette, or any such medically approved delivery vehicle.

II. Methods of Treatment with the GHB Compositions

Because GHB has been shown to be effective in treating narcolepsy and sleep disorders (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993), reducing alcohol craving and alcohol withdrawal symptoms, (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992), reducing opiate withdrawal symptoms (Gallimberti et al, 1994; Gallimberti et al., 1993), reducing pain (U.S. Pat. No. 4,393,236), reducing intracranial pressure in patients (Strong, A. 1984), and increasing growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970), the formulations of the present invention are also contemplated to be useful in the treatment of any of these disorders or conditions in patients. GHB has also been used alone as a narcotic in patients with a terminal carcinomatous state. GHB has been used with other analgesics, neuroleptics, or with a subliminal barbiturate dose for use as an anesthesia. GHB has been used in closed craniocerebral trauma and as a soporific (U.S. Pat. No. 5,380,937). The inventors contemplate the use of the GHB compositions of the present invention as a narcotic, hypnotic, or as a soporific. The inventors also contemplate the use of the GHB compositions of the present invention in combination with analgesics, neuroleptics or barbiturates for use as an anesthesia. The GHB compositions of the present invention may be prepared and administered by any of the means described herein. particularly those described in the section "Pharmaceutical Compositions" and the examples, or by any means as would be known to those of skill in the art.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the

examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

Preferred Embodiments

XYREM™ Clinical Trials

The inventors developed a liquid formulation composed of GHB, xylitol, and preservative in water (XYREM®). Subsequent instability of the preservative in this formulation and a desire to initiate clinical trials in a timely manner led to a change in the formulation to a foil pouch. One clinical trial utilized a twin-pouch dosage form, with one side (pouch 1) of the foil packet containing GHB and the other side (pouch 2) containing the flavoring agents (Xylitol, [NF]; Malic Acid, NF.

Patients were instructed to open the twin-pouch with a scissors, empty the contents into a dosing cup, add 2 ounces of water, snap the lid on the dosing cup, shake to dissolve, and drink the entire contents of the cup. Clinical trials conducted by the inventors have been performed using the twin-pouch dosage form.

However, the inventors have continued development of a liquid solution and have now overcome inherent problems with particular formulations and/or preservatives. The inventors have converted patients currently enrolled in a GHB open-label trial to a liquid solution composed of GHB, malic acid, and water—that is diluted with water immediately prior to oral administration.

The need for a liquid solution dosage form is further evidenced by the range of doses being used in a subsequent GHB open-label trial. Three sizes of pouches were prepared for the GHB open-label trial: 1.5 grams, 3.0 grams. and 4.5 grams. The initial dose for all patients in the GHB open-label trial was 6 grams of GHB nightly in divided doses. Dosage adjustments were permitted in the first two weeks of the trial as indicated for intolerance or lack of efficacy. The investigator was permitted to decrease the dose of GHB to 3 grams or 4.5 grams, or increase the dose to 7.5 grams or 9 grams nightly. After two weeks, further dosage adjustments were made if clinically indicated.

Thirty-five patients had their dose increased, and 16 patients had their dose decreased. Patients in the lowest dose group were disproportionately female and weighed 15 kg less than patients in the other two groups. Current dosing levels are noted below:

TABLE 3

Dosing Levels in the GHB Open-Label Trial

	Total	1.5 gram	3.0 gram	4.5 gram	6.0 gram	7.5 gram	9.0 gram
Number of Patients	95	0	4	10	39	12	30
PerCent of Patients	100%	0%	4%	10%	41%	13%	32%

To achieve these individualized doses, it has been necessary to provide a combination of different dose strengths. This complexity would be very difficult to achieve with a marketed product. In addition, a month's supply of twin-pouches is quite bulky. A liquid formulation allows for ease in dosing adjustment with one dosage form. In addition "child-resistant" packaging has been developed with the liquid formulation.

A number of patients have also complained about the flavor with the twin-pouches. As follow-up the inventors sent questionnaires to participants in the inventors' clinical trial, and performed taste testing in normal volunteers. The questionnaire responses, taste testing results, and the clinical experience in narcolepsy patients of the study administrator have all confirmed that unflavored solutions were acceptable.

The concentration and volume of the GHB solution that the patient administers will be the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. This is illustrated in FIG. **2** and Table 4:

TABLE 4

Comparison of Liquid Solution to Twin-Pouch

	Twin-Pouch	Liquid Solution
Amount of GHB	3 grams (1 pouch)	3 grams (6 mL)
Inactive Components	malic acid xylitol lemon/lime flavor orange flavor	malic acid
Final Concentration	50 mg/mL	50 mg/mL*
Final Volume	60 mL	60 mL

*Final concentration outside the range of the most stable formulation. This formulation strength may be only stable at short periods of time such as 48 hours. The twin pouch version could be solubilized at a a concentration within the preferred range of pH and GHB concentration for longer term storage.

Apart from the elimination of the sweetener (xylitol) and flavoring, the two formulations result in identical solutions.

Conclusions

The concentration and volume of the GHB solution that the patient administers is the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. Either method may be used to produce acceptably stable solutions of GHB.

EXAMPLE 2

Preferred Embodiments

Self Preserving Formulations of Gamma-Hydroxybutyrate

Summary of Formulation Studies

Liquid Xyrem™

I. Maximum Solubility Range

As seen in FIG. **1** and Table 1, the solubility of GHB varies with pH levels at room temperature (25° C.). Additional amounts of GHB can be solubilized in a gel if heat is applied, in which case a 1000 mg/ml concentration can be achieved. The inventors to contemplate that though the concentrations or contents of GHB shown in FIG. **1** and Table 1 are preferred for use, due to the ease of preparing and consuming unheated preparations, higher concentrations of GHB in aqueous medium may also be made, up to 1000 mg/ml.

II. Microbial Testing

The inventors used a three factor analysis involving pH, concentrations of GHB and the pH adjuster used. As seen in

FIG. **1**, and Table 2, unacceptably low resistance to microbial challenge was seen at 150 mg/ml GHB at pH 3, 5, 7, and 9.0, using HCl as the pH adjusting agent. 150 mg/ml GHB at pH 10.3 without a pH adjusting agent also proved unacceptably resistant to microbial challenge. Borderline acceptable microbial preservativeness was seen in a solution pH adjusted with HCl at 500 mg/ml GHB at pH 9. At a concentration of 500 mg/ml at pH 6.0 or 7.5, adjusted with either malic acid or HCl, and 500 mg/ml at pH 9.0 adjusted with HCl, the formulation is very effective in a microbial challenge test. The inventors contemplate that a concentration of greater than about 150 mg/ml of GHB, up to the maximal solubility in aqueous solution of GHB, will be suitably resistant to microbial challenge from about pH 3 to pH 10.3. Preferably, the aqueous medium will contain a pH-adjusting or buffering agent.

III. Gamma-Butyrolactone Degradation Range

GBL begins to form if the pH is about 6 or less with the formulation tested thus far.

A. Liquid Formulation Development

The objective of these experiments was to develop a commercial formulation for sodium gamma hydroxybutyric acid. The initial formulation for sodium gamma hydroxybutyric acid (GHB) was intended to be an aqueous liquid formulation containing 150 mg/ml GHB, preservatives and flavoring agents. To develop this formulation, studies were conducted to establish the: solubility of the drug in water and as a function of pH, type and concentrations of suitable preservatives, type and concentrations of flavor ingredients, and stability of the formulations.

1. Solubility

The feasibility of preparing formulations containing 150 mg/mL of GHB at pH 3, 5 and 7 was established. Solutions containing 150 mg/mL GHB were prepared. The initial pH was greater than pH 7.5 and the final pH was adjusted to 3, 5 or 7 with hydrochloric acid. The solutions were observed for precipitation and assayed by HPLC for GHB content. The results showed that no precipitation was observed and the drug concentration was found to be 150 mg/mL by HPLC. This information was used as the basis for additional formulation development studies.

2. Preservatives

Preservative effectiveness studies were conducted to identify a suitable preservative for the GHB liquid formulation. The following formulations shown in Table 5 were prepared and tested using *Staphylococcus aureus* (ATCC #6538), *Pseudomonas aeruginosa* (ATCC #9027) and *Aspergillus niger* (ATCC #16404).

TABLE 5

Liquid Formulations Used in Preservative Effectiveness Testing

Formulation	pH	Sodium Benzoate	Methylparaben Propylparaben	Potassium Sorbate	Control
1	3	X			
2	5	X			
3	7	X			
4	3		X		
5	5		X		
6	7		X		
7	3			X	
8	5			X	
9	7			X	
10	3				X
11	5				X
12	7				X
13	no pH adjustment				X

The preservative used in each formulation is marked with an X. The results showed that formulations #3, 4, 6 and 9 reduced all three challenge microorganisms by >99.99% in 48 h of contact time. Formulations #1, 5 and 7 reduced all three challenge microorganism by >99.99% in 7 days of contact time. Formulations #2, 8, 10, 11, 12 and 13 did not reduce *Aspergillus niger* mold to >99.99%, although some reduction occurred in 7 days of contact time. Controls #10, 11, 12 and 13 demonstrated activity against *Pseudomonas aeruginosa.*

3. Stability

Based on the results of the preservative effectiveness testing, five formulations were selected for stability testing. Table 6 shows the composition of the formulations.

TABLE 6

Liquid Formulations Used in Informal Stability Program

Chemical	1	2	3	4	5
Potassium Sorbate	0.4 gm	0.4 gm			
Sodium Benzoate			1.0 gm		
Methyl-paraben				0.36 gm	0.36 gm
Propyl-paraben				0.04 gm	0.04 gm
GHB	30 gm	30 gm	30 gm	30 gm	30 gm
Xylitol	40 gm	40 gm	40 gm	40 gm	40 gm
Water q.s.	200 mL	200 mL	200 mL	200 mL	200 mL
Initial pH	8.68	8.68	9.30	7.75	7.75
Formulation Adjusted pH	3.01	5.00	3.00	2.98	4.98

The formulations were packaged in 125 mL, amber PET bottles with safety lined child-resistant caps and stored upright and inverted at 60° C., 40° C./75% relative humidity (RH) and 25° C./60% relative humidity. Samples were removed from the stability chambers after 1, 2 and 3 months and assayed by high performance liquid chromatography (HPLC) for GHB content. Appearance and pH were also monitored.

Table 7 shows the results for the 3 month time point. Samples stored at 60° C. changed color but samples at all other conditions remained unchanged in color.

The pH of all formulations migrated upward over the three month stability period at 60° C. The percent increase in pH from initial to 3 months, was greater for the formulations which were initially adjusted to lower values.

For example, the migration of pH in formulations 1, 3 and 4 (adjusted down to pH 3) were 21-30 percent across all conditions in three months. The migration of pH in formulations 2 and 5 (adjusted down to pH 5) were 4.2-12 percent across all conditions in 3 months. Maintenance of pH becomes important for long term storage since preservatives are known to degrade in formulations having pH levels above approximately pH 6.

Additionally, development of flavor systems to mask the negative taste of preservatives is difficult.

TABLE 7

Table 7
Results of Liquid Formulation Informal Stability Study at Three Months

Formulation # (See Table 6)	Attribute	25° C./60% RH Upright	25° C./60% RH Inverted	40° C./75% RH Upright	40° C./75% RH Inverted	60° C. Upright
1	% t = 0	100.7	101.6	101.2	NA	NA
Potassium	pH	3.63	3.64	3.84	3.82	3.91
Sorbate (pH 3) at 3 months storage	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light yellow
2	% t = 0*	102.1	105.0	104.0	102.0	99.6
Potassium	pH	5.21	5.28	5.55	5.56	5.61
Sorbate (pH5)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light brown
3	% t = 0	102.4	104.1	99.1	102.6	97.0
Sodium	pH	3.60	3.74	3.78	3.75	3.79
Benzoate (pH3)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, colorless
4	% t = 0	101.5	102.7	100.6	101.2	93.7
4 Methyl &	pH	3.63	3.71	3.81	3.80	3.83
Propyl Parabens (pH3)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, colorless
5	% t = 0	103.1	105.8	101.9	103.1	95.6
4 methyl &	pH	5.22	5.55	5.55	5.56	5.60
Propyl Parabens (pH5)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light yellow

*% GHB at t = 0 percent of label claim
**initial time (t = 0)

4. Liquid Formulation Organoleptic Testing

Based on the above stability data and preservative effectiveness testing, a pH formulation containing potassium sorbate was selected as the primary base formulation for flavor system development and organoleptic testing. A pH 3 formulation containing potassium sarbate was selected as the back-up formulation.

B. Dry Powder Formulation Development

Developing a flavor system for the primary and back-up liquid formulations proved to be difficult and a decision was made to develop a dry powder formulation for reconstitution with water before consumption. This approach removed the need for a preservative system, the requirement to adjust pH to levels below pH 6, and allowed the development of a suitable flavor system.

1. Dry Powder Formulation Organoleptic Testing

To develop a flavor system for the powder formulation, several parameters were evaluated. The flavor attributes of a GHB solution was characterized by a professional sensory panel. A mimic base containing similar sensory properties as a GHB solution for flavor system was developed. Generally Recognized As Safe (GRAS) excipients for flavor system development were selected. Different excipients (flavorings, sweeteners, acidulants and flow agents) in the mimic base were screened. Three flavor systems for the focus group test were selected. A preferred flavor system was optimized based on comments obtained from the focus group testing. This final formulation with GHB was optimized.

Based on the above activities, the following formulations in Table 8 were selected for stability studies:

TABLE 8

Composition of Prototype Dry Powder Formulation

Ingredient	Composition (grams)	Purpose
GHB	3	Active
Xylitol	5.5	non-cariogenic sweetener

TABLE 8-continued

Composition of Prototype Dry Powder Formulation

Ingredient	Composition (grams)	Purpose
Malic acid	0.2	Acidulant
Flavor 1	0.2	Flavor ingredient
Flavor 2	0.04	Flavor ingredient
Silicon Dioxide (Cab-O-Sil ®)	0.03	Flow enhancer

2. Dry Powder Formulation Stability

A study was initiated to evaluate the stability of the above prototype formulation in two types of foil packages (high and moderate moisture resistant) as well as the stability of GHB alone in one type of foil package (high moisture resistant). Table 9 shows the Lots that were placed on stability. The foil packages were a high moisture resistant pouch and a moderate moisture resistant pouch. The study protocol, Table 10, required the samples to be stored at 40±2° C./75±5% relative humidity for six months, and 25±2° C./60±5% relative humidity for 12 months. Table 11 shows the tests, methods, number of packets/test and specifications for the study.

TABLE 9

Dry Powder Informal Stability Study Package Composition

Lot Number	Manufacture Date	Package Configuration	Special Comments
SPO #8018 A	Oct. 06, 1995	Foil Packet	Moderate moisture resistant pouch.
SPO #8018 B	Oct. 06, 1995	Foil Packet	Highest moisture protection pouch.
SPO #8018 C	Oct. 06, 1995	Foil Packet	Drug substance only. Highest moisture protection pouch.

TABLE 10

Dry Powder Informal Stability Study Protocol

	Stability Time in Months						
Storage Conditions	0	1	2	3	6	9	12
40 ± 2° C./75% ± 5% RH		X	X	X	X		
25 ± 2° C./60% ± 5% RH	X	X	C	C	R	R	R

X = Samples to be tested
C = Contingency Samples
R = Reduced testing; assay and H_2O only
RH = Relative Humidity

TABLE 11

Dry Powder Informal Stability Tests and Specifications

Test	Method	Packets/Test	Specification Limits
Appearance Dry Material	Visual	Use HPLC	White to off-white free flowing powder
Appearance Reconstituted Material	Visual	Use HPLC	Cloudy, off-white solution with visible particulates
Rate of Dissolution	Visual	Use HPLC	Material should dissolve completely in five min with mixing
Odor	Olfactory	Use HPLC	Characteristic Lemon/Lime odor
Assay: GHB	HPLC	3	90.0%-110.0%
Assay: Malic Acid	HPLC	Use HPLC	90.0%-110.0%
Impurities/ Degradants	HPLC	Use HPLC	Not more than 1% for any individual impurity/degradant and Not more than 3% total impurity/degradants
Vacuum Leak test	Visual	3	No Appearance of Leaking
pH	USP <791>	Use HPLC	For Information
Moisture	Karl Fisher	3	Report Value—to be determined

After two months at 40±2° C./75±5% relative humidity, the potency (% label claim) of Lots SPO SO ISA and SPO 80 188 was less than 94.0%, the lower limit of the specification, whereas Lot SPO 8018C showed no loss in potency. Lots 8018A and 8018B showed approximately 96% potencies after 2 months at 25° C.±2° C./65%±5% relative humidity. Lot SPO 8018C again showed no loss in potency at this lower storage condition.

3. Appearance

After 2 months at 40±2° C./75±5% relative humidity, Lots SPO 8018A and SPO 8018B showed significant melting, whereas Lot 8018C showed no melting. Lots SPO 8018A and SPO 8018B also showed partial melting after 2 months at 25° C.±2° C./65%±5% relative humidity. Lot SPO 8018C again showed no evidence of melting at this lower storage condition.

Based on the physical changes in state observed during the stability studies, it was apparent that a solid state interaction between GHB and the excipient blend had occurred. Since xylitol made up the majority of the excipient blend, it was assumed that xylitol was the primary source of the drug-excipient interaction. An alternative hypothesis was also proposed, based on the possibility that the package was mediating the interaction between GHB and xylitol. Three studies were initiated to test these hypotheses.

4. Stability of GHB Solids in a Set Container-System

In the first study, the samples that were stored at 25±2° C./60±5% relative humidity were transferred to glass vials and then stored at 40±2° C. I7±5% relative humidity. In the second study, mixtures of GHB and xylitol were gently rubbed between sheets of different types of foil packaging. The mixtures were observed for changes in physical appearance. In the third study, different mixtures of GHB and xylitol were prepared. Differential Scanning calorimetry (DSC) thermograms were then done to look for changes in the thermograms. The results of these studies are summarized below.

Transfer to Glass: Samples of Lot 8018A and Lot 8018C that were previously stored at 25±2° C./60±5% relative humidity were transferred to amber screw cap vials and stored at 40±2° C./75±5% relative humidity. Analyses similar to those shown in Table 6 were done. After 1 month, the potency of Lot 8018A was 94.6% whereas the potency of Lot 8018C (GHB only) was 100%. In addition, Lot 8018A also showed evidence of melting. The results supported the hypothesis that GHB and xylitol were interacting in the solid state and the interaction appeared to be independent of packaging.

Foil Study: Mixtures of GHB and xylitol were placed between folded sheets of several different foil packaging materials. Slight adhesion of the mixed granules with the foil lining was observed for all of the foils examined. No direct evidence of melting was observed, however, even when excessive force was applied to the outer foil surfaces. This data suggests that the packaging material was not responsible for the solid state interaction observed during the stability studies.

DSC thermographs were obtained for samples of GHB/xylitol containing GHB:xylitol mixtures of 33:66, 45:55 and 55 percent 45 respectively. The scans were conducted at a scan rate of 10° C./min. The thermograms showed that the sample containing GHB:xylitol 33:66 showed a broad endothermic transition starting at 35° C.-40° C. Samples with higher ratios of GHB:xylitol also showed broad endothermic transitions that started at temperatures of 45° C.-50° C. The changes seen in the thermograms supported the hypothesis that a solid state interaction may be occurring between GHB and. xylitol that resulted in low potencies for formulations containing mixtures of these two agents.

As a result of the changes seen in the DSC thermograms for different mixtures of GHB:xylitol, a study was initiated to investigate the stability of a formulation containing GHB: xylitol excipient blend 55:45. A formulation containing GHB:xylitol excipient blend 33:66 was used as a control sample. The formulations were packaged in glass vials and stored at 50° C., 40±2° C./75±5% relative humidity and 25±2° C./60±5% relative humidity. The appearance and potency of the formulations were monitored through analyses of stability samples. The stability study also showed potency losses after 1 month at 40° C.±2° C./75±5% relative humidity with both the 50/50 GHB:xylitol ratio as well as the original 33/66 ratio formulation. Partial evidence of melting was also observed in both formulations.

Studies with mixtures of GHB:xylitol excipient blend indicated that the mixture was incompatible in the solid state. However, when prepared as an aqueous solution, these mixtures were chemically compatible. Using this information, a decision was made to package the GHB formulation in dual pouches; one pouch containing GHB alone and the other containing a mixture of xylitol and the other flavor ingredients. The formulation wiH contain equal amounts of GHB and the excipient blend. This product will be prepared, packaged, and may be checked for stability.

EXAMPLE 3

The Pharmacokinetics of Gamma-Hydroxybutyrate

I. Study Objectives

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; patients generally ingested

the first dose of this medication prior to bedtime and the second dose from 2.5 to 4.0 h later) to narcoleptic patients who are maintained on a chronic regimen of GHB.

II. Study Design

This pharmacokinetic study was conducted as an open-label, single-center investigation in 6 narcoleptic patients. The study design is summarized as follows:

TABLE 12

Screening/Washout ⇒	Treatment/Blood Sampling ⇒	Follow-up
(1 or more days to dosing; washout, at least 8 h	(Two 3 g GHB oral doses, 4 h apart; 21 blood samples)	(Within 48 h after last blood sample)

Narcoleptic patients, 18 years of age or older, who volunteered for this study were screened at least one day prior to the treatment phase. Each patient was determined to be in stable health and evaluated for the presence of narcolepsy, defined for the purposes of this example as one or more years of medical history of narcolepsy as evidenced by a recent nocturnal polysomnogram (PSG) and a valid score from a Muhiple Sleep Latency Test (MSLT).

Patients maintained on GHB were allowed to participate. These patients had been weaned from antidepressants, hypnotics, sedatives, antihistamines, clonidine, and anticonvulsants though a stable regimen of methylphenidate (immediate release or sustained release) was allowed. Each patient passed a pre-study physical examination (which included hematology, blood chemistry, urinalysis, and vital signs measurements) prior to the commencement of the treatment phase.

Before oral administration of the first GHB dose, an indwelling catheter was placed in an arm vein and a baseline blood sample was collected. Each patient then ingested a 3 g dose of GHB before bedtime. Another 3 g GHB dose was administered 4 h after the first dose. Twenty-one sequential blood samples were collected over 12 h (starting at 10 min after the first dose and ending at 8 h after the second dose). Upon completion of the treatment phase, a follow-up physical examination which included the measurement of vital signs was performed on each patient within 48 h after the last blood sample. A detailed description of the trial methodology is presented in Section IV.

III. Inclusion Criteria

Patients were included in the study if they: had signed an informed consent prior to beginning protocol required procedures; had not participated in such a study at an earlier date; were willing and able to complete the entire study as described in the protocol; were 18 years of age or older at study entry; had not taken any investigational therapy other than GHB within the 30-day period prior to screening for this study; had an established diagnosis of narcolepsy for at least one year with documentation from a qualified laboratory by a nocturnal polysomnogram (PSG) and a Multiple Sleep Latency Test (MSLT) which demonstrated mean sleep latency to be less than 5 min and REM onset in at least 2 of 5 naps; had not been diagnosed with uncontrolled sleep apnea syndrome, defined as a sleep Apnea Index of 5 or an Apnea Hypopnea Index (AHI) greater than 10 per hour or any other cause of daytime sleepiness; and were free of any medication for their narcolepsy (including hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants) other than GHB and methylphenidate (IR or SR). Patients admitted to this study if they were not experiencing unstable cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, metabolic, neurological, pulmonary, and/or renal disease which would place them at risk during the study or compromise the protocol objective; did not have neurological or psychiatric disorders (including transient ischemic attacks, epilepsy, or multiple sclerosis) which, in the investigator's opinion, would preclude the patients' participation and completion of this study; did not have a current or recent (within one year) history of alcohol or drug abuse; did not have a serum creatinine greater than 2.0 mg/dL, abnormal liver function tests (SGOT or SGPT more than twice the upper limit of normal or serum bilirubin more than 1.5 times normal). Female patients were entered into the study if they were either post-menopausal (i.e. no menstrual period for a minimum of 6 months), surgically sterilized or provided evidence of effective birth control. Females of childbearing potential must agree to continue to use an IUD, diaphragm, or take their oral contraceptives for the duration of the study. Female patients of childbearing potential must have a negative pregnancy lest upon entry into the study.

IV. Trial Methodology

A time and events schedule is presented in Table 12.

A. Screening Period/Washout

Six narcoleptic patients who were chronically being treated with GHB were recruited to participate in this pharmacokinetic study. The screening period was at least one day prior to the treatment phase. During the screening period each patient completed the following procedures for the assessment of their physical condition: medical history evaluation; physical examination evaluation; clinical laboratory evaluation; inclusion criteria review. Each patient's GHB and methylphenidate regimen also were recorded on an appropriate case report form (CRF). The investigator also ensured that there was at least an 8-hour washout period for GHB prior to the treatment.

B. Treatment Period/Blood Samples Collection

All patients were hospitalized from approximately four hours prior to first GHB dosing (around 6 p.m.) until the end of the treatment period (around 10 a.m. the next morning). Patients ate their dinner at the clinical research unit soon after arrival and fasted until breakfast next morning. At least three hours elapsed between the completion of dinner and the administration of the first GHB dose. An indwelling catheter was placed in an arm vein of each patient for blood sampling at approximately 30 min and 1 h before the first GHB dose and a baseline blood sample (5 mL) was collected.

The first GHB dose (3 g) was administered at around 10 p.m. Dosing of individual patients were staggered. The second GHB dose was administered at 4 h after the first GHB dose (i.e. immediately after the 4 h blood sample). The exact dosing times in each patient were recorded on appropriate CRF pages. Blood samples (5 mL each) were collected through the indwelling catheter into heparinized tubes at 0.2, 0.4, 0.6, 0.8, 1, 1.5, 2, 3, 4, 4.2, 4.4, 4.6, 4, 8, 5, 5.5, 5, 7, 8, 10, and 12 h after the first GHB dose. Blood samples were processed according to the procedures described herein. Patients were monitored for adverse experiences throughout the study according to the specific procedures.

C. Follow-Up

Follow-up occurred within 48 h after the last blood sample had been collected. An abbreviated physical examination which included vital signs measurement was performed. Adverse experiences and concomitant medication use, if any, were assessed. Any ongoing adverse experiences and clinically important findings in a patient were followed to the investigator's and/or sponsor's satisfaction before the patient was discharged from the study.

D. Methods of Assessment

1. Medical History

The medical history was recorded during the screening period. The history included gender, age, race, height, prior reaction to drugs, use of alcohol and tobacco, history and treatment, if any, of cardiovascular pulmonary, gastrointestinal, hepatic, renal, immunologic, neurological, or psychiatric diseases and confirmation of inclusion criteria.

2. Physical Examination

Physical Examination included body system review as well as measurement of body weight and vital signs and a neurological examination.

3. Vital Signs

Vital signs measurements included recording of blood pressure, heart rate, respiration, and body temperature.

4. Clinical Laboratory

All clinical laboratory tests were performed at a local laboratory. The laboratory tests and analysis were required of each patient included: hematology, including hemoglobin, hematocrit, red blood cell count, white blood cell count and differential; fasting blood chemistries included blood urea nitrogen (BUN), uric acid, glucose, creatinine, calcium, phosphorus, total protein, albumin, sodium. potassium, SCOT (AST), SGPT (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), and total bilirubin; midstream catch urinalysis included specific gravity, pH, protein, occult blood, ketones and glucose by dipstick determination as well as a microscopic examination of urine sediment for RBC, WBC, epithelial cells or casts or crystals; and a urine pregnancy test. if applicable. Any laboratory parameter that was out of range and considered clinically significant excluded the patient from participation in this study. The investigator would provide an explanation of all observations that were significantly outside the reference range.

5. Concomitant Medication

The continued use of a fixed dose of methylphenidate immediate release or sustained release (IR or SR) is acceptable. The methylphenidate regimen was recorded on the appropriate case report form.

6. Adverse Experiences

An adverse experience are any undesirable event experienced by a patient or volunteer whether or not considered drug-related by the investigator. An undesirable event can be, but is not limited to, subjective symptoms experienced by a patient or, objective findings such as significant clinical laboratory abnormalities. Adverse experience is considered synonymous with the term "adverse event".

The investigators report in detail all adverse experiences and symptoms that occurred during or following the course of trial drug administration for up to 2 days. Included in the description was the nature of the sign or symptom; the date of onset; date or resolution (duration); the severity; the relationship to trial treatment or other therapy; the action taken, if any; and the outcome.

A serious adverse experience is defined as one that is fatal, life threatening, permanently disabling, or which results in or prolongs hospitalization. In addition, overdose, congenital anomaly and occurrences of malignancy are always considered to be serious adverse experiences. An unexpected adverse experience is one not previously reported.

Any serious or unexpected adverse experience (including death) due to any cause which occurs during the course of this investigation, whether or not it is related to the investigational drug, was reported within 24 h by telephone or facsimile. Appropriate authorities were to be informed if the serious or unexpected adverse experience, in the opinion of inventors, was likely to affect the safety of other patients or volunteers or the conduct of the trial.

7. Clinical Supplies-Study Medication

Formulation: Unit 3 g GHB doses (Lot PK1) were obtained from Orphan Medical. Each unit dose comprised twin foil pouches: one pouch containing GHB and the other containing a flavor excipient blend. (Table 8 formulation)

Labeling: The clinical supplies for individual patients were packaged in separate containers. Each container included two unit doses, i.e. two twin-pouches. Clinical supplies for eight patients (including those for two replacement patients) were delivered to the investigator. Foil twin-pouches were identified with a two-part label.

Dose Administration: The investigator or designee prepared the oral solution for dosing within 30 min prior to the first oral administration to individual patients. The contents of one twin-pouch was emptied into a dosing cup to which, two ounces of water were added. After replacing the lid of the dosing cup, it 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 ingesting in its entirety at 4 h after the first GHB dose.

Investigational Drug Accountability: At the conclusion of the study, all clinical supplies were accounted for on the drug accountability form and unused drug supplies were returned for proper disposition.

8. Determination of Plasma GHB Concentrations

Plasma samples were analyzed for GHB by the Department of Bioanalytical Chemistry (Covance (previously known as Hazelton Coming), Madison, Wis.) A gas chromatographic method with mass selective detection (GC-MSD) was used in the analysis.

9. Data Management and Analysis

Data Base: An EXCEL data base (spreadsheet) was constructed from data recorded on Case Report Forms (CRF) and plasma GHB concentration data sets received from Covance (Corning Hazleton). Each entry in the EXCEL spreadsheet was checked against the CRFs and any data entry error found was corrected.

Pharmacokinetic Analysis: Pharmacokinetic parameters were determined for individual sets of plasma GHB concentration vs. time data using the non-compartmental routine in WinNonlin Version 1.1. The peak GHB concentrations (C_{max}) and the times of their respectively occurrences (t_{max}) were observed values. Terminal half-life ($T_{1/2}$) was obtained by log-linear regression analysis of the terminal phase of concentration vs. time curves. The area under the curve (AUC_{inf}) and the area under the first moment curve ($AUMC_{inf}$) were calculated by the linear trapezoidal rule up to the last determined concentration and included extrapolated areas to time infinity. Apparent oral clearance (CL/F) was calculated as Dose/AUC_{inf}. Volume of distribution (V_z/F) was determined by taking the ratio between CL/F and λ_z (elimination rate constant). Mean residence time (MRT) was estimated from the ratio between $AUMC_{inf}$ and AUC_{inf}.

Safety Analyses: Results of physical examinations, vital signs, clinical laboratory data were summarized in tabular form and presented by patient number. Adverse events also were tabulated in a similar fashion.

10. Results

Patient and Study Accountability: Six narcoleptic patients were enrolled and all six completed the study in its entirety.

Protocol Compliance: There were no inclusion criteria violations. All patients admitted into the study met the study

entrance requirements and completed the screening phase at least one day before the treatment phase.

All six patients took non-study medications in addition to methylphenidate and GHB doses because none of their concomitant medications (Synthroid, Premarin, Lovastatin, Fluvastatin, furosemide, potassium, hydrochlorothiazide, lansoprazole, and verapamil) were on the exclusion list (which included hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants). Adverse experience probes, vital sign measurements, and essentially all pharmacokinetic blood samples were performed at protocol specified times; the few deviations in blood sampling times should not have any impact on the outcome of the study since actual blood sampling times were used in the pharmacokinetic analysis.

The diagnosis of narcolepsy for at least one year in each patient was verified by a nocturnal polysomnogram (NSG) and a Multiple Sleep Latency Test (MSLT) conducted at a qualified laboratory. Five patients have been maintained on GHB nightly for over 10 years and one patient has been receiving GHB nightly for two years. One patient (Subject 101) also had multiple sclerosis; however, the attending physician, judged that it would not interfere with the objective of this study. A few of the screening clinical laboratory results marginally fell outside the reference range but none was considered by the attending physician to be clinically significant.

Exposure to Study Drug: All patients ingested the two GHB doses as scheduled (immediately prior to bedtime). The GHB doses per kg body weight ranged from 26.4 to 52.4 mg/kg.

Plasma GHB Concentration Profiles: It was noted that, in certain cases, (Patients #103, and #106), plasma GHB concentrations did not decline from the first C_{max} to zero concentration at h 4. Upon achievement of the second C_{max} the semi-logarithmic plots of concentration versus time data in Patients #102, #103, and #105 exhibited a convex decline profile. Such a decline pattern suggested non-linear pharmacokinetics. The highest plasma GHB concentration observed in the study was 125.0 μg/mL which occurred in Subject 101 after the second 3 g GHB dose.

Pharmacokinetic Parameter Estimates: The mean (±SD) showed that maximum GHB concentrations (C_{max}) were 62.8±27.4 μg/mL and 91.2±25.6 μg/mL for the first and second GHB doses, respectively. The corresponding mean observed times to maximum concentrations were 40±6 and 36±7 min after the first and second GHB doses, respectively. The mean AUC_{inf} was 17732±4603 μg/mL·h. The mean CL/F was 4.2±mL/min/kg and the mean V_z/F was 307±96 mL/kg. The mean MRT_{inf} was 249±56 min. The mean GHB $T_{1/2}$, estimated by linear regression of log [C] vs. time data of the terminal phase of the second GHB dose was 53±19 min.

Adverse Experiences: No adverse experiences were reported in the study.

Follow-up Safety Assessments: Inspection of screen and follow-up physical examination results per individual patient did not identify any changes attributable to GHB.

11. Discussion

To the inventors' knowledge, the level of GHB in human systemic circulation has not been reported in the literature. Hence, baseline (0 h) plasma samples were analyzed for GHB concentrations. The GC-MSD method used in the present study had a limit of quantification (LOQ) of 7.02 μg/mL and analysis of the baseline plasma samples showed the endogenous levels of GHB are below this sensitivity limit. This finding was confirmed by adding known amounts of GHB (5, 10, and 25 μg per mL of plasma) to blank human plasma samples and subjected these samples to GC-MSD analysis. This method of standard addition allowed an estimation of the endogenous GHB level in human plasma which was found to average about 2.02 μg/mL, (i.e. approximately 2/7 of the Limit Of Quantitation (LOQ) for a validated assay. Hence, the endogenous GHB level was not subtracted from exogenous GHB concentrations prior to pharmacokinetic analysis.

Values of mean t_{max} (~40 min after dosing) and $t_{1/2}$ (~35 min) suggest that the GHB solution administered to narcoleptic patients in this study was readily absorbed and rapidly eliminated. In 3 out of 6 patients the drug was essentially gone from the systemic circulation by h 4 after the first GHB dose whereas in the remaining three patients residual GHB levels of ~15 μg/mL was still detected at h 4.

The convex nature of the decline of plasma GHB concentrations in three patients after achievement of the second c_{max} indicated that elimination of GHB from the systemic circulation in these three patients is capacity limited. Nevertheless, it should be noted that plasma GHB concentrations were no longer detectable by h 6 after the second GHB dose (10 h after the first GHB dose). The mean apparent oral clearance found in this study was 4.2±1.0 mL/min/kg and appeared to be comparable to the apparent oral clearance of 5.3±2.2 mL/min/kg reported in the literature for a group of alcohol dependent patients who were administered a dose of 50 mg/kg (Ferrara, 1992). While it appeared that the GHB dose (ranging from 26.4 to 52.4 mg/kg with a mean of 36.5 mg/kg) in the present study was lower than the comparison GHB dose (50 mg/kg) administered to the alcohol dependent patients (Ferrara, 1992), it should be noted that each patient in the present study was administered two consecutive GHB doses at four-hour interval and residual GHB levels were detected in three out of six patients immediately prior to the second GHB dose. The GHB pharmacokinetic non-linearity in alcohol dependent patients easily can be observed from the apparent oral clearance which increased to 8.1±4.8 mL/min/kg when the GHB dose is reduced to 25 mg/kg dose (Ferrara, 1992). In the present study, the non-linearity was less obvious because each narcoleptic patient received two consecutive fixed 3 g doses regardless of body weight.

The mean elimination half-life of GHB in the six narcoleptic patients was determined to be 53±19 min, longer than that in alcohol dependent patients after a 50 mg/kg GHB dose (Ferrara, 1992). The lengthening of GHB elimination half-life observed in this study partially was caused by the wider spacing in sampling time points. However, capacity limited elimination of this drug in some of the narcoleptic patients also could have contributed to this prolongation.

GHB appears to have a shortcoming in that its elimination from the body is capacity limited in some patients when the drug is administered at a fixed regimen of 3 g twice nightly at four-hour interval. However, from a therapeutic perspective, GHB offers an advantage in the treatment of narcolepsy because by the time a patient wakes tip in the morning (i.e. 8 to 10 h after the first GHB dose), all GHB, including that from the second dose, will have been eliminated from the systemic circulation. GHB was also well tolerated by narcoleptic patients in this study. No adverse experience was reported.

12. Conclusions

The capacity limited elimination kinetics was observed in three out of six patients who had been administered two consecutive 3 g oral doses of GHB, 4 h apart. From a pharmacokinetic perspective, dividing the nightly GHB dose into two portions and administering the two portions to narcoleptic patients at a 2.5- to 4-h interval was rational because the elimination half-life of GHB was short (<1 h). The pharmacokinetic profiles of GHB in narcoleptic patients who had

been receiving this agent nightly for years appeared to be comparable to those in alcohol dependent patients (Ferrara, 1992).

EXAMPLE 4

Sodium Oxybate Formulation Study

I. Study Objectives

This example described ways that sodium oxybate may be prepared and tested for stability to determine preferred formulations. Various formulations of sodium oxybate in water were prepared under different conditions of mixing and with addition of selected acidulents at multiple pH levels (Neo-Pharm Laboratories, Blainville, Quebec). Selected formulations were placed on real time and accelerated stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Therefore several acidulents across a range of 6.0-9.0 were evaluated.

II. Study Design—Part I

The following experimental work is designed to be performed in two stages. Initial studies were conducted to evaluate the impact of conditions of formulation, pH and acidulent on the resultant levels of impurities, specified and unspecified, and potency of sodium oxybate. Sodium oxybate was prepared (MDS Neo-Pharm Laboratories, Quebec Canada), under different conditions of mixing and with addition of selected acidulents at multiple pH levels. These formulations of sodium oxybate acidulent were then tested.

A. Preliminary Studies

1. Formulations Description

All formulations were prepared at a concentration of 500 mg/cc of sodium oxybate in water. Three acidulents (HCl, malic acid, and phosphoric acid), were selected and tested at pH 6.0, 7.5 and 9.0.

2. Method of Formulation

Solutions, were prepared using the described methods:

a. Rapid Mix Method:

Sodium oxybate was dissolved in water and concentrated acidulent was added immediately, without temperature control. Temperature of solution was monitored and recorded prior to and during addition of acidulent. The time of equilibration to room temperature was also recorded. After the solution reached ambient room temperature, it was filtered through a 10 μm filter.

b. Cool Mix Method:

Sodium oxybate was dissolved in water. Acidulent was diluted to 10% and slowly added. The solution was cooled by water with jacket or ice bath. Monitor and record the temperature of the solution was monitored and recorded during addition of acidulent. The time of equilibrium from room temperature was also recorded. The preferred maximum temperature should be maintained at less than 40° C. The solution was filtered through a 10 μm filter.

c. Reverse Order of Addition:

Acidulent was added to water and cooled to room temperature. The sodium oxybate was dissolved in the diluted acidulent solution. The temperature of solution was monitored and recorded during addition of sodium oxybate. The solution was filtered through a 10 μm filter.

d. Sodium Oxybate Control:

Sodium oxybate was dissolved in water to a concentration of 500 mg/cc with no added acidulent. The final pH was recorded and the solution was filtered through a 10 μm (micron or micrometer) filter.

3. Solution Data:

Data was recorded for each solution which included: 1) date of preparation 2) date of analysis, 3) amount of acidulent required to achieve target pH, 4) length of time for dissolution of sodium oxybate, 5) temperature profile of solution over time of solution preparation to be recorded at 15 minute intervals, 6) final pH of solution.

4. Testing Requirements:

The following methods were used to test the prepared solutions: pH, HPLC (High Pressure Liquid Chromatography) for potency (sodium oxybate), and for impurities. Time 0 analysis was performed immediately (within 24 h).

RRT=(relative retention time).

B. Summary of Part I:

1. Preliminary Evaluation of Sodium Oxybate Formulations

Tables 13, 14 and 15 provide test results for the three methods of preparation of sodium oxybate formulations.

Formulation Study/PR98068

Results of Formulation Study

Time Zero Determinations of Sodium Oxybate, GBL and Unspecified Impurities

TABLE 13

Preparation Method A					
Addition of Concentrated Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/cc % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (Apr. 23, 1998)	pH 9.0	9.0	509 mg/cc	0.009%	RRT 4.88 = 0.01%
(10 drops over 2 minutes)			101%		
(2.5 ml/4 minutes)	pH 7.5	7.5	507 mg/cc	0.01%	RRT 4.89 = 0.02%
			101%		
(45 ml/34 minutes)	pH 6.0	6.0	504 mg/cc	0.033%	RRT 4.89 = 0.33%
			101%		
Malic Acid (Apr. 24, 1998)	pH 9.0	9.1	498 mg/cc	0.009%	RRT 4.89 = 0.01%
(0.12 gm)			99.6%		
(1.6 gm)	pH 7.5	7.6	506 mg/cc	0.009%	RRT 4.89 = 0.01%
			101%		
(25 gm)	pH 6.0	6.2	493 mg/cc	0.011%	RRT 4.89 = 0.01%
			98.6%		
H_3PO_4 (Apr. 24, 1998)	pH 9.0	9.0	493 mg/cc	0.009%	RRT 4.89 = 0.01%
(2 drops)			98.6%		

TABLE 13-continued

Preparation Method A

Addition of Concentrated Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/cc % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
(1.0 ml)	pH 7.5	7.5	493 mg/cc 98.6%	0.009%	RRT 4.89 = 0.02%
(17.3 ml)	pH 6.0	6.1	497 mg/cc 99.4%	0.063%	RRT 4.89 = 0.02%
Sodium Oxybate Control No Acidulent	n.a.	9.8	500 mg/cc 100%	0.009%	RRT 4.89 = 0.04%

*Method A = Mix with Concentrated Acidulent and Temperature Monitoring

TABLE 14

Preparation Method B

Addition of Diluted Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (25%) (Apr. 28, 1998) (20 drops)	pH 9.0	9.1	500 mg/cc 100%	0.009%	RRT 4.88 = 0.01%
(8.0 ml)	pH 7.5	7.6	499 mg/cc 99.8%	0.009%	RRT 4.88 = 0.01%
(175 ml)	pH 6.0	6.0	502 mg/cc 101%	0.016%	RRT 4.88 = 0.02%
H_3PO_4 (25%) (Apr. 29, 1998) (0.3 ml)	pH 9.0	8.9	499 mg/cc 99.8%	0.007%	RRT 4.92 = 0.02%
(4.0 ml)	pH 7.5	7.5	497 mg/cc 99.4%	0.008%	RRT 4.89 = 0.02%
(120 ml)	pH 6.0	6.0	499 mg/cc 99.8%	0.019%	RRT 4.89 = 0.01%
Malic Acid (500 mg/cc) (Apr. 30, 1998) (0.115 gm/0.23 ml)	pH 9.0	9.0	495 mg/cc 99%	0.008%	RRT 4.92 = 0.02%
(1.75 gm/3.5 ml)	pH 7.5	7.4	488 mg/cc 97.5%	0.009%	RRT 4.92 = 0.01%
(35 gm/70 ml)	pH 6.0	6.0	487 mg/cc 97.0%	0.013%	RRT 4.92 = 0.01%

*Acidulent added slowly at the rate of 2-3 drops/second

TABLE 15

Preparation Method C

Reverse Order of Addition* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (May 1, 1998) (20 drops)	pH 9.0	9.0	497 mg/cc 99.4%	0.006%	RRT 4.92 = 0.03%
(2.4 ml)	pH 7.5	7.6	504 mg/cc 101%	0.004%	RRT 4.92 = 0.04%
(45 ml)	pH 6.0	6.0	493 mg/cc 98.6%	0.044%	RRT 4.92 = 0.04%
H_3PO_4 (May 4, 1998) (0.08 ml)	pH 9.0	8.9	496 mg/cc 99.2%	0.005%	RRT 4.91 = 0.03%
(1.0 ml)	pH 7.5	7.6	496 mg/cc 99.2%	0.004%	RRT 4.91 = 0.04%
(30 ml)	pH 6.0	6.1	489 mg/cc 97.8%	0.023%	RRT 4.91 = 0.04%
Malic Acid (May 5, 1998) (0.12 gm)	pH 9.0	9.0	495 mg/cc 99%	0.006%	RRT 4.93 = 0.02%
(1.6 gm)	pH 7.5	7.6	497 mg/cc 99.4%	0.004%	RRT 4.93 = 0.04%
(35 gm)	pH 6.0	6.2	495 mg/cc 99%	0.044%	RRT 4.93 = 0.04%

*Acidulent added to water first, GHB added second.

Review of the data indicated that the optimum method for preparation of sodium oxybate with minimal impurity levels is Method B: Controlled mixing with diluted acidulent. Method 2b resulted in formulations with lowest levels of GBL.

2. Conclusions.

Additional evaluations were carried out on selected formulations: 1) sodium oxybate with HCl as acidulent, at pH 7.5, and 2) sodium oxybate with malic acid as acidulent, pH 6.0, 7.5, and 9.0.

III. Study Design—Part II

Microbial Challenge and Stability Tested to determine the most preferred embodiments, the number of formulations was limited to three based on the data prepared from the above experiments.

A. Kinetic Stability Study with Selected Formulations

Samples of formulations are stored in tightly closed containers. Storage Conditions were 25° C., 40° C., and 60° C. Time points in brackets were tested at the inventor's discretion. The samples were tested according to the following schedule: at 25° C. storage temperature, the assay points will be 0, 14, 28, 45, 60 days and 120 days; at 40° C. storage temperature, the assay points will be 0, 7, 14, 28, 45, 60 days; at 60° C. storage temperature, the assay points will be at 0, 3, 7, 14, 28, 45 days, and, 60 days.

The testing requirements included pH, HPLC for sodium oxybate (duplicate injections of single sample preparation), and impurities, specified and unspecified.

B. Preservative Effectiveness Testing of Selected Formulations

Microbial challenge testing of formulations was preformed according to USP XXIII, <51>, Eighth Supplement. Solutions are determined to "Pass or Fail" based upon the USP criteria for preservative effectiveness which states: For Bacteria, "Not less than 1 log reduction from the initial microbial count at 14 days and no increase from the 14 days count at 28 days;" and for yeast and molds, "No increase from the initial calculated count at 14 and 28 days." Solutions which met these criteria were designated as "Pass" and those that did not meet these criteria were designated as "Fail".

C. Summary Stability Results:

1. Formulations Prepared with Malic Acid as Acidulents:

a. Malic Acid, pH 6.0 formulation (25°), GBL and impurity A levels were very low an Day 0, however, by Day 45 GBL levels had reached 2.8%. Impurity A increased from 0.01 to 1.0%, and pH increased from 6.0 to 6.3 by day 45. This formulation stored at 40° C. and 60° C. showed GBL levels up to 5.4%, impurity A levels increased to 2.3%, and pH increased to 6.3 by Day 14.

b. Malic Acid, pH 7.5 formulation (25° C.), GBL levels were 0.009% on Day 0, and increased to 0.17% by day 45. Impurity A increased from 0.01% to 0.1% and pH increased from 7.5 to 7.9. Malic acid, pH 7.5 GBL levels are reached (40° C.) and 60° C. a maximum of 0.22%. Impurity A levels reached 0.1% and pH increased to 8.0. Under accelerated conditions, all parameters reached an apparent maximum by Day 7 and did not increase significantly thereafter.

c. Malic Acid, pH 9.0 formulation (25° C.) GBL levels measure 0.008% on Day 0, and increased slightly to 0.013% on Day 45. Impurity A did not increase nor did pH increase. Under accelerated conditions, GBL increased from 0.008% to a maximum of 0.018% by Day 14. Impurity A increased slightly from 0.10 to 0.014% by Day 14.

2. Formulations Prepared with HCl as Acidulents.

HCl, pH 6.0 formulation (25°) GBL levels measured 2.8% by Day 30, and impurity A 0.004%. and pH 6.0. Accelerated storage conditions (40° C.) GBL levels were measured at 6.6%, and impurity A measured 3.1% by Day 30.

HCl, pH 7.5 formulation (25%) GBL levels measured 0.041% on Day 0, Impurity A measured 0.02%, and by Day 18 GBL measured to 0.12% and impurity A to 0.07%. Under accelerated conditions (40° C. and 60° C.), GBL increased to a maximum of 0.21%, impurity A increased from 0.02% to 0.1%, and pH increased from 7.5 to 8.0. As with Malic Acid at pH 7.5, the measured parameters reached maximum by Day 7 and did not increase significantly thereafter.

HCl, Ph 9.0 formulation (25° C.) GBL levels reached 0.022% by Day 18. Impurity A stayed constant at 0.01% for 18 days. Under accelerated conditions (40° C.) GBL levels were equivalent to 25° C. storage (0.21%). Impurity A showed no increase over 25° C. conditions.

3. Conclusions.

Formulations selected for microbial challenge testing were the following: HCl, Ph 7.5, and malic acid, Ph 7.5. The rationale for this decision was twofold. First, the formulations were selected based on minimal formation of GBL and impurity A. Second, the formulations were selected to maintain a Ph in the neutral range.

EXAMPLE 5

Further Evaluation of Sodium Oxybate Formulations

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of gamma-hydroxybultyrate.

Scope: Various formulations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple Ph levels. Solutions were prepared and tested at Neo-Pharm Laboratories, Blainville, Quebec. All formulations successfully prepared were placed on limited stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high Ph. Conditions of varying Ph and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Procedures: Solutions were prepared as summarized and microbial challenge testing carried out as follows:

B. Evaluation of Sodium Oxybate Formulations

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of gamma-hydroxybutyrate.

Scope: Various formulations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple Ph levels. Selected formulations were studied for limited stability. Earlier studies demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high Ph. Conditions of varying Ph and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Responsibility: It was the responsibility of Neo-Pharm Laboratories to prepare selected formulations and perform testing per this protocol. Orphan Medical, New Medicine Development and Quality Assurance were responsible for reviewing raw data at the defined decision point, defining which formulations will be included in stability testing. Orphan Medical was also responsible for reviewing final results (raw data) and the final report.

Procedure: The following formulations were prepared by scientists at Neo-Pharm following the steps listed below and

dispensed into containers (amber PET 240 ml bottle, OMI CS-460) and closures (Clic-Loc III, 24-400, OMI CS-470) to a volume of 200 ml each bottle. The bottles were tested by 28-day microbial challenge and by limited stability testing at 25° C. including appearance, Ph, potency, and impurity profile on day 1 (day of preparation) and day 28.

B. Formulations Prepared and Evaluated Using Sodium Oxybate:

TABLE 16

Formulations Prepared and Evaluated Using Sodium Oxybate

Formulation ID No.	Sodium Oxybate Concentration	Acidulent	Final Ph
1	500 mg/cc	Malic Acid	7.5
2	250 mg/cc	Malic Acid	7.5
3	350 mg/cc	Malic Acid	7.5
4	450 mg/cc	Malic Acid	7.5
5	550 mg/cc	Malic Acid	7.5
6	650 mg/cc	Malic Acid	7.5
7	500 mg/cc	Citric Acid	7.5
8	500 mg/cc	Malic Acid	5.0

1. Preparation: Method for preparation of various formulations: As previously determined in PR98068, the method of choice for preparation of liquid formulations of sodium oxybate was the following:
   a. For a one liter quantity of product, add the sodium oxybate in 500 ml of purified and stir until dissolved. Prepare a 10% solution of the acid (Malic or Citric) and add slowly to the solution of sodium oxybate. The solution should be monitored for Ph and temperature and both variables recorded at reasonable intervals (every 10 or 15 minutes). When the target Ph is attained, the solution will be Q. S. to 1 liter and Ph rechecked and recorded.
   b. The final solutions will be filtered through 10 μm filters and 200 Ml dispensed into 5 amber PET bottles with closures (provide by Orphan Medical, Inc.). Two bottles will be used for microbial challenge studies and the remaining three bottles will be placed on limited stability.
2. Testing: Formulations were tested by two methods of evaluation:
   a. Limited stability evaluation:
      (1) Storage Conditions: 25° C.
      (2) Pull Points: Day 0 (day of preparation), and day 28
      (3) Testing Requirements:

Test	Method
Appearance	Visual
Potency	HPLC Neopharm 764
Impurities	HPLC Neopharm 793DT
Ph	USP <791>

   b. Microbial challenge:
      (1) Storage Conditions: Microbial challenge studies of above formulations were set up with 5 microorganisms and stored for 28 days at 20-25° C., per USP<51> Eighth Supplement.
      (2) Microorganisms: After a sufficient quantity of each formulation is prepared, aliquots were inoculated with 5 microorganisms at a concentration of at least 10^5 microorganisms/cc:
         (a) *Escherichia coli*, ATCC 8739
         (b) *Pseudomonas aeruginosa*, ATCC 9027
         (d) *Staphylococcus aureus*, ATCC 6538
         (d) *Aspergillus niger*, ATCC 18404
         (e) *Candida albicans*, ATCC 10231
      (3) Time Points: A determination of the viable cell concentration in each inoculated container was performed after 0, 1, 3, 7, 14, 21 and 28 days.

B. Formulations To Be Prepared From Alternative Salts of Gamma-Hydroxybutyrate: This work may be staged to take place at a later time than the work described above.

TABLE 17

Formulation Detail

Formulation ID No.	Salt of GHB	Concentration of Salt of GHB	Acidultent	Final pH
9	Calcium salt	500 mg/cc (Or maximum possible*)	Malic Acid (If compatible)	7.5

1. Solubility determination: Little information is available about the solubility of this alternative salt of gamma-hydroxybutyrate and a determination of solubility was done in advance of efforts to prepare formulations for evaluation by stability and microbial challenge. Maximum solubility is evaluated for pH unadjusted soluations and within the pH range desired for this formulation (pH 6.0-8.0). If solubility is limited, the formulation will be changed to accommodate the solubility limitations. The preferred acidulent for this work is Malic acid. If acid is not compatible with the salt, then an alternative acid can be selected.
2. Preparation: Method for preparation of alternative salt formulations:
   a. The previously described method (Part A) is used for preparation of formulations of calcium gamma-hydroxybutyrate at the concentrations and specified pH determined by solubility experiments.
   b. The final solutions were filtered through 10 μm filters and dispensed into 5 amber PET bottles with closures (provided by Orphan Medical, Inc.). Two bottles are used for microbial challenge studies and two bottles are placed on limited stability. The remaining bottles are retained for any additional studies at a future time.
3. Testing: Formulations are tested as described above.

C. Reporting of Results: The results will be reported for the Stability and Microbial Challenge results in standard format as defined by the described Orphan Medical Development. Copies of HPLC chromatograms and any raw data from these studies will be provided with results.

D. Acceptance Criteria: Specific acceptance criteria for this study can be described analogous to those for sodium oxybate.

Results: Summarized as follows in Tables 18, 19 and 20 for various studies.

TABLE 18

Result Summary
Results of Protocol 98126 Microbial Challenge Study

Lot Number MCH1064-33						
GHB, pH 7.50, 500 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	490,000	5,500	<100	<10	<10	<10
P. aeruginosa	141,000	21,600	<100	<10	<10	<10
S. aureus	1,035,000	405,000	79,500	8,300	1,645	375
C. albicans	835,000	147,000	<100	<10	<10	<10
A. niger	370,000	285,000	120,500	246,500	148,500	183,000
Lot Number MCH1064-35						
GHB, pH 7.50, 250 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	705,000	229,500	<100	<10	<10	<10
P. aeruginosa	224,500	5,200	<100	<10	<10	<10
S. aureus	1,135,000	390,000	262,500	31,500	4,250	155
C. albicans	705,000	435,000	52,000	850	<10	<10
A. niger	510,000	515,000	155,500	176,000	147,500	184,000
Lot Number MCH1064-37						
GHB, pH 7.50, 300 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	365,000	310,000	13,400	<10	<10	<10
P. aeruginosa	205,000	15,600	50	<10	<10	<10
S. aureus	1,170,500	605,000	67,500	<60	60	<10
C. albicans	870,000	355,000	8,300	<10	<10	<10
A. niger	540,000	525,000	172,000	155,500	155,500	163,500
Lot Number MCH1064-43						
GHB, pH 7.50, 550 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	425,000	63,500	700	<10	<10	<10
P. aeruginosa	171,500	211,550	250	<10	<10	<10
S. aureus	1,020,000	520,000	41,500	1,050	180	10
C. albicans	880,000	157,500	800	<10	<10	<10
A. niger	545,000	505,000	131,000	156,500	205,000	187,500
Lot Number MCH1064-45						
GHB, pH 7.50, 550 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	660,000	58,500	450	<10	<10	<10
P. aeruginosa	896,000	14,450	900	<10	<10	<10
S. aureus	860,000	132,000	19,750	935	110	45
C. albicans	1,125,000	166,000	<100	<10	<10	<10
A. niger	530,000	530,000	105,500	153,000	157,500	177,000
Lot Number MCH1064-47						
GHB, pH 7.50, 650 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	630,000	119,000	1,350	<10	<10	<10
P. aeruginosa	183,500	5,900	50	<10	<10	<10
S. aureus	890,000	650,000	76,000	14,550	510	1,150
C. albicans	675,000	145,500	<100	<10	<10	<10
A. niger	535,000	385,000	103,000	162,000	187,000	173,000
Lot Number MCH1064-85						
Ca-Oxybate, pH 7.50, 500 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	425,000	121,000	1,650	<10	<10	<10
P. aeruginosa	420,000	22,000	300	<10	<10	<10
S. aureus	265,000	2,000	<100	<10	<10	<10

TABLE 18-continued

Result Summary Results of Protocol 98126 Microbial Challenge Study						
C. albicans	565,000	440,000	29,500	<1000	<10	<10
A. niger	1,310,000	965,000	370,000	640,000	690,000	675,000
Lot Number MCH1064-49						
GHB, pH 7.50, 500 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	615,000	6,500	<100	<10	<10	<10
P. aeruginosa	69,500	14,600	<100	<10	<10	<10
S. aureus	650,000	305,000	1,700	<10	<10	<10
C. albicans	720,000	107,000	<100	<10	<10	<10
A. niger	375,000	380,000	99,500	178,500	212,500	165,500

TABLE 19

Result Summary Data from Dec. 30, 1997									
GHB (pH 7.5) 750 mg/cc	(n = 3) Inoculu	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	
E. coli	470,000	160,000	64,500	4,300	420	<10	<10	<10	
P. aeruginosa	437,500	152,000	3,500	10	<10	<10	<10	<10	
S. aureus	447,500	330,000	24,500	42,000	8,050	1,935	15	10	
C. albicans	375,000	234,500	28,000	1,950	<10	<10	10	<10	
A. niger	475,500	395,000	395,000	229,000	101,500	161,500	101,000	202,000	
750 mg/cc + 0.2% MP/PP, pH 7.50									
E. coli	470,000	127,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	61,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	350,000	3,000	4,050	<10	<10	<10	<10	
C. albicans	375,000	103,500	<1,000	<10	<10	<10	<10	<10	
A. niger	457,500	315,000	415,000	35,500	79,500	38,500	87,500	6,400	
750 mg/cc + 0.1% MP/PP, pH 7.5									
E. coli	470,000	157,000	7,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	90,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	239,000	5,500	16,950	600	<10	<10	<10	
C. albicans	375,000	169,000	<1,000	<100	<10	<10	<10	<10	
A. niger	457,500	335,000	425,000	34,500	168,500	90,500	95,500	99,000	
750 mg/cc + 0.2% Potassium sorbate, pH 7.5									
E. coli	470,000	180,000	735,000	6,200	475	<10	<10	<10	
P. aeruginosa	437,500	152,000	1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	264,000	27,500	49,800	14,550	2,370	<10	<10	
C. albicans	375,000	300,000	41,500	3,800	<10	<10	<10	<100	
A. niger	457,500	325,000	360,000	25,000	202,000	500,000	345,000	425,000	
GHB (pH 6.0) 500 mg/cc	Inoculu	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Results
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10	
P. aeruginosa	437,500	172,000	3,000	<10	<10	<10	<10	<10	
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10	
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10	
A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600	
									PASS
500 mg/cc + 0.2% MP/PP, pH 6.0									
E. coli	470,000	163,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	60,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	243,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	150,500	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	400,000	38,000	<10	<10	<10	<10	<10	
									PASS
500 mg/cc + 0.1% MP/PP, pH 6.0									
E. coli	470,000	206,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	118,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	330,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	221,000	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	355,000	93,500	59,000	8,700	315	35	>10	
									PASS
500 mg/cc + 0.2% Potassium sorbate, pH 6.0									
E. coli	470,000	222,000	46,500	150	<10	<10	<10	<10	
P. aeruginosa	437,500	136,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	410,000	<1,000	130	<10	<10	<10	<10	

TABLE 19-continued

Result Summary									
C. albicans	375,000	395,000	28,500	<100	<10	<10	<10	<10	
A. niger	475,500	405,000	270,000	63,000	51,000	49,500	39,000	11,150	PASS

TABLE 20

Result Summary								
Data from Study Dated Dec. 30, 1997								
GHB (pH 6.0) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10
P. aeruginosa	437,500	172,000	3,000	<10	<10	<10	<10	<10
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10
A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600
Data From Study Begun Mar. 12, 1998								
GHB (pH 6.0) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	500,000	370,000	Nd	Nd	<100	<10	<10	<10
P. aeruginosa	350,000	198,500	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	480,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	340,000	Nd	Nd	<100	<10	<10	<10
A. niger	450,000	445,000	Nd	Nd	9,050	20,500	9,450	1,120
E. coli	500,000	199,000	Nd	Nd	<100	<10	<10	<10
P. acruginosa	350,000	192,500	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	300,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	370,000	Nd	nd	<100	<10	<10	<10
A. niger	450,000	445,000	Nd	Nd	10,100	22,750	3,800	4,050
Data From Study Begun Mar. 12, 1998								
GHB (pH 9.0) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	500,000	320,000	Nd	Nd	<100	<10	<10	<10
P. aeruginosa	350,000	12,000	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	495,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	380,000	Nd	Nd	<100	<10	<10	<10
A. niger	450,000	355,000	Nd	Nd	12,550	157,500	365,000	365,000
GHB (pH 6.0 + Excipients) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	500,000	96,000	Nd	Nd	<100	<10	<10	<10
P. aeruginosa	350,000	26,000	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	155,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	205,000	Nd	Nd	<100	<10	<10	<10
A. niger	450,000	131,500	Nd	Nd	6,250	1,825	870	370
GHB (pH 6.0 + Excipients) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	500,000	93,000	Nd	Nd	<100	<10	<10	<10
P. aeruginosa	350,000	30,500	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	185,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	135,000	Nd	Nd	<100	<10	<10	<10
A. niger	450,000	121,500	Nd	Nd	5,400	1,785	795	505

TABLE 21

Result Summary								
Jul. 2, 1998 Start Date								
GHB (pH 7.50) 500 mg/cc	HCl Initial Cone	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	97000	82000	19200	Nd	1000	<10	<10	<10
P. aeruginosa	48500	29500	520	Nd	<10	<10	<10	<10

TABLE 21-continued

S. aureus	54500	58000	42350	Nd	4950	245	<10	<10
C. albicans	58500	38500	1060	Nd	<100	<10	<10	<10
A. niger	77500	48000	21450	Nd	46000	46000	38000	54000

GHB (pH 7.50) 500 mg/cc	Malic Acid Initial Cone	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	97000	83000	44450	Nd	3050	70	<10	<10
P. aeruginoas	48500	15650	545	Nd	<10	<10	<10	<10
S. aureus	54500	59500	48400	Nd	17400	6500	820	505
C. albicans	58500	44000	6200	Nd	500	<10	<10	<10
A. niger	77500	35500	24100	Nd	28000	49000	44500	44000

For Category IC Products:
Bacteria: Not less than 1 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days.
Yeast and Molds: No increase from the initial calculated count at 14 and 28 days.

Jul. 2, 1998 Start Date

GHB (pH 7.50) 500 mg/cc	HCl Initial Co	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	9.70E+04	8.20E+04	1.92E+04	nd	1.00E+03	<10	<10	<10
P. aeruginosa	4.85E+04	2.95E+04	5.20E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.80E+04	4.24E+04	nd	4.95E+03	2.45E+02	<10	<10
C. albicans	5.85E+04	3.85E+04	1.06E+03	nd	<100	<10	<10	<10
A. niger	7.75E+04	4.80E+04	2.15E+04	nd	4.60E+04	4.60E+04	3.80E+04	5.40E+04

GHB (pH 7.50) 500 mg/cc	Malic Acid Initial Co	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	9.70E+04	8.30E+04	4.45E+04	nd	3.05E+03	7.00E+01	<10	<10
P. aeruginosa	4.85E+04	1.57E+04	5.45E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.95E+04	4.84E+04	nd	1.74E+04	6.50E+03	8.20E+02	5.05E+02
C. albicans	5.85E+04	4.40E+04	6.20E+03	nd	5.00E+02	<10	<10	<10
A. niger	7.75E+04	3.55E+04	2.41E+04	nd	2.80E+04	4.90E+04	4.45E+04	4.40E+04

TABLE 22

pH Variable Result Summary

GHB, pH 7.5 750 mg/cc Dec. 30, 1997	Inoculum	0	Day 14	Day 28	GHB, pH 6.0 500 mg/cc Dec. 30, 1997	Inoculum	0	Day 14	Day 28
E. coli	470,000	160,000	<10	<10	*E. coli*	470,000	221,000	<10	<10
P. aeruginosa	437,500	152,000	<10	<10	*P. aeruginosa*	437,500	172,000	<10	<10
S. aureus	447,500	330,000	1,935	10	*S. aureus*	447,500	320,000	<10	<10
C. albicans	375,000	234,500	<10	<10	*C. albicans*	375,000	310,000	<10	<10
A. niger	475,500	395,000	161,500	202,000	*A. niger*	475,500	270,000	48,500	8,600
GHB, pH 7.5 750 mg/cc + 0.2% MP/PP Dec. 30, 1997					GHB, pH 6.0 500 mg/cc + 0.2% MP/PP Dec. 30, 1997				
E. coli	470,000	127,000	<10	<10	*E. coli*	470,000	163,000	<10	<10
P. aeruginosa	437,500	61,000	<10	<10	*P. aeruginosa*	437,500	60,000	<10	<10
S. aureus	447,500	350,000	<10	<10	*S. aureus*	447,500	243,000	<10	<10
C. albicans	375,000	103,500	<10	<10	*C. albicans*	375,000	150,500	<10	<10
A. niger	457,500	315,000	38,500	6,400	*A. niger*	475,500	400,000	<10	<10
GHB, pH 7.5 750 mg/cc + 0.1% MP/PP					GHB, pH 6.0 500 mg/cc + 0.1% MP/PP Dec. 30, 1997				
E. coli	470,000	157,000	<10	<10	*E. coli*	470,000	200,000	<10	<10
P. aeruginosa	437,500	90,000	<10	<10	*P. aeruginosa*	437,500	118,000	<10	<10
S. aureus	447,500	239,000	<10	<10	*S. aureus*	447,500	330,000	<10	<10
C. albicans	375,000	169,000	<10	<10	*C. albicans*	375,000	221,000	<10	<10
A. niger	457,500	335,000	90,500	99,000	*A. niger*	475,500	355,000	315	<10
GHB, pH 7.5 750 mg/cc + 0.2% Potassium sorbate	xxxxxx				GHB, pH 6.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28

TABLE 22-continued

pH Variable Result Summary

E. coli *P. aeruginosa* *S. aureus* *C. albicans* *A. niger*					*E. coli* *P. aeruginosa* *S. aureus* *C. albicans* *A. niger*				
GHB, pH 6.0 500 mg/cc + 0.2% Potassium sorbate Dec. 30, 1997					GHB, pH 6.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coli	470,000	222,000	<10	<10	*E. coli*	500,000	199,000	<10	<10
P. aeruginosa	437,500	136,000	<10	<10	*P. aeruginosa*	350,000	192,500	<10	<10
S. aureus	447,500	410,000	<10	<10	*S. aureus*	280,000	300,000	<10	<10
C. albicans	375,000	395,000	<10	<10	*C. albicans*	450,000	370,000	<10	<10
A. niger	475,500	405,000	49,500	11,150	*A. niger*	450,000	445,000	22,750	4,050
GHB, pH 6.0 500 mg/cc + Excipients Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 6.0 500 mg/cc + Excipients Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	93,000	<10	<10	*E. coli*	500,000	96,000	<10	<10
P. aeruginosa	350,000	30,500	<10	<10	*P. aeruginosa*	350,000	26,000	<10	<10
S. aureus	280,000	185,000	<10	<10	*S. aureus*	280,000	155,000	<10	<10
C. albicans	450,000	135,000	<10	<10	*C. albicans*	450,000	205,000	<10	<10
A. niger	450,000	121,500	1,785	505	*A. niger*	450,000	131,500	1,825	370
GHB, pH 9.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 7.50 500 mg/cc HCl Jul. 2, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	320,000	<10	<10	*E. coli*	97000	82000	<10	<10
P. aeruginosa	350,000	12,000	<10	<10	*P. aeruginosa*	48500	29500	<10	<10
S. aureus	280,000	530,000	<10	<10	*S. aureus*	54500	58000	245	<10
C. albicans	450,000	510,000	<10	<10	*C. albicans*	58500	38500	<10	<10
A. niger	450,00	345,000	158,500	110,500	*A. niger*	77500	48000	46000	54,000
GHB, pH 9.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 7.5 500 mg/cc, Malic Acid Jul. 2, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	305,000	<10	<10	*E. coli*	97000	83000	70	<10
P. aeruginosa	350,000	20,000	<10	<10	*P. aeruginosa*	48500	15650	<10	<10
S. aureus	280,000	495,000	<10	<10	*S. aureus*	54500	59500	6500	505
C. albicans	450,000	380,000	<10	<10	*C. albicans*	58500	44000	<10	<10
A. niger	450,000	355,000	157,500	365,000	*A. niger*	77500	35500	49000	44,000

Short term stability testing was carried out as described in Appendix A and results are summarized in—Results of Limited Stability Testing—XYREM® oral solution—are shown as follows:

TABLE 23-A

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333198

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	512 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.068%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.021%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.02% RRT 3.79: 0.007%	NPLC-793D

TABLE 23-A-continued

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333198

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
PH	Report	7.6	USP <791>
Challenge Test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 1: 500 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328841

TABLE 23-B

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331347

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	510 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.36%	NPLC-793-D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.23% RRT 4.31: 0.1%	NPLC-793-D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 days (25° C., 60% RH)
Formulation 1: 500 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.02%
RRT 3.93: 0.008%

TABLE 23-C

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333197

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	258 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.045%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.016% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.79: 0.009%	NPLC-793D

TABLE 23-C-continued

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333197

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 2: 250 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328845

TABLE 23-D

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331346

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
(28 DAY CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	256 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.18%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.13% RRT 4.31: 0.03%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 days (25° C., 60% RH)
Formulation 2: 250 mg/cc; Malic acid; pH 7.5
*A: RRT 1.29: 0.007%
RRT 3.93: 0.008%

TABLE 23-E

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333196

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	360 mg/ml (103%)	NPLC-793
Impurities total	≦2.0%	0.050%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.017% RRT 4.17: 0.02%	NPLC-793D

TABLE 23-E-continued

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333196

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.006% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.7	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 3: 350 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328847

TABLE 23-F

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331345

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	363 mg/ml (104%)	NPLC-793-D
Impurities total	≦2.0%	0.21%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.14% RRT 4.31: 0.05%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	8.0	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 3: 350 mg/cc; Malic acid; pH 7.5
*A: RRT 1.29: 0.009%
RRT 3.93: 0.008%

TABLE 23-G

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333195

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE: 1741
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	461 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.065%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.018%	NPLC-793D

TABLE 23-G-continued

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333195

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE: 1741
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
GBL-RRT 1.6	(RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.02% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 4: 450 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328875

TABLE 23-H

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331343

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	454 mg/ml (101%)	NPLC-793-D
Impurities total	≦2.0%	0.40%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.26% RRT 4.31: 0.1%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 4: 450 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.03%
RRT 3.93: 0.008%

TABLE 23-I

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333194

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	563 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.077%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.020%	NPLC-793D

TABLE 23-I-continued

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333194

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
GBL-RRT 1.6	(RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.29: 0.03% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 5: 550 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328883

TABLE 23-J

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO.: 331341

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	561 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.56%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.31% RRT 4.31: 0.2%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 5: 550 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.04%
RRT 3.93: 0.007%

TABLE 23-K

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333193

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	666 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.10%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.025%	NPLC-793D

TABLE 23-K-continued

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333193

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
GBL-RRT 1.6	(RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.05% RRT 3.78: 0.007%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 6: 650 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328885

TABLE 23-L

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331336

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	660 mg/ml (102%)	NPLC-764
Impurities total	≦2.0%	0.81%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.43% RRT 4.31: 0.3%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 6: 650 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.07%
RRT 3.93: 0.007%

TABLE 23-M

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333192

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	518 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.065%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.018%	NPLC-793D

TABLE 23-M-continued

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333192

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
GBL-RRT 1.6	(RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.79: 0.007% RRT 5.99: 0.02%	NPLC-793D
PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 7: 500 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 329033

TABLE 23-N

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331335

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	515 mg/ml (101%)	NPLC-793-D
Impurities total	≦2.0%	0.38%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.27% RRT 4.31: 0.1%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	3.93: 0.007%	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 7: 500 mg/cc; Malic acid; pH 7.5

TABLE 23-O

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 09 Feb. 1999
NO: 330721

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Challenge Test	Conforms to USP (0, 1, 7, 14, 21 and 28 days)	Conforms	USP 23 <51> S.8
Potency	Report	501 mg/ml (100%)	NPLC-793
Impurities total	≦2.0%	1.2%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D

TABLE 23-O-continued

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 09 Feb. 1999
NO: 330721

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone Report:	RRT 1.46: 0.013%	NPLC-793D
PH	Report	7.3	USP <791>
Solubility study	Report	*B	PR 98126 IIA

COMMENTS:
Initial test
500 mg/cc; Malic acid; pH 7.5
*A: RRT 1.31: 0.02% RRT 1.67: 0.008%
RRT 1.91: Interference with peak dilution solvent cannot calculate
RRT 3.47: 0.1% RRT 3.79: 0.009% RRT 3.84: 0.01%
RRT 4.18: 0.06% RRT 5.10: 0.008% RRT 5.35: 0.02%
RRT 6.74: 0.9% RRT 6.90: 0.08% RRT 7.41: 0.006%
*B: Maximum solubility: 700 mg/ml no pH adjustment.

TABLE 23-P

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Feb. 1999
NO: 331307

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM, LIQUID FORM.
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	508 mg/ml (102%)	NPLC-793
Impurities total	≤2.0%	0.70%	NPLC-793D
Impurities unspecified	Ind. imp. ≤0.1%	*A	NPLC-793D
Impurities specified	Gamma-Butyrolactone Report:	RRT 1.37: 0.054%	NPLC-793D
PH	Report	7.6	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
500 mg/ml cc; Malic acid; pH 7.5
*A: RRT 1.17: 0.03% RRT 3.47: 0.2%
RRT 5.46: 0.01% RRT 6.87: 0.3%
RRT 7.04: 0.007%
RRT 1.78: Can not calculate because it interfere with a dilution solvent peak.

This report summarizes the results of the above described study and provides a summary of previous development work which evaluated conditions other than those evaluated in this study. The purposes of this information is to define the scope and limitations of the self-preserving properties of Xyrem® oral solution for completion of patent application.

II. Summary of Results:

A. Preparation of Various Formulations of Sodium Oxybate and Formulations Using an Alternative Salt of GHB.

1. Various formulations of sodiwn oxybate were prepared as directed in the above Protocol. Sodium oxybate. 500 mg/cc with Malic Acid was not soluble at pH 5.0, and further evaluation of this solution was discontinued. All other solutions were successfully prepared as described.
2. The preparation of an alternative salt of gamma-hydroxybutyrare was described as the calcium salt, prepared at 500 mglcc (or maximum possible) with Malic Acid at pH 7.5.
   a. The calcium salt of gamma-hydroxybutyrate was prepared by Toronto Research and shipped to NeoPharm for determination of solubility and evaluation according to the Protocol. The absolute limit of solubility, without pH adjustment, was determined to be 700 mg/cc. The pH of this solution was 8.4. Solutions of lower pH were more difficult to prepare at 500 mg/cc using Malic acid, as acidulant. When pH was adjusted to 6.0 with Malic acid. the solubility of the calcium oxybate was limited (longer stirring required to solubilize). The desired solution of 500 mg/cc, pH 7.5 was prepared with Malic acid as acidulant without diffi-

culty. Appearance of the final solution was slightly yellow in color. Copies of the laboratory record for preparation of these solutions is available.

B. Microbial Challenge Testing of the Various Formulations Prepared by MDS NeoPharm.

The microbial challenge testing was carried as specified in the Protocol and the following table summarizes the results of microbial challenge testing of various formulations of sodium oxybate and the single calcium oxybate formulation prepared.

TABLE 24

Testing of Sodium and Calcium GHB Salts

	pH of Solution	Microbial Challenge Result
Sodium Oxybate Concentration		
1. 500 mg/cc	7.5 (Malic acid)	Pass
2. 250 mg/cc	7.5 (Malic acid)	Pass
3. 350 mg/cc	7.5 (Malic acid)	Pass
4. 450 mg/cc	7.5 (Malic acid)	Pass
5. 550 mg/cc	7.5 (Malic acid)	Pass
6. 650 mg/cc	7.5 (Malic acid)	Pass
7. 500 mg/cc	7.5 (Citric acid)	Pass
Calcium Oxybate Conctration		
500 mg/cc	7.5	Pass

C. Short Term Stability Evaluation of Various Formulations of Sodium Oxybate and a Formulation of Calcium Oxybate.

Solutions were tested on day zero (preparation day) and day 28 according to the described Protocol. The results of the stability evaluation are summarized in Table 25 below:

TABLE 25

Sodium and Calcium GHB Evaluation

Sodium oxybate solution	Potency mg/cc (%)	Impurities (Total)	Impurities (Unspecified)	Impurities (Specified—GBL)	pH
500 mg/cc pH 7.5 Malic Acid Day 0	512 mg/cc (102%)	0.68%	0.041%	0.027%	7.6
Day 28	510 mg/cc (103%)	0.36%	0.33%	0.028%	7.9
250 mg/cc pH 7.5 Malic Acid Day 0	258 mg/cc (103%)	0.045%	0.009%	0.026%	7.6
Day 28	256 mg/cc (102%)	0.18%	0.015%	0.16%	7.9
350 mg/cc pH 7.5 Malic Acid Day 0	360 mg/cc (103%)	0.050%	0.013%	0.037%	7.7
Day 28	363 mg/cc (104%)	0.21%	0.017%	0.19%	8.0
450 mg/cc pH 7.5 Malic Acid Day 0	461 mg/cc (102%)	0.065%	0.027%	0.038%	7.5
Day 28	454 mg/cc (101%)	0.40%	0.038%	0.36%	7.8
550 mg/cc pH 7.5 Malic Acid Day 0	563 mg/cc (102%)	0.077%	0.037%	0.040%	7.6
Day 28	561 mg/cc (102%)	0.56%	0.047%	0.51%	7.9
650 mg/cc pH 7.5 Malic Acid Day 0	666 mg/cc (102%)	0.10%	0.057%	0.045%	7.6
Day 28	660 mg/cc (102%)	0.81%	0.077%	0.73%	7.8
500 mg/cc pH 7.5 Citric Acid Day 0	518 mg/cc (104%)	0.065%	0.027%	0.038%	7.5
Day 28	515 mg/cc (103%)	0.38%	0.007%	0.37%	7.9
500 mg/cc pH 7.5 Malic Acid Day 0	501 mg/cc (100%)	1.2%	>0.1% (See C of A Attached)	0.013%	7.3
Day 28	508 mg/cc (102%)	0.70%	>0.1% (See C of A)	0.054%	7.6

D. Summary of Pertinent Solubility and Microbial Challenge Data are Shown in Tables 26 and 27.

TABLE 26

Limits of Solubility

	pH of Solution	Comments
Sodium oxybate Maximum Solubility		
450 mg/cc	pH 4 (HCl)	25°
500 mg/cc	pH 5 (HCl)	25°
600 mg/cc	pH 6 (HCl)	25°
750 mg/cc	pH 6.8 (HCl)	25°
1000 mg/cc	pH (unadjusted)	65° Soluble, 25° gel
Calcium oxybate Maximum Solubility		
700 mg/cc	pH 8.4 (unadjusted)	25°
500 mg/cc	pH 6.0	25°

TABLE 27

Microbial Challenge Results

	pH of Solution	Microbial Challenge Results
Sodium oxybate Concentration (Date)		
750 mg/cc (December 1997)	7.5 (HCl)	pass
500 mg/cc (December 1997)	6.0 (HCl)	pass
500 mg/cc + Excipients (Xylitol) (March 1998)	6.0 (Malic Acid)	pass
500 mg/cc (March 1998)	9.0 (HCl)	pass (Borderline *aspergillus*)
150 mg/cc (BDL 1995)	5.0 (HCl)	fail (*aspergillus* only)
150 mg/cc (BDL 1995)	7.0 (HCl)	fail (*aspergillus* and *staph*)
150 mg/cc (BDL 1995)	3.0 (HCl)	fail (*aspergillus* only)
150 mg/cc (BDL 1995)	10.3 (HCl)	fail (*aspergillus* and *staph*)
500 mg/cc (May 1998)	6.0 (Malic Acid)	discontinued
500 mg/cc (May 1998)	7.5 (Malic Acid)	pass
500 mg/cc (May 1998)	9.0 (Malic Acid)	discontinued
500 mg/cc (May 1998)	7.5 (HCl)	pass
500 mg/cc	7.5 (Malic Acid)	pass
250 mg/cc	7.5 (Malic Acid)	pass
350 mg/cc	7.5 (Malic Acid)	pass
450 mg/cc	7.5 (Malic Acid)	pass
550 mg/cc	7.5 (Malic Acid)	pass
650 mg/cc	7.5 (Malic Acid)	pass
500 mg/cc	7.5 (Citric Acid)	pass
Calcium oxybate Concentration (Date)		
500 mg/cc	7.5 (Malic Acid)	pass

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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The invention claimed is:

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 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.

* * * * *

EXHIBIT G

US008324275B2

(12) **United States Patent**
Cook et al.

(10) **Patent No.: US 8,324,275 B2**
(45) **Date of Patent: *Dec. 4, 2012**

(54) **MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY**

(75) Inventors: **Harry Cook**, Eden Prairie, MN (US); **Martha Hamilton**, St. Paul, MN (US); **Douglas Danielson**, Otsego, MI (US); **Colette Goderstad**, St. Paul, MN (US); **Dayton T. Reardan**, Shorewood, MN (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/446,892**

(22) Filed: **Apr. 13, 2012**

(65) **Prior Publication Data**

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Related U.S. Application Data

(60) Continuation of application No. 12/913,644, filed on Oct. 27, 2010, which is a continuation of application No. 11/777,877, filed on Jul. 13, 2007, now Pat. No. 7,851,506, which is a division of application No. 10/841,709, filed on May 7, 2004, now Pat. No. 7,262,219, which is a division of application No. 10/194,021, filed on Jul. 11, 2002, now Pat. No. 6,780,889, which is a division of application No. 09/470,570, filed on Dec. 22, 1999, now Pat. No. 6,472,431.

(60) Provisional application No. 60/113,745, filed on Dec. 23, 1998.

(51) **Int. Cl.**

A01N 37/00	(2006.01)
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A61K 31/19	(2006.01)
A61K 31/045	(2006.01)

(52) **U.S. Cl.** **514/557**; 514/724

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial growth. Also disclosed are formulations of gammahydroxybutyrate that are also resistant to the conversion into GBL. Disclosed are methods to treat sleep disorders, including narcolepsy, with these stable formulations of GHB. The present invention also provides methods to treat alcohol and opiate withdrawal, reduced levels of growth hormone, increased intracranial pressure, and physical pain in a patient.

4 Claims, 2 Drawing Sheets

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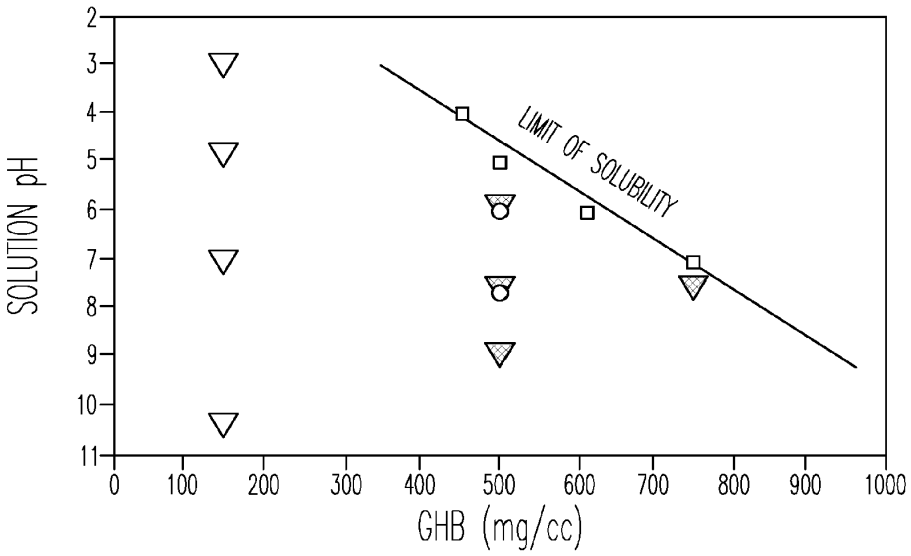

□ DATA POINTS INDICATING LIMIT OF SOLUBILITY OF GHB AS A FUNCTION OF CONCENTRATION AND pH, SEE TABLE 1.

▽ SOLUTIONS SUSCEPTIBLE TO MICROBIAL GROWTH, DESIGNATED "FAIL". (ALL SOLUTIONS DEMONSTRATED ACTIVITY AGAINST PSEUDOMONAS AERUGINOSA. SOME REDUCTION OF ASPERGILLUS NIGER MOLD OCCURRED IN 7 DAYS OF CONTACT TIME.)

▽ SOLUTIONS RESISTANT TO MICROBIAL GROWTH, DESIGNATED "PASS". RATE OF REDUTION OF MICROORGANISM COUNTS WAS SLIGHTLY HIGHER AT pH 7.5 AND 6.0 THAN pH 9.0. THE RATE OF REDUCTION OF FORMULATIONS AT 750mg/cc GHB WERE SLIGHTLY LOWER THAN FORMULATIONS AT 500 mg/cc GHB.)

○ SOLUTIONS RESISTANT TO MICROBIAL GROWTH, DESIGNATED "PASS". RESULTS WERE SIMILAR FOR MALIC ACID AND HCl. TASTE VARIATIONS HAS IMPLICATIONS FOR DEVELOPMENT OF FLAVOR SYSTEMS.

▽ ▽ INDICATES pH ADJUSTMENT WITH HCl.

○ INDICATES pH ADJUSTMENT WITH MALIC ACID.

NOTE: SOLUTIONS WITH pH AT 9.0 ARE NOT PALATABLE OR SAFE FOR ORAL CONSUMPTION.

Fig. 1

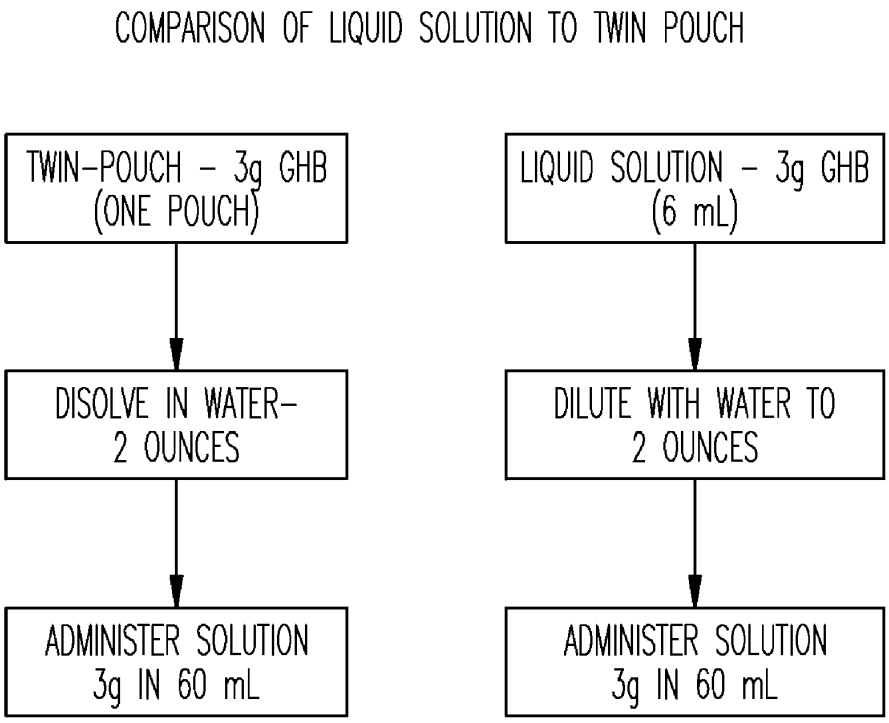
COMPARISON OF LIQUID SOLUTION TO TWIN POUCH
TWIN-POUCH - 3g GHB (ONE POUCH)
DISOLVE IN WATER- 2 OUNCES
ADMINISTER SOLUTION 3g IN 60 mL
LIQUID SOLUTION - 3g GHB (6 mL)
DILUTE WITH WATER TO 2 OUNCES
ADMINISTER SOLUTION 3g IN 60 mL

Fig. 2

MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY

RELATED APPLICATIONS

This patent application is a continuation of U.S. application Ser. No. 12/913,644, filed on Oct. 27, 2010, which is a continuation of U.S. application Ser. No. 11/777,877 filed on Jul. 13, 2007 and issued on Dec. 14, 2010 as U.S. Pat. No. 7,851,506, which is a divisional of U.S. application Ser. No. 10/841,709, filed on May 7, 2004 and issued on Aug. 28, 2007 as U.S. Pat. No. 7,262,219, which is a divisional of U.S. application Ser. No. 10/194,021, filed Jul. 11, 2002 and issued on Aug. 24, 2004 as U.S. Pat. No. 6,780,889, which is a divisional of U.S. application Ser. No. 09/470,570, filed Dec. 22, 1999 and issued on Oct. 29, 2002 as U.S. Pat. No. 6,472,431, which claims priority from U.S. Provisional Patent Application Ser. No. 60/113,745, filed Dec. 23, 1998. These applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention relates generally to the fields of pharmaceutical compositions to be used in treatments, such as, sleeping disorders, such as, e.g., narcolepsy (particularly cataplexy), drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or for an increased level of intracranial pressure or the like. The present 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, e.g.

II. Description of Related Art

GHB is an endogenous compound with hypnotic properties that is found in many human body tissues. GHB is present, for example, in the mammalian brain and other tissues. In brain the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter (Snead and Moriey, 1981). The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB is converted to succinate and then metabolized via the Krebs cycle. Clinical trials have shown that GHB increases delta sleep and improves the continuity of sleep (Ladinsky et al., 1983; Anden and Stock, 1973; Stock et al., 1973; Laborit, 1973; Lapierre et al., 1988; Lapierre et al., 1990; Yamda et al., 1967; Grove-White and Kelman, 1971; Scharf, 1985).

GHB has typically been administered in clinical trials as an oral solution (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993). GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e. daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency (Mamelak et al, 1973; Yamada et al., 1967; Bedard et al., 1989), reduces sleep apnea (Series et al, 1992; Scrima et al., 1987), and improves general anesthesia (Hasenbos and Gielen, 1985).

GHB has several clinical applications other than narcolepsy and sleep disorders. GHB has been reported to reduce alcohol craving, the number of daily drinks consumed, and the symptoms of alcohol withdrawal in patients (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992). GHB has been used to decrease the symptoms of opiate withdrawal, including both heroin and methadone withdrawal (Gallimberti et al., 1994; Gallimberti et al., 1993). It has analgesic effects that make it suitable as a pain reliever (U.S. Pat. No. 4,393,236). Intravenous administration of GHB has been reported to reduce intracranial pressure in patients (Strong, A. 1984). Also, administration of GHB was reported to increase growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970).

A good safety profile for GHB consumption, when used long term for treatment of narcolepsy has been reported. Patients have been safely treated for many years with GHB without development of tolerance (Scharf, 1985). Clinical laboratory tests carried out periodically on many patients have not indicated organ or other toxicities (Lammers, 1993; Scrima, 1990; Scharf, 1985; Mamelack, 1977; Mamelak, 1979; Gallimberti, 1989; Gallimberti, 1992; Gessa, 1992). The side effects of GHB treatment have been minimal in incidence and degree of severity, though they include sleepwalking, enuresis, headache, nausea and dizziness (Broughton and Mamelak, 1979; Mamelak et al., 1981; Mamelak et al., 1977; Scrima et al., 1989; Scrima et al., 1990; Scharf et al., 1985).

The pharmacokinetics of GHB have been investigated in alcohol dependent patients (Ferrara et al., 1992) and in normal healthy males (Palatini et al., 1993) after oral administration. GHB possesses a rapid onset and short pharmacological effect (Ferrara et al., 1992; Palatine et al., 1993; Lee, C., 1977; van der Bogert; Gallimberti, 1989; Gallimberti, 1992; Lettieri and Fung, 1978; Arena and Fung, 1980; Roth and Giarman, 1966; Vickers, 1969; Lee, 1977). In alcohol dependent patients, GHB absorption into and elimination from the systemic circulation were fast processes. Virtually no unchanged drug could be recovered in the urine. There were preliminary indications that the pharmacokinetics of GHB might be non-linear or dose-dependent (Ferrara et al., 1992). In the healthy volunteers study, the pharmacokinetics of three rising GHB doses (12.5, 25, and 50 mg/kg) were investigated. These findings indicate that both the oral absorption and elimination processes of GHB were capacity-limited though the degree of dose dependency was moderate (Palatini et al., 1993).

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). 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.

SUMMARY OF THE INVENTION

The present invention overcomes deficiencies in the prior art by providing compositions of GHB in an aqueous medium

that are resistant to microbial growth. These compositions are also resistant to the uncontrolled degradation of GHB into GBL or other substances. The compositions of the present invention are stable compositions of GHB that improve shelf-life, and provide a titratable formulation of GHB for easy dose measurement. In addition, the concentrated solutions embodied in this invention reduce shipping and storage requirements and allow patients to carry more drugs for their convenience. The present invention provides methods to treat a number of conditions treatable by GHB, referred to herein as "therapeutic categories." Therapeutic categories for the present invention include, but are not limited to, sleeping disorders, drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders, such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or an increased level of intracranial pressure or other conditions treatable with GHB.

The invention first provides a pharmaceutical composition of GHB rendered chemically stable and/or resistant to microbial growth in an aqueous medium. Preferred GHB salts of the present invention include sodium, ammonium and calcium. As used herein in certain embodiments, "stable" may mean resistant to degradation of GHB into its known or unknown decomposition elements. The level of GBL that is acceptable can be up to 0.1% of the formulation as per the ICH guidelines for shelf-life determination. As used herein in certain embodiments, "resistant to microbial growth" or "resistant to microbial challenge" means that the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days. As used herein in certain embodiments, an "aqueous medium" may mean a liquid comprising more than about 50% water. In certain preferred embodiments, an "aqueous medium" may be a solution, suspension, gel or emulsion of GHB, with a solution of GHB being most preferred. Preferred gels are thixotropic gels. Compositions that are resistant to microbial growth are created by dissolving or mixing GHB in an aqueous medium to a concentration or content of greater than of about 150 mg/ml GHB to the maximal solubility of GHB. The solubility of GHB is up to about 750 mg/ml at room temperature (20° C. to about 25° C.), however, heating the aqueous medium during preparation up to 100° C. will increase GHB solubility to at least about 1000 mg/ml. A preferred concentration or content of GHB is about 500 mg/ml.

The amount of GHB that may be mixed or dissolved into an aqueous medium and still be resistant to microbial growth depends upon the pH of the aqueous medium. In certain embodiments the presence of a preservative may allow the amount of GHB contained in the compositions of the present invention to be increased and still maintain resistance to chemical degradation and/or microbial growth. In one embodiment of the present invention, the pH of the aqueous medium of the pharmaceutical composition is about 3 to about 10.

In a preferred embodiment, the pH of said aqueous medium is about 6 to about 7.5. The pH may be from about 3.0 to about 10.3, namely of about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0, about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, about 10.0, about 10.1, about 10.2, or about 10.3, and all pH values between each of the listed pH values, of the aqueous media. This will produce a GHB composition that is resistant to microbial growth as defined by the test described herein. As used herein, the term "about" generally means within about 10-20%.

These pH values will produce compositions resistant to microbial growth in an aqueous medium if the amount of GHB added, admixed, or dissolved is from above about 150 mg/ml to about 450 mg/ml, namely, above about 150 mg/ml, about 160 mg/ml, about 170 mg/ml, about 180 mg/ml, about 190 mg/ml, about 200 mg/ml, about 210 mg/ml, about 220 mg/ml, about 230 mg/ml, about 240 mg/ml, about 250 mg/ml, about 260 mg/ml, about 270 mg/ml, about 280 mg/ml, about 290 mg/ml, about 300 mg/ml, about 310 mg/ml, about 320 mg/ml, about 330 mg/ml, about 340 mg/ml, about 350 mg/ml, about 360 mg/ml, about 370 mg/ml, about 380 mg/ml, about 390 mg/ml, about 400 mg/ml, about 410 mg/ml, about 420 mg/ml, about 430 mg/ml, about 440 mg/ml, to about 450 mg/ml, and all amounts of GHB between the values listed.

At the medium to high end of the concentration or content of GHB that may be dissolved or mixed in the aqueous medium, the maximal pH that may be used is reduced at room temperature. This is shown in FIG. **1**, a graphical presentation of acceptable formulation ranges. At a concentration or content of about 450 mg/ml GHB, the pH may be of about 3.9 to about 10.3. At a concentration or content of about 500 mg/ml GHB, the pH may be of about 4.75 to about 10.3. At a concentration or content of about 600 mg/ml GHB, the pH may be of about 6.1 to about 10.3. At a concentration or content of about 750 mg/ml GHB, the pH may be of about 7.0 to about 10.3. Of course, all pH and concentration or content values in between each of the listed pH and concentration or content values are encompassed by the invention.

Certain embodiments may be selected as sub-ranges from these values of GHB content and aqueous medium pH. For example, a specific embodiment may be selected as a content of about 170 mg/ml to about 440 mg/ml GHB in an aqueous medium, at a pH range of about pH 5.5 to about pH 8.7. Another example of how a range may be selected in an embodiment would be the selection of a content of about 155 mg/ml of GHB, which is a value between the above listed values, to a content of about 350 mg/ml of GHB, and the selection of a pH range of the aqueous medium, such as a pH range of about 8.87, which is a value between the listed pH values, to a pH of about 8.93, which is another value between the listed values of pH. A third example of ranges that may be selected for a specific embodiment would be selection of a single content or concentration of GHB, such as about 200 mg/ml of GHB, and the selection of a pH range, such as a pH of about 3.5 to about 8.2. A fourth example of ranges that may be selected for a specific embodiment would be selection of a content or concentration of GHB over a range, such as about 300 mg/ml to about 400 mg/ml, and the selection of a single pH value for the aqueous medium, such as a pH of about 3. Another example of a range selected for an embodiment may be the selection of a single content or concentration of GHB, such as 400 mg/ml GHB, and a single pH value of the aqueous medium, such as pH 7.7.

Other examples of how a range of an embodiment of GHB content or concentration may be selected include a range of GHB content or concentration from about 200 mg/ml to about 460 mg/ml GHB, encompassing the ranges for GHB described herein, and a range of pH for the aqueous medium may be from about pH 4.3 to about pH 7, encompassing ranges for GHB in an aqueous medium at room temperature described herein. Another example would be the selection of a range of GHB content or concentration from about 153 mg/ml to about 750 mg/ml, and a pH range of about 7 to about 9, encompassing ranges between the listed values of GHB content and pH described herein. An example may be the selection as a GHB concentration or content of about 170 mg/ml to about 640 mg/ml in an aqueous medium, at a pH range of about pH 6.5 to about pH 7.7. Another example of how a range may be selected in an embodiment would be a content or concentration of about 185 mg/ml of GHB, which is a value between the listed values, to a content or concentration of about 750 mg/ml of GHB, at a pH range of about 7.87, which is a value between the listed pH values, to a pH of about 8.91, which is another value between the listed values of pH. An additional example of ranges that may be selected for a specific embodiment would be a content or concentration of about 200 mg/ml of GHB at a pH of about 7 to about 8.2. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 750 mg/ml to about 400 mg/ml at a pH of about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 300 mg/ml to about 750 mg/ml at a pH of about 8.5 to about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 400 mg/ml to about 600 mg/ml at a pH of about 9 to about 5.8. And so forth. Thus, all ranges of pH and GHB concentration or content that can be selected from the values herein and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

The chemical stability of GHB is affected by pH, with compositions of GHB in an aqueous medium with a pH below about 6 being less effective in maintaining the chemical stability of GHB. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, all concentrations or content of GHB in an aqueous medium, as described herein, and as would be understood by those of ordinary skill in the art, may be selected to produce compositions of the present invention.

Additionally, the ranges described above are for a composition at room temperature, which is defined herein as from about 20° C. to about 25° C., namely, about 20° C. about 21° C., about 22° C., about 23° C., about 24° C., to about 25° C. Within the values and ranges of pH described above, the ranges of concentration or content of GHB may increase at temperatures greater than room temperature. Thus, the maximal content or concentration of GHB in an aqueous medium at a temperature of from about 26° C. about 100° C., namely about 26° C., about 27° C., about 28° C., about 29° C., about 30° C., about 31° C., about 32° C., about 33° C., about 34° C., about 35° C., about 36° C., about 37° C., about 38° C., about 39° C., about 40° C., about 41° C., about 42° C., about 43° C., about 44° C., about 45° C., about 46° C., about 47° C., about 48° C., about 49° C., about 50° C., about 51° C., about 52° C., about 53° C., about 54° C., about 55° C., about 56° C., about 57° C., about 58° C., about 59° C., about 60° C., about 61° C., about 62° C., about 63° C., about 64° C., about 65° C., about 66° C., about 67° C., about 68° C., about 69° C., about 70° C., about 71° C., about 72° C., about 73° C., about 74° C., about 75° C., about 76° C., about 77° C., about 78° C., about 79° C., about 80° C., about 81° C., about 82° C., about 83° C., about 84° C., about 85° C., about 86° C., about 87° C., about 88° C., about 89° C., about 90° C., about 91° C., about 92° C., about 93° C., about 94° C., about 95° C., about 96° C., about 97° C., about 98° C., about 99° C., to about 100° C. may be from about 750 to about 1 g/ml, namely to about 751 mg/ml, about 760 mg/ml, about 770 mg/ml, about 780 mg/ml, about 790 mg/ml, about 800 mg/ml, about 810 mg/ml, about 820 mg/ml, about 830 mg/ml, about 840 mg/ml, about 850 mg/ml, about 860 mg/ml, about 870 mg/ml, about 880 mg/ml, about 890 mg/ml, about 900 mg/ml, about 910 mg/ml, about 920 mg/ml, about 930 mg/ml, about 940 mg/ml, about 950 mg/ml, about 960 mg/ml, about 970 mg/ml, about 980 mg/ml, about 990 mg/ml, to about 1000 mg/ml. At temperatures below room temperature, the solubility of GHB may decrease, and compositions at lower temperature and solubility of GHB at the pH values and ranges described herein are also encompassed by the invention. Additionally, differences of atmospheric pressure may also increase or decrease the solubility of GHB within the ranges described, and embodiments of the invention with an increased or decreased content of GHB due to changes in pressure are also encompassed by the invention. Of course, it is understood that the present invention encompasses embodiments of GHB concentration or content in an aqueous medium at higher or lower temperature within the values described herein, such as about 980 mg/ml to about 200 mg/ml at 95° C. GHB at a pH of about 9 to about 7.5. Or about 150 mg/ml GHB at about 17° C. at about pH 6 to about pH 7. And so forth. Thus, all ranges of pH and GHB content that can be selected at various temperatures and pressures from the values above, and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

In certain other embodiments of the present invention, the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids, bases, or combinations thereof. In certain embodiments, the acid may be an organic acid, preferably a carboxylic acid or alphahydroxy carboxylic acid. In certain other embodiments, the acid is selected from the group including, but not limited to, acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like. In a preferred embodiment, the acid is malic or hydrochloric acid. In certain other embodiments, the pH adjusting agent may be a base selected from the group including, but not limited to, acetanilide, ammonia, apomorphine, atropine, benzocaine, caffeine, calcium hydroxide, cocaine, codeine, ephedrine, morphine, papaverine, physostigmine, pilocarpine, potassium bicarbonate, potassium hydroxide, procaine, quinine, reserpine, sodium bicarbonate, sodium dihydrogen phosphate, sodium citrate, sodium taitrate, sodium carbonate, sodium hydroxide, theobromine, thiourea or urea. 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.

In certain embodiments, the composition may contain one or more salts. A "salt" is understood herein to mean certain embodiments to mean a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base. Various salts, including salts of GHB, are also encompassed by ***the invention, particularly as pH adjusting or buffering agents. Pharmaceutically acceptable salts, include inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as malic, acetic, oxalic, tartaric, mandelic, and the like. Salts formed can also be derived from inorganic bases such as, for example, sodium, potassium, silicates, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropyamine, trimethylamine, histidine, procaine and the like. Alkali metal salts such as lithium, potassium, sodium, and the like may be used, preferably with an acid to form a pH adjusting agent. Other salts may comprise ammonium, calcium, magnesium and the like. In one embodiment, a salt of GHB comprising an alkali metal may be combined with an acid to create a composition that achieves the desired pH when admixed with an aqueous medium. In another embodiment, a weak base may be combined with GHB to create a composition that achieves the desired pH when admixed with an aqueous solution. Of course, other salts can be formed from compounds disclosed herein, or as would be known to one of ordinary skill in the art, and all such salts are encompassed by the invention.

In certain embodiments, excipients may be added to the invention. An "excipient" as used herein shall mean certain embodiments which are more or less inert substances added as diluents or vehicles or to give form or consistency when the remedy is in a solid form, though they may be contained in liquid form preparations, e.g. syrups, aromatic powders, honey, and various elixirs. Excipients may also enhance resistance to microbial growth, and thus act as a preservative. Such excipients include, but are not limited to, xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, cellulose derivatives, magnesium carbonate and the like.

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, propyl gallate BP, sorbic acid, chlorobutanol, dihydroacetic acid, monothioglycerol, potassium benzoate, propylparaben, benzoic acid, benzalkonium chloride, alcohol, benzoic acid, benzalkonium chloride, benzethonium chloride, benzyl alcohol, butylparaben, cetylpyridinium chloride, ethylenediamine, ethylparaben, ethyl vanillin, glycerin, hypophosphorus acid, methylparaben, phenol, phenylethyl alcohol, phenylmercuric nitrate, propylparaben, sassafras oil, sodium benzoate, sodium propionate, thimerosal and potassium sorbate. Preferred preservatives may be selected from the group comprising, but not limited to, xylitol, sodium benzoate, methylparaben, propylparaben and potassium sorbate. Xylitol is particularly preferred in certain compositions of the invention, because it acts as an preservative and a sweetener, is a caries preventative, is less laxative than other sweeteners, and is recommended for diabetics.

In certain embodiments, the pharmaceutical composition may also contain an antioxidant. An "antioxidant" is understood herein to mean certain embodiments which are substances that inhibits oxidation. Such antioxidants include, but are not limited to, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, potassium metabisulfite, sodium metabisulfite, anoxomer and maleic acid BP.

In certain embodiments, the pharmaceutical composition may also contain a flavoring agent. A "flavoring agent" is understood herein to mean certain embodiments which are substances that alters the flavor of the composition during oral consumption. A type of "flavoring agent" would be a sweetener. Preferred sweeteners or flavoring agents would be microbially non-metabolizable. Especially preferred sweeteners or flavoring agents would be carbohydrates such as xylitol and sorbitol. Such flavoring agents include, but are not limited to, acacia syrup, anethole, anise oil, aromatic elixir, benzaldehyde, benzaldehyde elixir-compound, caraway, caraway oil, cardamom oil, cardamom seed, cardamom spirit, cardamom tincture-compound, cherry juice, cherry syrup, cinnamon, cinnamon oil, cinnamon water, citric acid, citric acid syrup, clove oil, coca, coca syrup. coriander oil, dextrose, eriodictyon, eriodictyon fluidextract, eriodictyon syrup aromatic, ethyl acetate, ethyl, vanillin, fennel oil, ginger, ginger fluidextract, ginger oleoresin, glucose, glycerin, glycyrrhiza, glycyrrhiza elixir, glycyrrhiza extract, glycyrrhiza extract-pure, glycyrrhiza fluidextract, glycyrrhiza syrup, honey, non-alcoholic elixir, lavender oil, citrus extract or oil, lemon oil, lemon tincture, mannitol, methyl salicylate, nutmeg oil, orange-bitter-elixir, orange-bitter-oil, orange flower oil, orange flower water, orange oil, orange peel-bitter, orange-peel-sweet-tincture, orange spirit-compound, compound, orange syrup, peppermint, peppermint oil, peppermint spirit, peppermint water, phenylethyl alcohol, raspberry juice, raspberry syrup, rosemary oil, rose oil, rose water, saccharin, saccharin calcium, saccharin sodium, sarsaparilla syrup, sorbitol solution, spearmint, spearmint oil, sucrose, syrup, thyme oil, tolu balsam, tolu balsam syrup, vanilla, vanilla tincture, vanillin or wild cherry syrup.

Salts, excipients, pH adjusting agents such as acids, bases and buffering agents, flavoring agents, and other agents that may be combined with the compositions of the present invention, or may be used to prepare the compositions of the present invention, are well known in the art, (see for example, "Remington's Pharmaceutical Sciences" 8th and 15th Editions, and Nema et al., 1997, incorporated herein in their entirety), and are encompassed by the invention.

In certain other embodiments, the pharmaceutical composition comprises GHB, a pH adjusting or buffering agent, and an aqueous medium, wherein the components are admixed (sequentially or simultaneously) to prepare said pharmaceutical composition. The pH adjusting or buffering agent and aqueous medium may be any described herein.

The invention also provides a method of preparing a chemically stable and microbial growth-resistant pharmaceutical composition for the treatment of a condition responsive to GHB, comprising admixing GHB and a pH-adjusting or buffering agent in an aqueous medium. In certain embodiments, the method of preparing the pharmaceutical composition further comprises admixing a preservative with the pharmaceutical composition. Other components, such as flavoring agents, salts, and the like, may be added to the composition. The pH adjusting or buffering agent, aqueous medium, preservative, flavoring agents, salts, or other ingredient may be any described herein.

In certain other embodiments, the method of preparing the pharmaceutical composition comprises admixing GHB, a pH adjusting or buffering agent, and an aqueous medium soon before administration to a patient suspected of having a condition responsive to GHB.

The invention also provides a method of treating any therapeutic category of disorder responsive to GHB, comprising

administering to a patient suspected of having such a condition a therapeutic amount of a pharmaceutical composition comprising chemically stable GHB (e.g. 1-10 gms.) in an aqueous medium resistant to microbial growth. In certain embodiments, the method of treating a condition responsive to GHB comprises a patient taking a first dosage of from about 0.1 g to about 10 g, namely about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1-9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0 about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, to about 10 grams of GHB, or as needed by the patient as would be recognized by one of skill in the art. Of course, it will be understood that all values in between those listed, such as 9.45 grams, 6.32 grams, etc. may be administered, and those values are encompassed well. In preferred embodiments, the first dose is administered within an hour of sleep. In preferred embodiments, a second dose of GHB within the values described above may be administered. This second dose is administered preferably within about 2.0 to about 5.0 hrs, namely about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, to about 5.0 hours after the first dose, though it may be administered at a time outside of the preferred range.

In certain embodiments, a second pharmaceutical may be administered with the composition of GHB. Such a second pharmaceutical may be e.g., a stimulant administered within the same 24 hour period as the first dose of GHB. The stimulant may be, e.g., but not limited to, methylphenidate or pemoline to counter the residual effects of GHB treatment during periods of wakefulness. In certain embodiments, the method of treating a sleep disorder may include the discontinuation of other second pharmaceuticals used to control a sleep disorder. Such second pharmaceuticals may include, but are not limited to, a tricyclic antidepressant.

In certain embodiments, the invention provides a method of treating any appropriate therapeutic category of disorder, by administration of GHB compositions of the present invention as described above for the treatment of sleep disorders. When GHB is used in methods of treating any therapeutic category of disorder, the GHB composition of the present invention may be mixed with the aqueous medium, and optionally pH adjusting or buffering agent or other additives, by the patient or administrator soon before consumption. The patient may prepare the composition within a few minutes to hours before administration. Alternatively, one or more of the components may be premixed for ready use. The components of the GHB composition of the present invention, GHB, an aqueous medium, pH adjusting or buffering agent, excipients, preservatives, flavoring agents, and/or other components or additives may be stored in a container means suitable to aid preservation. Preferably, the container means is in the form of a set. A "set" as used herein certain embodiments is one or more components of the composition packaged in a container or other suitable storage means.

The present invention also provides a set for the treatment of a condition responsive to GHB comprising, in suitable storage means, GHB and a pH adjusting or buffering agent. In certain embodiments, the GHB and the pH-adjusting or buffering agent are separately packaged. In certain other embodiments the GHB and the pH adjusting or buffering agent may be mixed. The set may contain an aqueous medium. In certain other embodiments, at least one component selected from the group including, but not limited to, GHB, the pH-adjusting or buffering agent and/or an aqueous medium is separately packaged. In certain other embodiments, at least two of the components selected from the group comprising GHB, a pH adjusting or buffering agent and an aqueous medium are mixed together. In some embodiments, the set further contains a preservative. Such a set may have one, two, or more components from the group comprising GHB, a pH-adjusting or buffering agent, an aqueous medium or a preservative packaged separately. Such a set may have two or more components mixed together. Thus, both liquid and dry formulations of GHB and other components may be packaged in a set for mixing before administration, or one or more components may be premixed and packaged together with other components, or all the components may be premixed and packaged in a set.

It is understood that the compositions of the present invention, including those in a set, may be dispersed in a pharmaceutically acceptable carrier solution as described below. Such a solution would be sterile or aseptic and may include water, co-solvent vehicle buffers, isotonic agents, pharmaceutical aids or other ingredients known to those of skill in the art that would cause no allergic or other harmful reaction when administered to an animal or human subject. Therefore, the present invention may also be described as a pharmaceutical composition of GHB with increased stability in a pharmaceutically acceptable carrier solution.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also as used herein, the term "a" "an" or "the" is understood to include the meaning "one or more". Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. **1**. The Range of Gamma-Hydroxybutyrate's Resistance to Microbial Growth and Chemical Stability in Aqueous Solution. The ordinate is the pH of solutions of GHB. The axis is the concentration (mg/ml) of GHB in aqueous solution. The region below the diagonal line [/] is the range of GHB solubility at room temperature. Greater solubility can be achieved, up to 1 g/ml, by heating the solution up to 100° C.

FIG. **2** illustrates the concentration and volume of GHB solution that a patient administers (see also Table 4).

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

I. Formulations of Gamma-Hydroxybutyrate

A. Microbial Growth and Gamma-butyrolactone Formation

The present invention arises from the discovery of chemically stable and microorganism resistant formulations of GHB in an aqueous medium, preferably a solution, and the efficacy of these formulations in the treatment of therapeutic categories of disorders, such as narcolepsy and other sleep disorders. Specifically, GHB is prepared at a concentration greater than about 150 mg/ml in an aqueous medium, up to the limits of GHB's solubility or retention in an aqueous medium, to produce the compositions of the present invention.

The maximum solubility of GHB is affected by the pH of the aqueous medium. At about pH 4, the maximum amount of sodium-GHB that can be dissolved is about 450 mg/ml. The value of pH that is conducive to GHB solubility increases, as is shown at FIG. **1**, so that the minimal pH that will dissolve 750 mg/ml GHB was found to be about pH 6.8. This is shown in Table 1.

TABLE 1

	Limits of Sodium Oxybate Solubility		
ID A	Sodium Oxybate Maximum Solubility	pH of Solution	Temperature
B	450 mg/cc	pH 4 (HCl)	25°
C	500 mg/cc	pH 5 (HCl)	25°
D	600 mg/cc	pH 6 (HCl)	25°
E	750 mg/cc	pH 6.8 (HCl)	25°
F	750 mg/cc+	pH 10.3	25°
G	1000 mg/cc	pH unadjusted	65° Soluble 25° Gel

The pH of the aqueous medium also affects the resistance of the composition to microbial growth at about 500 mg/ml GHB. GHB at this concentration in an aqueous medium that is between about pH 5 and pH 9 is resistant to microbial growth, with compositions at about pH 6 to about pH 7.5 being particularly resistant to microbial growth. However, at concentrations of GHB greater than about 750 mg/ml above about pH 7.5, the resistance to microbial growth is reduced. This is shown at Table 2.

TABLE 2

	Microbial Challenge Data Summary		
ID H	Sodium Oxybate Concentration	pH of Solution	Microbial Challenge Result
I	750 mg/cc	7.5 (HCl)	pass
J	500 mg/cc	6.0 (HCl)	pass
K	500 mg/cc + Excipients (Xylitol)	6.0 (Malic Acid)	pass
L	500 mg/cc	9.0 (HCl)	pass (borderline *aspergillus*)
M	150 mg/cc (BDL 1995)	5.0 (HCl)	fail (*aspergillus* only)
N	150 mg/cc (BDL 1995)	7.0 (HCl)	fail (*aspergillus & staph*)
O	150 mg/cc (BDL 1995)	3.0 (HCl)	fail (*aspergillus* only)
P	150 mg/cc (BDL 1995)	10.3 (unadjusted)	fail (*aspergillus & staph*)
Q	500 mg/cc	6.0 (Malic Acid)	discontinued
R	500 mg/cc	7.5 (Malic Acid)	pass
S	500 mg/cc (May 1998)	9.0 (Malic Acid)	discontinued
T	500 mg/cc (May 1998)	7.5 (HCl)	pass*
U	Others: 200 mg/cc-800 mg/cc	5.0-9.0	pending

*pass is generally defined as:
For Category 1C Products
Bacteria: Not less than 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days' count at 28 days.
Yeast and Molds: No increase from the initial calculated count at 14 and 28 days.

The data from Table 1 and Table 2 are graphically shown in FIG. **1**. The concentration of GHB in the composition, when evaluated in relationship to the pH, affects the resistance of the GHB composition to microbial challenge. Compositions of GHB at or below 150 mg/ml are poorly resistant to microbial challenge from a pH range of about pH 3 to about pH 9. However, concentrations of GHB of greater than about 150 mg/ml, up to about 1000 mg/ml of GHB, are believed to be suitably resistant to microbial contamination at these pH ranges.

The chemical stability of GHB is affected by pH. Accordingly, the method for preparing GHB, as described herein, particularly as disclosed in the specific examples, varies with pH. GBL begins to form if the pH is about 6 or less. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of 15 GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, any pH or range of pH values where a clinically acceptable amount of GBL is produced is also contemplated as being preferred, and is encompassed by the present invention. The range of GBL could be regulatorily broadened with availability of sufficient toxicological data.

In certain embodiments of the invention, a pH-adjusting agent may be added to the composition. The choice of a pH adjusting agent may affect the resistance to microbial challenge and/or the stability of GHB, as measured by the reduction in assayable GHB. Compositions of GHB, pH adjusted with malic acid are resistant to both microbial growth and chemical degradation of GHB, and are preferred. Other pH adjusting or buffering agents may be selected. Agents that adjust pH that are selected on this basis will undergo a taste testing study. However, any pH adjusting agent disclosed herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the invention. Of course, any salt, flavoring agent, excipient, or other pharmaceutically acceptable addition described herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the invention.

Any of the above formulations may be prepared and/or packaged as a powdered or dry form for mixing with an aqueous medium before oral administration, or they may be prepared in an aqueous medium and packaged. After mixing with an aqueous medium, preferably to prepare a solution, these formulations are resistant to both microbial growth and chemical conversion of GHB to GBL, thereby increasing the shelf-life of therapeutic formulations of GHB in an aqueous medium. These formulations-then provide an easily titratable liquid medium for measuring the dosage of GHB to be administered to a patient. Additional embodiments of the composition and methods of preparation are described below and in the examples.

B. Pharmaceutical Compositions

1. Pharmaceutically Acceptable Carriers

Aqueous compositions of the present invention comprise an effective amount of GHB dissolved or dispersed in a pharmaceutically acceptable carrier and/or an aqueous medium. The phrases "pharmaceutically or pharmacologically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is not appropriate. Supplementary compatible active ingredients can be incorporated into the compositions. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by the Food and Drug Administration (FDA).

The GHB may be lyophilized for more ready formulation into a desired vehicle where appropriate. The active compounds may be formulated for parenteral administration, e.g., formulated for injection via intravenous, intraarterial, intramuscular, sub-cutaneous, intralesional, intraperitoneal or other parenteral routes. The preparation of an aqueous composition that contains a GHB agent as an active component or ingredient will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for using to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including, e.g., aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

Solutions of the active compounds as free acid or pharmacologically acceptable salts can be prepared in water suitably mixed with hydroxypropylcellulose and/or a pharmaceutically acceptable surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof as well as in oils. Under ordinary conditions of storage and use, these preparation may best contain a preservative to further prevent the growth of microorganisms.

A GHB composition of the present invention can be formulated into a composition in a neutral or salt form. Such salts can be formed from any of the acids and bases described herein particularly depending on the particular GHB or GHB salt used, or as would be known to one of ordinary skill in the art.

The carrier can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, or the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a substance, such as lecithin (e.g. a coating), by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by any of the preservatives described herein, or as would be known to one of ordinary skill in the art, including various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The preparation of more, or highly, concentrated solutions for direct injection is also contemplated, where the use of DMSO as solvent (although DMSO may not now be a permitted human drug) is envisioned to result in extremely rapid penetration, delivering high concentrations of the active agents to a small area.

Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above, but drug release capsules and the like can also be employed.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences"15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The active GHB may be formulated within a therapeutic mixture to comprise about 100 to about 10,000 milligrams per dose. Multiple doses can also be administered.

In addition to the compounds formulated for parenteral administration, such as intravenous or intramuscular injection, other pharmaceutically acceptable forms include, e.g., tablets or other solids; liposomal formulations; time release capsules; and any other form currently used, including cremes, which then may be admixed with an aqueous medium for oral administration.

One may also use nasal solutions or sprays, aerosols or inhalants in the present invention. Nasal solutions are usually aqueous solutions designed to be administered to the nasal passages in drops or sprays. Nasal solutions are prepared so that they are similar in many respects to nasal secretions, so that normal ciliary action is maintained. Thus, the aqueous nasal solutions usually are isotonic and slightly buffered to maintain a pH of 5.5 to 6.5, though other pH ranges disclosed

herein the specific examples, such as pH 3 to about pH 9, or pH 6 to about 7.5, are contemplated. In addition, preservatives, similar to those used in ophthalmic preparations, and appropriate drug stabilizers, if required, may be included in the formulation. Various commercial nasal preparations are known and include, for example, antibiotics and antihistamines and are used for asthma prophylaxis.

The preferred oral formulations may include such normally employed excipients, as, for example, pharmaceutical grades of xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate and the like. These compositions can take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders to be admixed with an aqueous medium. In certain defined embodiments, oral pharmaceutical compositions will comprise an inert diluent or assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsule, or they may be compressed into tablets, or the GHB may be packaged separately from or in combination with the excipients, salts, flavorings or any other components described herein, to be admixed with an aqueous medium for oral or injectable formulations, or they may be incorporated directly with the food (i.e. a beverage) of the diet.

For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of tablets, buccal tablets or tabs, troches, capsules, elixirs, suspensions, syrups, wafers, and the like, to be admixed with an aqueous medium. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 75% of the weight of the unit, or preferably between 25-60%. The amount of active compounds in such therapeutically useful compositions is such that a suitable dosage will be obtained.

The tablets, troches, pills, capsules and the like may also contain the following: a binder, natural as gum tragacanth, acacia, cornstarch, or gelatin or synthetic as polyvinyl acetate; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a natural or synthetic flavoring agent. When the dosage unit form is a capsule for admixing with a specific volume of an aqueous medium, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with sugar, natural or synthetic polymers, or both. A syrup or elixir may contain the active compounds, sucrose as a sweetening agent, a preservative, a dye and/or a flavoring.

Additionally, any excipient, salt, acid, pH-mediating, adjusting or buffering compound or agent, flavoring, solution, solvent, dispersion, glycerol, glycol, oil, antibacterial and antifungal agents, antibiotics and antihistamines, binders, disintegrating agents, lubricants, sweetening agents, or any other additive or ingredient from those enumerated above or in the examples, or in any pharmaceutically acceptable composition or carrier described herein, or as would be known by one of skill in the art, is contemplated for use in aqueous mediums or solid forms of the GHB compositions of the invention. One or more of these compositions may be packaged with GHB or packaged separately from GHB prior to consumption. If packaged separately, useful compositions of GHB may be obtained by mixing GHB with the other components with an aqueous medium prior to consumption. Such components may be packaged in a set, described below.

2. Sets

Therapeutic sets of the present invention are sets comprising GHB. Such sets will generally contain, in suitable container, a pharmaceutically acceptable formulation of GHB. The set may have a single container, or it may have distinct container for each component, or distinct container for various combinations of components.

When the components of the set are provided in one or more liquid formulations, the liquid formulation is an aqueous medium, with a sterile aqueous solution being particularly preferred. The GHB compositions may also be formulated into a syringeable composition. In which case, the container means may itself be a syringe, pipette, vial, ampule or other such like apparatus, from which the formulation may be applied to an infected area of the body, injected into an animal, or even applied to and mixed with the other components of the set.

However, the components of the set may be provided as dried powder(s). When reagents or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent. It is envisioned that the solvent may also be provided in another container means.

The container means will generally include at least one vial, test tube, flask, bottle, pouch syringe or other container means, into which the GHB formulation or components thereof are placed, preferably, suitably allocated. The sets may also comprise a second container means for containing a sterile, pharmaceutically acceptable buffer or other diluent.

The sets of the present invention will also typically include a means for containing the vials in close confinement for commercial sale, such as, e.g., injection or blow-molded plastic containers into which the desired vials are retained.

Irrespective of the number or type of containers, the sets of the invention may also comprise, or be packaged with, an instrument for assisting with the injection/administration or placement of the GHB composition within the body of an animal. Such an instrument may be a drinking cup, syringe, pipette, or any such medically approved delivery vehicle.

II. Methods of Treatment with the GHB Compositions

Because GHB has been shown to be effective in treating narcolepsy and sleep disorders (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993), reducing alcohol craving and alcohol withdrawal symptoms, (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992), reducing opiate withdrawal symptoms (Gallimberti et al, 1994; Gallimberti et al., 1993), reducing pain (U.S. Pat. No. 4,393,236), reducing intracranial pressure in patients (Strong, A. 1984), and increasing growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970), the formulations of the present invention are also contemplated to be useful in the treatment of any of these disorders or conditions in patients. GHB has also been used alone as a narcotic in patients with a terminal carcinomatous state. GHB has been used with other analgesics, neuroleptics, or with a subliminal barbiturate dose for use as an anesthesia. GHB has been used in closed craniocerebral trauma and as a soporific (U.S. Pat. No. 5,380,937). The inventors contemplate the use of the GHB compositions of the present invention as a narcotic, hypnotic, or as a soporific. The inventors also contemplate the use of the GHB compositions of the present invention in combination with analgesics, neuroleptics or barbiturates for use as an anesthe-

sia. The GHB compositions of the present invention may be prepared and administered by any of the means described herein. particularly those described in the section "Pharmaceutical Compositions" and the examples, or by any means as would be known to those of skill in the art.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1

Preferred Embodiments

Xyrem™ Clinical Trials

The inventors developed a liquid formulation composed of GHB, xylitol, and preservative in water (XYREM®). Subsequent instability of the preservative in this formulation and a desire to initiate clinical trials in a timely manner led to a change in the formulation to a foil pouch. One clinical trial utilized a twin-pouch dosage form, with one side (pouch 1) of the foil packet containing GHB and the other side (pouch 2) containing the flavoring agents (Xylitol, [NF]; Malic Acid, NF.

Patients were instructed to open the twin-pouch with a scissors, empty the contents into a dosing cup, add 2 ounces of water, snap the lid on the dosing cup, shake to dissolve, and drink the entire contents of the cup. Clinical trials conducted by the inventors have been performed using the twin-pouch dosage form.

However, the inventors have continued development of a liquid solution and have now overcome inherent problems with particular formulations and/or preservatives. The inventors have converted patients currently enrolled in a GHB open-label trial to a liquid solution composed of GHB, malic acid, and water—that is diluted with water immediately prior to oral administration.

The need for a liquid solution dosage form is further evidenced by the range of doses being used in a subsequent GHB open-label trial. Three sizes of pouches were prepared for the GHB open-label trial: 1.5 grams, 3.0 grams. and 4.5 grams. The initial dose for all patients in the GHB open-label trial was 6 grams of GHB nightly in divided doses. Dosage adjustments were permitted in the first two weeks of the trial as indicated for intolerance or lack of efficacy. The investigator was permitted to decrease the dose of GHB to 3 grams or 4.5 grams, or increase the dose to 7.5 grams or 9 grams nightly. After two weeks, further dosage adjustments were made if clinically indicated.

Thirty-five patients had their dose increased, and 16 patients had their dose decreased. Patients in the lowest dose group were disproportionately female and weighed 15 kg less than patients in the other two groups. Current dosing levels are noted below:

TABLE 3

Dosing Levels in the GHB Open-Label Trial

	Total	1.5 gram	3.0 gram	4.5 gram	6.0 gram	7.5 gram	9.0 gram
Number of Patients	95	0	4	10	39	12	30
Percent of Patients	100%	0%	4%	10%	41%	13%	32%

To achieve these individualized doses, it has been necessary to provide a combination of different dose strengths. This complexity would be very difficult to achieve with a marketed product. In addition, a month's supply of twin-pouches is quite bulky. A liquid formulation allows for ease in dosing adjustment with one dosage form. In addition "child-resistant" packaging has been developed with the liquid formulation.

A number of patients have also complained about the flavor with the twin-pouches. As follow-up the inventors sent questionnaires to participants in the inventors' clinical trial, and performed taste testing in normal volunteers. The questionnaire responses, taste testing results, and the clinical experience in narcolepsy patients of the study administrator have all confirmed that unflavored solutions were acceptable.

The concentration and volume of the GHB solution that the patient administers will be the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. This is illustrated in FIG. **2** and Table 4:

TABLE 4

Comparison of Liquid Solution to Twin-Pouch

	Twin-Pouch	Liquid Solution
Amount of GHB	3 grams (1 pouch)	3 grams (6 mL)
Inactive Components	malic acid xylitol lemon/lime flavor orange flavor	malic acid
Final Concentration	50 mg/mL	50 mg/mL*
Final Volume	60 mL	60 mL

*Final concentration outside the range of the most stable formulation. This formulation strength may be only stable at short periods of time such as 48 hours. The twin pouch version could be solubilized at a a concentration within the preferred range of pH and GHB concentration for longer term storage.

Apart from the elimination of the sweetener (xylitol) and flavoring, the two formulations result in identical solutions.

Conclusions

The concentration and volume of the GHB solution that the patient administers is the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. Either method may be used to produce acceptably stable solutions of GHB.

Example 2

Preferred Embodiments

Self Preserving Formulations of Gamma-Hydroxybutyrate

Summary of Formulation Studies

Liquid Xyrem™

I. Maximum Solubility Range

As seen in FIG. **1** and Table 1, the solubility of GHB varies with pH levels at room temperature (25° C.). Additional

amounts of GHB can be solubilized in a gel if heat is applied, in which case a 1000 mg/ml concentration can be achieved. The inventors to contemplate that though the concentrations or contents of GHB shown in FIG. **1** and Table 1 are preferred for use, due to the ease of preparing and consuming unheated preparations, higher concentrations of GHB in aqueous medium may also be made, up to 1000 mg/ml.

II. Microbial Testing

The inventors used a three factor analysis involving pH, concentrations of GHB and the pH adjuster used. As seen in FIG. **1**, and Table 2, unacceptably low resistance to microbial challenge was seen at 150 mg/ml GHB at pH 3, 5, 7, and 9.0, using HCl as the pH adjusting agent. 150 mg/ml GHB at pH 10.3 without a pH adjusting agent also proved unacceptably resistant to microbial challenge. Borderline acceptable microbial preservativeness was seen in a solution pH adjusted with HCl at 500 mg/ml GHB at pH 9. At a concentration of 500 mg/ml at pH 6.0 or 7.5, adjusted with either malic acid or HCl, and 500 mg/ml at pH 9.0 adjusted with HCl, the formulation is very effective in a microbial challenge test. The inventors contemplate that a concentration of greater than about 150 mg/ml of GHB, up to the maximal solubility in aqueous solution of GHB, will be suitably resistant to microbial challenge from about pH 3 to pH 10.3. Preferably, the aqueous medium will contain a pH-adjusting or buffering agent.

III. Gamma-Butyrolactone Degradation Range

GBL begins to form if the pH is about 6 or less with the formulation tested thus far.

A. Liquid Formulation Development

The objective of these experiments was to develop a commercial formulation for sodium gamma hydroxybutyric acid. The initial formulation for sodium gamma hydroxybutyric acid (GHB) was intended to be an aqueous liquid formulation containing 150 mg/ml GHB, preservatives and flavoring agents. To develop this formulation, studies were conducted to establish the: solubility of the drug in water and as a function of pH, type and concentrations of suitable preservatives, type and concentrations of flavor ingredients, and stability of the formulations.

1. Solubility

The feasibility of preparing formulations containing 150 mg/mL of GHB at pH 3, 5 and 7 was established. Solutions containing 150 mg/mL GHB were prepared. The initial pH was greater than pH 7.5 and the final pH was adjusted to 3, 5 or 7 with hydrochloric acid. The solutions were observed for precipitation and assayed by HPLC for GHB content. The results showed that no precipitation was observed and the drug concentration was found to be 150 mg/mL by HPLC. This information was used as the basis for additional formulation development studies.

2. Preservatives

Preservative effectiveness studies were conducted to identify a suitable preservative for the GHB liquid formulation. The following formulations shown in Table 5 were prepared and tested using *Staphylococcus aureus* (ATCC #6538), *Pseudomonas aeruginosa* (ATCC #9027) and *Aspergillus niger* (ATCC #16404).

TABLE 5

Liquid Formulations Used in Preservative Effectiveness Testing

Formulation	pH	Sodium Benzoate	Methylparaben Propylparaben	Potassium Sorbate	Control
1	3	X			
2	5	X			
3	7	X			
4	3		X		
5	5		X		
6	7		X		
7	3			X	
8	5			X	
9	7			X	
10	3				X
11	5				X
12	7				X
13	no pH adjustment				X

The preservative used in each formulation is marked with an X. The results showed that formulations #3, 4, 6 and 9 reduced all three challenge microorganisms by >99.99% in 48 h of contact time. Formulations #1, 5 and 7 reduced all three challenge microorganism by >99.99% in 7 days of contact time. Formulations #2, 8, 10, 11, 12 and 13 did not reduce *Aspergillus niger* mold to >99.99%, although some reduction occurred in 7 days of contact time. Controls #10, 11, 12 and 13 demonstrated activity against *Pseudomonas aeruginosa.*

3. Stability

Based on the results of the preservative effectiveness testing, five formulations were selected for stability testing. Table 6 shows the composition of the formulations.

TABLE 6

Liquid Formulations Used in Informal Stability Program

Chemical	1	2	3	4	5
Potassium Sorbate	0.4 gm	0.4 gm			
Sodium Benzoate			1.0 gm		
Methylparaben				0.36 gm	0.36 gm
Propylparaben				0.04 gm	0.04 gm
GHB	30 gm	30 gm	30 gm	30 gm	30 gm
Xylitol	40 gm	40 gm	40 gm	40 gm	40 gm
Water q.s.	200 mL	200 mL	200 mL	200 mL	200 mL
Initial pH	8.68	8.68	9.30	7.75	7.75
Formulation Adjusted pH	3.01	5.00	3.00	2.98	4.98

The formulations were packaged in 125 mL, amber PET bottles with safety lined child-resistant caps and stored upright and inverted at 60° C., 40° C./75% relative humidity (RH) and 25° C./60% relative humidity. Samples were removed from the stability chambers after 1, 2 and 3 months and assayed by high performance liquid chromatography (HPLC) for GHB content. Appearance and pH were also monitored.

Table 7 shows the results for the 3 month time point. Samples stored at 60° C. changed color but samples at all other conditions remained unchanged in color.

The pH of all formulations migrated upward over the three month stability period at 60° C. The percent increase in pH from initial to 3 months, was greater for the formulations which were initially adjusted to lower values.

For example, the migration of pH in formulations 1, 3 and 4 (adjusted down to pH 3) were 21-30 percent across all conditions in three months. The migration of pH in formulations 2 and 5 (adjusted down to pH 5) were 4.2-12 percent across all conditions in 3 months. Maintenance of pH becomes important for long term storage since preservatives are known to degrade in formulations having pH levels above approximately pH 6.

Additionally, development of flavor systems to mask the negative taste of preservatives is difficult.

TABLE 7

Table 7
Results of Liquid Formulation Informal Stability Study at Three Months

Formulation # (See Table 6)	Attribute	25° C./60% RH Upright	25° C./60% RH Inverted	40° C./75% RH Upright	40° C./75% RH Inverted	60° C. Upright
1	% t = 0	100.7	101.6	101.2	NA	NA
Potassium	pH	3.63	3.64	3.84	3.82	3.91
Sorbate (pH 3) at 3 months storage	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light yellow
2	% t = 0*	102.1	105.0	104.0	102.0	99.6
Potassium	pH	5.21	5.28	5.55	5.56	5.61
Sorbate (pH 5)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	c brown
3	% t = 0	102.4	104.1	99.1	102.6	97.0
Sodium	pH	3.60	3.74	3.78	3.75	3.79
Benzoate (pH 3)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, colorless
4	% t = 0	101.5	102.7	100.6	101.2	93.7
4 Methyl &	pH	3.63	3.71	3.81	3.80	3.83
Propyl Parabens (pH 3)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, colorless
5	% t = 0	103.1	105.8	101.9	103.1	95.6
4 methyl &	pH	5.22	5.55	5.55	5.56	5.60
Propyl Parabens (pH 5)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light yellow

*% GHB at t = 0 percent of label claim
**initial time (t = 0)

4. Liquid Formulation Organoleptic Testing

Based on the above stability data and preservative effectiveness testing, a pH 5 formulation containing potassium sorbate was selected as the primary base formulation for flavor system development and organoleptic testing. A pH 3 formulation containing potassium sarbate was selected as the back-up formulation.

B. Dry Powder Formulation Development

Developing a flavor system for the primary and back-up liquid formulations proved to be difficult and a decision was made to develop a dry powder formulation for reconstitution with water before consumption. This approach removed the need for a preservative system, the requirement to adjust pH to levels below pH 6, and allowed the development of a suitable flavor system.

1. Dry Powder Formulation Organoleptic Testing

To develop a flavor system for the powder formulation, several parameters were evaluated. The flavor attributes of a GHB solution was characterized by a professional sensory panel. A mimic base containing similar sensory properties as a GHB solution for flavor system was developed. Generally Recognized As Safe (GRAS) excipients for flavor system development were selected. Different excipients (flavorings, sweeteners, acidulants and flow agents) in the mimic base were screened. Three flavor systems for the focus group test were selected. A preferred flavor system was optimized based on comments obtained from the focus group testing. This final formulation with GHB was optimized.

Based on the above activities, the following formulations in Table 8 were selected for stability studies:

TABLE 8

Composition of Prototype Dry Powder Formulation

Ingredient	Composition (grams)	Purpose
GHB	3	Active
Xylitol	5.5	non-cariogenic sweetener

TABLE 8-continued

Composition of Prototype Dry Powder Formulation

Ingredient	Composition (grams)	Purpose
Malic acid	0.2	Acidulant
Flavor 1	0.2	Flavor ingredient
Flavor 2	0.04	Flavor ingredient
Silicon Dioxide (Cab-O-Sil ®)	0.03	Flow enhancer

2. Dry Powder Formulation Stability

A study was initiated to evaluate the stability of the above prototype formulation in two types of foil packages (high and moderate moisture resistant) as well as the stability of GHB alone in one type of foil package (high moisture resistant). Table 9 shows the Lots that were placed on stability. The foil packages were a high moisture resistant pouch and a moderate moisture resistant pouch. The study protocol, Table 10, required the samples to be stored at 40±2° C./75±5% relative humidity for six months, and 25±2° C./60±5% relative humidity for 12 months. Table 11 shows the tests, methods, number of packets/test and specifications for the study.

TABLE 9

Dry Powder Informal Stability Study Package Composition

Lot Number	Manufacture Date	Package Configuration	Special Comments
SPO #8018 A	Oct. 6, 1995	Foil Packet	Moderate moisture resistant pouch.
SPO #8018 B	Oct. 6, 1995	Foil Packet	Highest moisture protection pouch.
SPO #8018 C	Oct. 6, 1995	Foil Packet	Drug substance only. Highest moisture protection pouch.

TABLE 10

Dry Powder Informal Stability Study Protocol

	Stability Time in Months						
Storage Conditions	0	1	2	3	6	9	12
40 ± 2° C./75% ± 5% RH		X	X	X	X		
25 ± 2° C./60% ± 5% RH	X	X	C	C	R	R	R

X = Samples to be tested
C = Contingency Samples
R = Reduced testing; assay and H_2O only
RH = Relative Humidity

TABLE 11

Dry Powder Informal Stability Tests and Specifications

Test	Method	Packets/Test	Specification Limits
Appearance Dry Material	Visual	Use HPLC	White to off-white free flowing powder
Appearance Reconstituted Material	Visual	Use HPLC	Cloudy, off-white solution with visible particulates
Rate of Dissolution	Visual	Use HPLC	Material should dissolve completely in five min with mixing
Odor	Olfactory	Use HPLC	Characteristic Lemon/Lime odor
Assay: GHB	HPLC	3	90.0%-110.0%
Assay: Malic Acid	HPLC	Use HPLC	90.0%-110.0%
Impurities/ Degradants	HPLC	Use HPLC	Not more than 1% for any individual impurity/degradant and Not more than 3% total impurity/degradants
Vacuum Leak test	Visual	3	No Appearance of Leaking
pH	USP <791>	Use HPLC	For Information
Moisture	Karl Fisher	3	Report Value—to be determined

After two months at 40±2° C./75±5% relative humidity, the potency (% label claim) of Lots SPO SO ISA and SPO 80 188 was less than 94.0%, the lower limit of the specification, whereas Lot SPO 8018C showed no loss in potency. Lots 8018A and 8018B showed approximately 96% potencies after 2 months at 25° C.±2° C./65%±5% relative humidity. Lot SPO 8018C again showed no loss in potency at this lower storage condition.

3. Appearance

After 2 months at 40±2° C./75±5% relative humidity, Lots SPO 8018A and SPO 8018B showed significant melting, whereas Lot 8018C showed no melting. Lots SPO 8018A and SPO 8018B also showed partial melting after 2 months at 25° C.±2° C./65%±5% relative humidity. Lot SPO 8018C again showed no evidence of melting at this lower storage condition.

Based on the physical changes in state observed during the stability studies, it was apparent that a solid state interaction between GHB and the excipient blend had occurred. Since xylitol made up the majority of the excipient blend, it was assumed that xylitol was the primary source of the drug-excipient interaction. An alternative hypothesis was also proposed, based on the possibility that the package was mediating the interaction between GHB and xylitol. Three studies were initiated to test these hypotheses.

4. Stability of GHB Solids in a Set Container-System

In the first study, the samples that were stored at 25±2° C./60±5% relative humidity were transferred to glass vials and then stored at 40±2° C.I7±5% relative humidity. In the second study, mixtures of GHB and xylitol were gently rubbed between sheets of different types of foil packaging. The mixtures were observed for changes in physical appearance. In the third study, different mixtures of GHB and xylitol were prepared. Differential Scanning calorimetry (DSC) thermograms were then done to look for changes in the thermograms. The results of these studies are summarized below.

Transfer to Glass: Samples of Lot 8018A and Lot 8018C that were previously stored at 25±2° C./60±5% relative humidity were transferred to amber screw cap vials and stored at 40±2° C./75±5% relative humidity. Analyses similar to those shown in Table 6 were done. After 1 month, the potency of Lot 8018A was 94.6% whereas the potency of Lot 8018C (GHB only) was 100%. In addition, Lot 8018A also showed evidence of melting. The results supported the hypothesis that GHB and xylitol were interacting in the solid state and the interaction appeared to be independent of packaging.

Foil Study: Mixtures of GHB and xylitol were placed between folded sheets of several different foil packaging materials. Slight adhesion of the mixed granules with the foil lining was observed for all of the foils examined. No direct evidence of melting was observed, however, even when excessive force was applied to the outer foil surfaces. This data suggests that the packaging material was not responsible for the solid state interaction observed during the stability studies.

DSC thermographs were obtained for samples of GHB/xylitol containing GHB:xylitol mixtures of 33:66, 45:55 and 55 percent 45 respectively. The scans were conducted at a scan rate of 10° C./min. The thermograms showed that the sample containing GHB:xylitol 33:66 showed a broad endothermic transition starting at 35° C.-40° C. Samples with higher ratios of GHB:xylitol also showed broad endothermic transitions that started at temperatures of 45° C.-50° C. The changes seen in the thermograms supported the hypothesis that a solid state interaction may be occurring between GHB and xylitol that resulted in low potencies for formulations containing mixtures of these two agents.

As a result of the changes seen in the DSC thermograms for different mixtures of GHB:xylitol, a study was initiated to investigate the stability of a formulation containing GHB:xylitol excipient blend 55:45. A formulation containing GHB:xylitol excipient blend 33:66 was used as a control sample. The formulations were packaged in glass vials and stored at 50° C., 40±2° C./75±5% relative humidity and 25±2° C./60±5% relative humidity. The appearance and potency of the formulations were monitored through analyses of stability samples. The stability study also showed potency losses after 1 month at 40° C.±2° C./75±5% relative humidity with both the 50/50 GHB:xylitol ratio as well as the original 33/66 ratio formulation. Partial evidence of melting was also observed in both formulations.

Studies with mixtures of GHB:xylitol excipient blend indicated that the mixture was incompatible in the solid state.

However, when prepared as an aqueous solution, these mixtures were chemically compatible. Using this information, a decision was made to package the GHB formulation in dual pouches; one pouch containing GHB alone and the other containing a mixture of xylitol and the other flavor ingredients. The formulation wiH contain equal amounts of GHB and the excipient blend. This product will be prepared, packaged, and may be checked for stability.

Example 3

The Pharmacokinetics of Gamma-Hydroxybutyrate

I. Study Objectives

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; patients generally ingested the first dose of this medication prior to bedtime and the second dose from 2.5 to 4.0 h later) to narcoleptic patients who are maintained on a chronic regimen of GHB.

II. Study Design

This pharmacokinetic study was conducted as an open-label, single-center investigation in 6 narcoleptic patients. The study design is summarized as follows:

TABLE 12

Screening/Washout⇒	Treatment/Blood Sampling⇒	Follow-up
(1 or more days to dosing; washout, at least 8 h	(Two 3 g GHB oral doses, 4 h apart; 21 blood samples)	(Within 48 h after last blood sample)

Narcoleptic patients, 18 years of age or older, who volunteered for this study were screened at least one day prior to the treatment phase. Each patient was determined to be in stable health and evaluated for the presence of narcolepsy, defined for the purposes of this example as one or more years of medical history of narcolepsy as evidenced by a recent nocturnal polysomnogram (PSG) and a valid score from a Multiple Sleep Latency Test (MSLT).

Patients maintained on GHB were allowed to participate. These patients had been weaned from antidepressants, hypnotics, sedatives, antihistamines, clonidine, and anticonvulsants though a stable regimen of methylphenidate (immediate release or sustained release) was allowed. Each patient passed a pre-study physical examination (which included hematology, blood chemistry, urinalysis, and vital signs measurements) prior to the commencement of the treatment phase.

Before oral administration of the first GHB dose, an indwelling catheter was placed in an arm vein and a baseline blood sample was collected. Each patient then ingested a 3 g dose of GHB before bedtime. Another 3 g GHB dose was administered 4 h after the first dose. Twenty-one sequential blood samples were collected over 12 h (starting at 10 min after the first dose and ending at 8 h after the second dose). Upon completion of the treatment phase, a follow-up physical examination which included the measurement of vital signs was performed on each patient within 48 h after the last blood sample. A detailed description of the trial methodology is presented in Section IV.

III. Inclusion Criteria

Patients were included in the study if they: had signed an informed consent prior to beginning protocol required procedures; had not participated in such a study at an earlier date; were willing and able to complete the entire study as described in the protocol; were 18 years of age or older at study entry; had not taken any investigational therapy other than GHB within the 30-day period prior to screening for this study; had an established diagnosis of narcolepsy for at least one year with documentation from a qualified laboratory by a nocturnal polysomnogram (PSG) and a Multiple Sleep Latency Test (MSLT) which demonstrated mean sleep latency to be less than 5 min and REM onset in at least 2 of 5 naps; had not been diagnosed with uncontrolled sleep apnea syndrome, defined as a sleep Apnea Index of 5 or an Apnea Hypopnea Index (AHI) greater than 10 per hour or any other cause of daytime sleepiness; and were free of any medication for their narcolepsy (including hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants) other than GHB and methylphenidate (IR or SR). Patients admitted to this study if they were not experiencing unstable cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, metabolic, neurological, pulmonary, and/or renal disease which would place them at risk during the study or compromise the protocol objective; did not have neurological or psychiatric disorders (including transient ischemic attacks, epilepsy, or multiple sclerosis) which, in the investigator's opinion, would preclude the patients' participation and completion of this study; did not have a current or recent (within one year) history of alcohol or drug abuse; did not have a serum creatinine greater than 2.0 mg/dL, abnormal liver function tests (SGOT or SGPT more than twice the upper limit of normal or serum bilirubin more than 1.5 times normal). Female patients were entered into the study if they were either post-menopausal (i.e. no menstrual period for a minimum of 6 months), surgically sterilized or provided evidence of effective birth control. Females of childbearing potential must agree to continue to use an IUD, diaphragm, or take their oral contraceptives for the duration of the study. Female patients of childbearing potential must have a negative pregnancy lest upon entry into the study.

IV. Trial Methodology

A time and events schedule is presented in Table 12.

A. Screening Period/Washout

Six narcoleptic patients who were chronically being treated with GHB were recruited to participate in this pharmacokinetic study. The screening period was at least one day prior to the treatment phase. During the screening period each patient completed the following procedures for the assessment of their physical condition: medical history evaluation; physical examination evaluation; clinical laboratory evaluation; inclusion criteria review. Each patient's GHB and methylphenidate regimen also were recorded on an appropriate case report form (CRF). The investigator also ensured that there was at least an 8-hour washout period for GHB prior to the treatment.

B. Treatment Period/Blood Samples Collection

All patients were hospitalized from approximately four hours prior to first GHB dosing (around 6 p.m.) until the end of the treatment period (around 10 a.m. the next morning). Patients ate their dinner at the clinical research unit soon after arrival and fasted until breakfast next morning. At least three hours elapsed between the completion of dinner and the administration of the first GHB dose. An indwelling catheter was placed in an arm vein of each patient for blood sampling at approximately 30 min and 1 h before the first GHB dose and a baseline blood sample (5 mL) was collected.

The first GHB dose (3 g) was administered at around 10 p.m. Dosing of individual patients were staggered. The second GHB dose was administered at 4 h after the first GHB dose (i.e. immediately after the 4 h blood sample). The exact dosing times in each patient were recorded on appropriate CRF pages. Blood samples (5 mL each) were collected

through the indwelling catheter into heparinized tubes at 0.2, 0.4, 0.6, 0.8, 1, 1.5, 2, 3, 4, 4.2, 4.4, 4.6, 4, 8, 5, 5.5, 5, 7, 8, 10, and 12 h after the first GHB dose. Blood samples were processed according to the procedures described herein. Patients were monitored for adverse experiences throughout the study according to the specific procedures.

C. Follow-Up

Follow-up occurred within 48 h after the last blood sample had been collected. An abbreviated physical examination which included vital signs measurement was performed. Adverse experiences and concomitant medication use, if any, were assessed. Any ongoing adverse experiences and clinically important findings in a patient were followed to the investigator's and/or sponsor's satisfaction before the patient was discharged from the study.

D. Methods of Assessment

1. Medical History

The medical history was recorded during the screening period. The history included gender, age, race, height, prior reaction to drugs, use of alcohol and tobacco, history and treatment, if any, of cardiovascular pulmonary, gastrointestinal, hepatic, renal, immunologic, neurological, or psychiatric diseases and confirmation of inclusion criteria.

2. Physical Examination

Physical Examination included body system review as well as measurement of body weight and vital signs and a neurological examination.

3. Vital Signs

Vital signs measurements included recording of blood pressure, heart rate, respiration, and body temperature.

4. Clinical Laboratory

All clinical laboratory tests were performed at a local laboratory. The laboratory tests and analysis were required of each patient included: hematology, including hemoglobin, hematocrit, red blood cell count, white blood cell count and differential; fasting blood chemistries included blood urea nitrogen (BUN), uric acid, glucose, creatinine, calcium, phosphorus, total protein, albumin, sodium potassium, SCOT (AST), SGPT (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), and total bilirubin; midstream catch urinalysis included specific gravity, pH, protein, occult blood, ketones and glucose by dipstick determination as well as a microscopic examination of urine sediment for RBC, WBC, epithelial cells or casts or crystals; and a urine pregnancy test, if applicable. Any laboratory parameter that was out of range and considered clinically significant excluded the patient from participation in this study. The investigator would provide an explanation of all observations that were significantly outside the reference range.

5. Concomitant Medication

The continued use of a fixed dose of methylphenidate immediate release or sustained release (IR or SR) is acceptable. The methylphenidate regimen was recorded on the appropriate case report form.

6. Adverse Experiences

An adverse experience are any undesirable event experienced by a patient or volunteer whether or not considered drug-related by the investigator. An undesirable event can be, but is not limited to, subjective symptoms experienced by a patient or, objective findings such as significant clinical laboratory abnormalities. Adverse experience is considered synonymous with the term "adverse event".

The investigators report in detail all adverse experiences and symptoms that occurred during or following the course of trial drug administration for up to 2 days. Included in the description was the nature of the sign or symptom; the date of onset; date or resolution (duration); the severity; the relationship to trial treatment or other therapy; the action taken, if any; and the outcome.

A serious adverse experience is defined as one that is fatal, life threatening, permanently disabling, or which results in or prolongs hospitalization. In addition, overdose, congenital anomaly and occurrences of malignancy are always considered to be serious adverse experiences. An unexpected adverse experience is one not previously reported.

Any serious or unexpected adverse experience (including death) due to any cause which occurs during the course of this investigation, whether or not it is related to the investigational drug, was reported within 24 h by telephone or facsimile. Appropriate authorities were to be informed if the serious or unexpected adverse experience, in the opinion of inventors, was likely to affect the safety of other patients or volunteers or the conduct of the trial.

7. Clinical Supplies-Study Medication

Formulation: Unit 3 g GHB doses (Lot PK1) were obtained from Orphan Medical. Each unit dose comprised twin foil pouches: one pouch containing GHB and the other containing a flavor excipient blend. (Table 8 formulation)

Labeling: The clinical supplies for individual patients were packaged in separate containers. Each container included two unit doses, i.e. two twin-pouches. Clinical supplies for eight patients (including those for two replacement patients) were delivered to the investigator. Foil twin-pouches were identified with a two-part label.

Dose Administration: The investigator or designee prepared the oral solution for dosing within 30 min prior to the first oral administration to individual patients. The contents of one twin-pouch was emptied into a dosing cup to which, two ounces of water were added. After replacing the lid of the dosing cup, it 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 ingesting in its entirety at 4 h after the first GHB dose.

Investigational Drug Accountability: At the conclusion of the study, all clinical supplies were accounted for on the drug accountability form and unused drug supplies were returned for proper disposition.

8. Determination of Plasma GHB Concentrations

Plasma samples were analyzed for GHB by the Department of Bioanalytical Chemistry (Covance (previously known as Hazelton Coming), Madison, Wis.) A gas chromatographic method with mass selective detection (GC-MSD) was used in the analysis.

9. Data Management and Analysis

Data Base: An EXCEL data base (spreadsheet) was constructed from data recorded on Case Report Forms (CRF) and plasma GHB concentration data sets received from Covance (Corning Hazleton). Each entry in the EXCEL spreadsheet was checked against the CRFs and any data entry error found was corrected.

Pharmacokinetic Analysis: Pharmacokinetic parameters were determined for individual sets of plasma GHB concentration vs. time data using the non-compartmental routine in WinNonlin Version 1.1. The peak GHB concentrations (C_{max}) and the times of their respectively occurrences (t_{max}) were observed values. Terminal half-life ($T_{1/2}$) was obtained by log-linear regression analysis of the terminal phase of concentration vs. time curves. The area under the curve (AUC_{inf}) and the area under the first moment curve ($AUMC_{inf}$) were calculated by the linear trapezoidal rule up to the last determined concentration and included extrapolated areas to time infinity. Apparent oral clearance (CL/F) was

calculated as Dose/AUC_{inf}. Volume of distribution (V_z/F) was determined by taking the ratio between CL/F and λ_z (elimination rate constant). Mean residence time (MRT) was estimated from the ratio between $AUMC_{inf}$ and AUC_{inf}.

Safety Analyses: Results of physical examinations, vital signs, clinical laboratory data were summarized in tabular form and presented by patient number. Adverse events also were tabulated in a similar fashion.

10. Results

Patient and Study Accountability: Six narcoleptic patients were enrolled and all six completed the study in its entirety.

Protocol Compliance: There were no inclusion criteria violations. All patients admitted into the study met the study entrance requirements and completed the screening phase at least one day before the treatment phase.

All six patients took non-study medications in addition to methylphenidate and GHB doses because none of their concomitant medications (Synthroid, Premarin, Lovastatin, Fluvastatin, furosemide, potassium, hydrochlorothiazide, lansoprazole, and verapamil) were on the exclusion list (which included hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants). Adverse experience probes, vital sign measurements, and essentially all pharmacokinetic blood samples were performed at protocol specified times; the few deviations in blood sampling times should not have any impact on the outcome of the study since actual blood sampling times were used in the pharmacokinetic analysis.

The diagnosis of narcolepsy for at least one year in each patient was verified by a nocturnal polysomnogram (NSG) and a Multiple Sleep Latency Test (MSLT) conducted at a qualified laboratory. Five patients have been maintained on GHB nightly for over 10 years and one patient has been receiving GHB nightly for two years. One patient (Subject 101) also had multiple sclerosis; however, the attending physician, judged that it would not interfere with the objective of this study. A few of the screening clinical laboratory results marginally fell outside the reference range but none was considered by the attending physician to be clinically significant.

Exposure to Study Drug: All patients ingested the two GHB doses as scheduled (immediately prior to bedtime). The GHB doses per kg body weight ranged from 26.4 to 52.4 mg/kg.

Plasma GHB Concentration Profiles: It was noted that, in certain cases, (Patients #103, and #106), plasma GHB concentrations did not decline from the first C_{max} to zero concentration at h 4. Upon achievement of the second C_{max} the semi-logarithmic plots of concentration versus time data in Patients #102, #103, and #105 exhibited a convex decline profile. Such a decline pattern suggested non-linear pharmacokinetics. The highest plasma GHB concentration observed in the study was 125.0 μg/mL which occurred in Subject 101 after the second 3 g GHB dose.

Pharmacokinetic Parameter Estimates: The mean (±SD) showed that maximum GHB concentrations (C_{max}) were 62.8±27.4 μg/mL and 91.2±25.6 μg/mL for the first and second GHB doses, respectively. The corresponding mean observed times to maximum concentrations were 40±6 and 36±7 min after the first and second GHB doses, respectively. The mean AUC_{inf} was 17732±4603 μg/mL·h. The mean CL/F was 4.2±mL/min/kg and the mean V_z/F was 307±96 mL/kg. The mean MRT_{inf} was 249±56 min. The mean GHB $T_{1/2}$, estimated by linear regression of log [C] vs. time data of the terminal phase of the second GHB dose was 53±19 min.

Adverse Experiences: No adverse experiences were reported in the study.

Follow-up Safety Assessments: Inspection of screen and follow-up physical examination results per individual patient did not identify any changes attributable to GHB.

11. Discussion

To the inventors' knowledge, the level of GHB in human systemic circulation has not been reported in the literature. Hence, baseline (0 h) plasma samples were analyzed for GHB concentrations. The GC-MSD method used in the present study had a limit of quantification (LOQ) of 7.02 μg/mL and analysis of the baseline plasma samples showed the endogenous levels of GHB are below this sensitivity limit. This finding was confirmed by adding known amounts of GHB (5, 10, and 25 μg per mL of plasma) to blank human plasma samples and subjected these samples to GC-MSD analysis. This method of standard addition allowed an estimation of the endogenous GHB level in human plasma which was found to average about 2.02 μg/mL, (i.e. approximately 2/7 of the Limit Of Quantitation (LOQ) for a validated assay. Hence, the endogenous GHB level was not subtracted from exogenous GHB concentrations prior to pharmacokinetic analysis.

Values of mean t_{max} (~40 min after dosing) and $t_{1/2}$ (~35 min) suggest that the GHB solution administered to narcoleptic patients in this study was readily absorbed and rapidly eliminated. In 3 out of 6 patients the drug was essentially gone from the systemic circulation by h 4 after the first GHB dose whereas in the remaining three patients residual GHB levels of ~15 μg/mL was still detected at h 4.

The convex nature of the decline of plasma GHB concentrations in three patients after achievement of the second c_{max} indicated that elimination of GHB from the systemic circulation in these three patients is capacity limited. Nevertheless, it should be noted that plasma GHB concentrations were no longer detectable by h 6 after the second GHB dose (10 h after the first GHB dose). The mean apparent oral clearance found in this study was 4.2±1.0 mL/min/kg and appeared to be comparable to the apparent oral clearance of 5.3±2.2 mL/min/kg reported in the literature for a group of alcohol dependent patients who were administered a dose of 50 mg/kg (Ferrara, 1992). While it appeared that the GHB dose (ranging from 26.4 to 52.4 mg/kg with a mean of 36.5 mg/kg) in the present study was lower than the comparison GHB dose (50 mg/kg) administered to the alcohol dependent patients (Ferrara, 1992), it should be noted that each patient in the present study was administered two consecutive GHB doses at four-hour interval and residual GHB levels were detected in three out of six patients immediately prior to the second GHB dose. The GHB pharmacokinetic non-linearity in alcohol dependent patients easily can be observed from the apparent oral clearance which increased to 8.1±4.8 mL/min/kg when the GHB dose is reduced to 25 mg/kg dose (Ferrara, 1992). In the present study, the non-linearity was less obvious because each narcoleptic patient received two consecutive fixed 3 g doses regardless of body weight.

The mean elimination half-life of GHB in the six narcoleptic patients was determined to be 53±19 min, longer than that in alcohol dependent patients after a 50 mg/kg GHB dose (Ferrara, 1992). The lengthening of GHB elimination half-life observed in this study partially was caused by the wider spacing in sampling time points. However, capacity limited elimination of this drug in some of the narcoleptic patients also could have contributed to this prolongation.

GHB appears to have a shortcoming in that its elimination from the body is capacity limited in some patients when the drug is administered at a fixed regimen of 3 g twice nightly at four-hour interval. However, from a therapeutic perspective, GHB offers an advantage in the treatment of narcolepsy because by the time a patient wakes tip in the morning (i.e. 8

to 10 h after the first GHB dose), all GHB, including that from the second dose, will have been eliminated from the systemic circulation. GHB was also well tolerated by narcoleptic patients in this study. No adverse experience was reported.

12. Conclusions

The capacity limited elimination kinetics was observed in three out of six patients who had been administered two consecutive 3 g oral doses of GHB, 4 h apart. From a pharmacokinetic perspective, dividing the nightly GHB dose into two portions and administering the two portions to narcoleptic patients at a 2.5- to 4-h interval was rational because the elimination half-life of GHB was short (<1 h). The pharmacokinetic profiles of GHB in narcoleptic patients who had been receiving this agent nightly for years appeared to be comparable to those in alcohol dependent patients (Ferrara, 1992).

Example 4

Sodium Oxybate Formulation Study

I. Study Objectives

This example described ways that sodium oxybate may be prepared and tested for stability to determine preferred formulations. Various formulations of sodium oxybate in water were prepared under different conditions of mixing and with addition of selected acidulents at multiple pH levels (Neo-Pharm Laboratories, Blainville, Quebec). Selected formulations were placed on real time and accelerated stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Therefore several acidulents across a range of 6.0-9.0 were evaluated.

II. Study Design-Part I

The following experimental work is designed to be performed in two stages. Initial studies were conducted to evaluate the impact of conditions of formulation, pH and acidulent on the resultant levels of impurities, specified and unspecified, and potency of sodium oxybate. Sodium oxybate was prepared (MDS Neo-Pharm Laboratories, Quebec Canada), under different conditions of mixing and with addition of selected acidulents at multiple pH levels. These formulations of sodium oxybate acidulent were then tested.

A. Preliminary Studies

1. Formulations Description

All formulations were prepared at a concentration of 500 mg/cc of sodium oxybate in water. Three acidulents (HCl, malic acid, and phosphoric acid), were selected and tested at pH 6.0, 7.5 and 9.0.

2. Method of Formulation

Solutions, were prepared using the described methods:

a. Rapid Mix Method:

Sodium oxybate was dissolved in water and concentrated acidulent was added immediately, without temperature control. Temperature of solution was monitored and recorded prior to and during addition of acidulent. The time of equilibration to room temperature was also recorded. After the solution reached ambient room temperature, it was filtered through a 10 μm filter.

b. Cool Mix Method:

Sodium oxybate was dissolved in water. Acidulent was diluted to 10% and slowly added. The solution was cooled by water with jacket or ice bath. Monitor and record the temperature of the solution was monitored and recorded during addition of acidulent. The time of equilibrium from room temperature was also recorded. The preferred maximum temperature should be maintained at less than 40° C. The solution was filtered through a 10 μm filter.

c. Reverse Order of Addition:

Acidulent was added to water and cooled to room temperature. The sodium oxybate was dissolved in the diluted acidulent solution. The temperature of solution was monitored and recorded during addition of sodium oxybate. The solution was filtered through a 10 μm filter.

d. Sodium Oxybate Control:

Sodium oxybate was dissolved in water to a concentration of 500 mg/cc with no added acidulent. The final pH was recorded and the solution was filtered through a 10 μm (micron or micrometer) filter.

3. Solution Data:

Data was recorded for each solution which included: 1) date of preparation 2) date of analysis, 3) amount of acidulent required to achieve target pH, 4) length of time for dissolution of sodium oxybate, 5) temperature profile of solution over time of solution preparation to be recorded at 15 minute intervals, 6) final pH of solution.

4. Testing Requirements:

The following methods were used to test the prepared solutions: pH, HPLC (High Pressure Liquid Chromatography) for potency (sodium oxybate), and for impurities. Time 0 analysis was performed immediately (within 24 h). RRT= (relative retention time).

B. Summary of Part I:

1. Preliminary Evaluation of Sodium Oxybate Formulations

Tables 13, 14 and 15 provide test results for the three methods of preparation of sodium oxybate formulations.

TABLE 13

Formulation Study/PR98068
Results of Formulation Study - Time Zero determinations of
Sodium Oxybate, GBL and Unspecified Impurities
Preparation Method A

Addition of Concentrated Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/cc % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (Apr. 23, 1998)	pH 9.0	9.0	509 mg/cc	0.009%	RRT 4.88 = 0.01%
(10 drops over 2 minutes)			101%		
(2.5 ml/4 minutes)	pH 7.5	7.5	507 mg/cc	0.01%	RRT 4.89 = 0.02%
			101%		
(45 ml/34 minutes)	pH 6.0	6.0	504 mg/cc	0.033%	RRT 4.89 = 0.33%
			101%		
Malic Acid (Apr. 24, 1998)	pH 9.0	9.1	498 mg/cc	0.009%	RRT 4.89 = 0.01%
(0.12 gm)			99.6%		

TABLE 13-continued

Formulation Study/PR98068
Results of Formulation Study - Time Zero determinations of
Sodium Oxybate, GBL and Unspecified Impurities
Preparation Method A

Addition of Concentrated Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/cc % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
(1.6 gm)	pH 7.5	7.6	506 mg/cc 101%	0.009%	RRT 4.89 = 0.01%
(25 gm)	pH 6.0	6.2	493 mg/cc 98.6%	0.011%	RRT 4.89 = 0.01%
H_3PO_4 (Apr. 24, 1998) (2 drops)	pH 9.0	9.0	493 mg/cc 98.6%	0.009%	RRT 4.89 = 0.01%
(1.0 ml)	pH 7.5	7.5	493 mg/cc 98.6%	0.009%	RRT 4.89 = 0.02%
(17.3 ml)	pH 6.0	6.1	497 mg/cc 99.4%	0.063%	RRT 4.89 = 0.02%
Sodium Oxybate Control No Acidulent	n.a.	9.8	500 mg/cc 100%	0.009%	RRT 4.89 = 0.04%

*Method A = Mix with Concentrated Acidulent and Temperature Monitoring

TABLE 14

Preparation Method B

Addition of Diluted Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (25%) (Apr. 28, 1998) (20 drops)	pH 9.0	9.1	500 mg/cc 100%	0.009%	RRT 4.88 = 0.01%
(8.0 ml)	pH 7.5	7.6	499 mg/cc 99.8%	0.009%	RRT 4.88 = 0.01%
(175 ml)	pH 6.0	6.0	502 mg/cc 101%	0.016%	RRT 4.88 = 0.02%
H_3PO_4 (25%) (Apr. 29, 1998) (0.3 ml)	pH 9.0	8.9	499 mg/cc 99.8%	0.007%	RRT 4.92 = 0.02%
(4.0 ml)	pH 7.5	7.5	497 mg/cc 99.4%	0.008%	RRT 4.89 = 0.02%
(120 ml)	pH 6.0	6.0	499 mg/cc 99.8%	0.019%	RRT 4.89 = 0.01%
Malic Acid (500 mg/cc) (Apr. 30, 1998) (0.115 gm/0.23 ml)	pH 9.0	9.0	495 mg/cc 99%	0.008%	RRT 4.92 = 0.02%
(1.75 gm/3.5 ml)	pH 7.5	7.4	488 mg/cc 97.5%	0.009%	RRT 4.92 = 0.01%
(35 gm/70 ml)	pH 6.0	6.0	487 mg/cc 97.0%	0.013%	RRT 4.92 = 0.01%

*Acidulent added slowly at the rate of 2-3 drops/second

TABLE 15

Preparation Method C

Reverse Order of Addition* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (May 1, 1998) (20 drops)	pH 9.0	9.0	497 mg/cc 99.4%	0.006%	RRT 4.92 = 0.03%
(2.4 ml)	pH 7.5	7.6	504 mg/cc 101%	0.004%	RRT 4.92 = 0.04%
(45 ml)	pH 6.0	6.0	493 mg/cc 98.6%	0.044%	RRT 4.92 = 0.04%
H_3PO_4 (May 4, 1998) (0.08 ml)	pH 9.0	8.9	496 mg/cc 99.2%	0.005%	RRT 4.91 = 0.03%
(1.0 ml)	pH 7.5	7.6	496 mg/cc 99.2%	0.004%	RRT 4.91 = 0.04%

TABLE 15-continued

Preparation Method C					
Reverse Order of Addition* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
(30 ml)	pH 6.0	6.1	489 mg/cc 97.8%	0.023%	RRT 4.91 = 0.04%
Malic Acid (May 5, 1998) (0.12 gm)	pH 9.0	9.0	495 mg/cc 99%	0.006%	RRT 4.93 = 0.02%
(1.6 gm)	pH 7.5	7.6	497 mg/cc 99.4%	0.004%	RRT 4.93 = 0.04%
(35 gm)	pH 6.0	6.2	495 mg/cc 99%	0.044%	RRT 4.93 = 0.04%

*Acidulent added to water first, GHB added second.

Review of the data indicated that the optimum method for preparation of sodium oxybate with minimal impurity levels is Method B: Controlled mixing with diluted acidulent. Method 2b resulted in formulations with lowest levels of GBL.

2. Conclusions.

Additional evaluations were carried out on selected formulations: 1) sodium oxybate with HCl as acidulent, at pH 7.5, and 2) sodium oxybate with malic acid as acidulent, pH 6.0, 7.5, and 9.0.

III. Study Design—Part II

Microbial Challenge and Stability Tested to determine the most preferred embodiments, the number of formulations was limited to three based on the data prepared from the above experiments.

A. Kinetic Stability Study with Selected Formulations

Samples of formulations are stored in tightly closed containers. Storage Conditions were 25° C., 40° C., and 60° C. Time points in brackets were tested at the inventor's discretion. The samples were tested according to the following schedule: at 25° C. storage temperature, the assay points will be 0, 14, 28, 45, 60 days and 120 days; at 40° C. storage temperature, the assay points will be 0, 7, 14, 28, 45, 60 days; at 60° C. storage temperature, the assay points will be at 0, 3, 7, 14, 28, 45 days, and, 60 days.

The testing requirements included pH, HPLC for sodium oxybate (duplicate injections of single sample preparation), and impurities, specified and unspecified.

B. Preservative Effectiveness Testing of Selected Formulations

Microbial challenge testing of formulations was preformed according to USP XXIII, <51>, Eighth Supplement. Solutions are determined to "Pass or Fail" based upon the USP criteria for preservative effectiveness which states: For Bacteria, "Not less than 1 log reduction from the initial microbial count at 14 days and no increase from the 14 days count at 28 days;" and for yeast and molds, "No increase from the initial calculated count at 14 and 28 days." Solutions which met these criteria were designated as "Pass" and those that did not meet these criteria were designated as "Fail".

C. Summary Stability Results:

1. Formulations Prepared with Malic Acid as Acidulents:

a. Malic Acid, pH 6.0 formulation (25°), GBL and impurity A levels were very low an Day 0, however, by Day 45 GBL levels had reached 2.8%. Impurity A increased from 0.01 to 1.0%, and pH increased from 6.0 to 6.3 by day 45. This formulation stored at 40° C. and 60° C. showed GBL levels up to 5.4%, impurity A levels increased to 2.3%, and pH increased to 6.3 by Day 14.

b. Malic Acid, pH 7.5 formulation (25° C.), GBL levels were 0.009% on Day 0, and increased to 0.17% by day 45. Impurity A increased from 0.01% to 0.1% and pH increased from 7.5 to 7.9. Malic acid, pH 7.5 GBL levels are reached (40° C.) and 60° C. a maximum of 0.22%. Impurity A levels reached 0.1% and pH increased to 8.0. Under accelerated conditions, all parameters reached an apparent maximum by Day 7 and did not increase significantly thereafter.

c. Malic Acid, pH 9.0 formulation (25° C.) GBL levels measure 0.008% on Day 0, and increased slightly to 0.013% on Day 45. Impurity A did not increase nor did pH increase. Under accelerated conditions, GBL increased from 0.008% to a maximum of 0.018% by Day 14. Impurity A increased slightly from 0.10 to 0.014% by Day 14.

2. Formulations Prepared with HCl as Acidulents.

HCl, pH 6.0 formulation (25°) GBL levels measured 2.8% by Day 30, and impurity A 0.004%. and pH 6.0. Accelerated storage conditions (40° C.) GBL levels were measured at 6.6%, and impurity A measured 3.1% by Day 30.

HCl, pH 7.5 formulation (25%) GBL levels measured 0.041% on Day 0, Impurity A measured 0.02%, and by Day 18 GBL measured to 0.12% and impurity A to 0.07%. Under accelerated conditions (40° C. and 60° C.), GBL increased to a maximum of 0.21%, impurity A increased from 0.02% to 0.1%, and pH increased from 7.5 to 8.0. As with Malic Acid at pH 7.5, the measured parameters reached maximum by Day 7 and did not increase significantly thereafter.

HCl, Ph 9.0 formulation (25° C.) GBL levels reached 0.022% by Day 18. Impurity A stayed constant at 0.01% for 18 days. Under accelerated conditions (40° C.) GBL levels were equivalent to 25° C. storage (0.21%). Impurity A showed no increase over 25° C. conditions.

3. Conclusions.

Formulations selected for microbial challenge testing were the following: HCl, Ph 7.5, and malic acid, Ph 7.5. The rationale for this decision was twofold. First, the formulations were selected based on minimal formation of GBL and impurity A. Second, the formulations were selected to maintain a Ph in the neutral range.

Example 5

Further Evaluation of Sodium Oxybate Formulations

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of gamma-hydroxybultyrate.

Scope: Various formulations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple Ph levels. Solutions were prepared and tested at Neo-Pharm Laboratories, Blainville, Quebec. All formulations successfully prepared were placed on limited stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high Ph. Conditions of varying Ph and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Procedures: Solutions were prepared as summarized and microbial challenge testing carried out as follows:

B. Evaluation of Sodium Oxybate Formulations

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of gamma-hydroxybutyrate.

Scope: Various formulations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple Ph levels. Selected formulations were studied for limited stability. Earlier studies demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high Ph. Conditions of varying Ph and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Responsibility: It was the responsibility of Neo-Pharm Laboratories to prepare selected formulations and perform testing per this protocol. Orphan Medical, New Medicine Development and Quality Assurance were responsible for reviewing raw data at the defined decision point, defining which formulations will be included in stability testing. Orphan Medical was also responsible for reviewing final results (raw data) and the final report.

Procedure: The following formulations were prepared by scientists at Neo-Pharm following the steps listed below and dispensed into containers (amber PET 240 ml bottle, OMI CS-460) and closures (Clic-Loc III, 24-400, OMI CS-470) to a volume of 200 ml each bottle. The bottles were tested by 28-day microbial challenge and by limited stability testing at 25° C. including appearance, Ph, potency, and impurity profile on day 1 (day of preparation) and day 28.

B. Formulations Prepared and Evaluated Using Sodium Oxybate:

TABLE 16

Formulations Prepared and Evaluated Using Sodium Oxybate

Formulation ID No.	Sodium Oxybate Concentration	Acidulent	Final Ph
1	500 mg/cc	Malic Acid	7.5
2	250 mg/cc	Malic Acid	7.5
3	350 mg/cc	Malic Acid	7.5
4	450 mg/cc	Malic Acid	7.5
5	550 mg/cc	Malic Acid	7.5
6	650 mg/cc	Malic Acid	7.5
7	500 mg/cc	Citric Acid	7.5
8	500 mg/cc	Malic Acid	5.0

1. Preparation: Method for preparation of various formulations: As previously determined in PR98068, the method of choice for preparation of liquid formulations of sodium oxybate was the following:
   a. For a one liter quantity of product, add the sodium oxybate in 500 ml of purified and stir until dissolved. Prepare a 10% solution of the acid (Malic or Citric) and add slowly to the solution of sodium oxybate. The solution should be monitored for Ph and temperature and both variables recorded at reasonable intervals (every 10 or 15 minutes). When the target Ph is attained, the solution will be Q. S. to 1 liter and Ph rechecked and recorded.
   b. The final solutions will be filtered through 10 μm filters and 200 Ml dispensed into 5 amber PET bottles with closures (□rovide by Orphan Medical, Inc.). Two bottles will be used for microbial challenge studies and the remaining three bottles will be placed on limited stability.
2. Testing: Formulations were tested by two methods of evaluation:
   a. Limited stability evaluation:
      (1) Storage Conditions: 25° C.
      (2) Pull Points: Day 0 (day of preparation), and day 28
      (3) Testing Requirements:

Test	Method
Appearance	Visual
Potency	HPLC Neopharm 764
Impurities	HPLC Neopharm 793DT
Ph	USP <791>

   b. Microbial Challenge:
      (1) Storage Conditions: Microbial challenge studies of above formulations were set up with 5 microorganisms and stored for 28 days at 20–25° C., per USP <51> Eighth Supplement.
      (2) Microorganisms: After a sufficient quantity of each formulation is prepared, aliquots were inoculated with 5 microorganisms at a concentration of at least 10^5 microorganisms/cc:
         (a) *Escherichia coli*, ATCC 8739
         (b) *Pseudomonas aeruginosa*, ATCC 9027
         (c) *Staphylococcus aureus*, ATCC 6538
         (d) *Aspergillus niger*, ATCC 18404
         (e) *Candida albicans*, ATCC 10231
      Time Points: A determination of the viable cell concentration in each inoculated container was performed after 0, 1, 3, 7, 14, 21 and 28 days.

B. Formulations To Be Prepared From Alternative Salts of Gamma-Hydroxybutyrate: This work may be staged to take place at a later time than the work described above.

TABLE 17

Formulation Detail

Formulation ID No.	Salt of GHB	Concentration of Salt of GHB	Acidultent	Final pH
9	Calcium salt	500 mg/cc (Or maximum possible*)	Malic Acid (If compatible)	7.5

1. Solubility determination: Little information is available about the solubility of this alternative salt of gamma-hydroxybutyrate and a determination of solubility was done in advance of efforts to prepare formulations for evaluation by stability and microbial challenge. Maximum solubility is evaluated for pH unadjusted solutions and within the pH range desired for this formulation (pH 6.0-8.0). If solubility is limited, the formulation will be changed to accommodate the solubility limitations. The preferred acidulent for this work is Malic acid. If acid is not compatible with the salt, then an alternative acid can be selected.

2. Preparation: Method for preparation of alternative salt formulations:
   a. The previously described method (Part A) is used for preparation of formulations of calcium gamma-hydroxybutyrate at the concentrations and specified pH determined by solubility experiments.
   b. The final solutions were filtered through 10 μm filters and dispensed into 5 amber PET bottles with closures (provided by Orphan Medical, Inc.). Two bottles are used for microbial challenge studies and two bottles are placed on limited stability. The remaining bottles are retained for any additional studies at a future time.
3. Testing: Formulations are tested as described above.

C. Reporting of Results: The results will be reported for the Stability and Microbial Challenge results in standard format as defined by the described Orphan Medical Development. Copies of HPLC chromatograms and any raw data from these studies will be provided with results.

D. Acceptance Criteria: Specific acceptance criteria for this study can be described analogous to those for sodium oxybate.

Results: Summarized as follows in Tables 18, 19 and 20 for various studies.

TABLE 18

Result Summary
Results of Protocol 98126 Microbial Challenge Study

Lot Number MCH1064-33						
GHB, pH 7.50, 500 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	490,000	5,500	<100	<10	<10	<10
P. aeruginosa	141,000	21,600	<100	<10	<10	<10
S. aureus	1,035,000	405,000	79,500	8,300	1,645	375
C. albicans	835,000	147,000	<100	<10	<10	<10
A. niger	370,000	285,000	120,500	246,500	148,500	183,000
Lot Number MCH1064-35						
GHB, pH 7.50, 250 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	705,000	229,500	<100	<10	<10	<10
P. aeruginosa	224,500	5,200	<100	<10	<10	<10
S. aureus	1,135,000	390,000	262,500	31,500	4,250	155
C. albicans	705,000	435,000	52,000	850	<10	<10
A. niger	510,000	515,000	155,500	176,000	147,500	184,000
Lot Number MCH1064-37						
GHB, pH 7.50, 300 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	365,000	310,000	13,400	<10	<10	<10
P. aeruginosa	205,000	15,600	50	<10	<10	<10
S. aureus	1,170,500	605,000	67,500	<60	60	<10
C. albicans	870,000	355,000	8,300	<10	<10	<10
A. niger	540,000	525,000	172,000	155,500	155,500	163,500
Lot Number MCH1064-43						
GHB, pH 7.50, 550 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	425,000	63,500	700	<10	<10	<10
P. aeruginosa	171,500	211,550	250	<10	<10	<10
S. aureus	1,020,000	520,000	41,500	1,050	180	10
C. albicans	880,000	157,500	800	<10	<10	<10
A. niger	545,000	505,000	131,000	156,500	205,000	187,500
Lot Number MCH1064-45						
GHB, pH 7.50, 550 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	660,000	58,500	450	<10	<10	<10
P. aeruginosa	896,000	14,450	900	<10	<10	<10
S. aureus	860,000	132,000	19,750	935	110	45
C. albicans	1,125,000	166,000	<100	<10	<10	<10
A. niger	530,000	530,000	105,500	153,000	157,500	177,000

TABLE 18-continued

Result Summary
Results of Protocol 98126 Microbial Challenge Study

Lot Number MCH1064-47						
GHB, pH 7.50, 650 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	630,000	119,000	1,350	<10	<10	<10
P. aeruginosa	183,500	5,900	50	<10	<10	<10
S. aureus	890,000	650,000	76,000	14,550	510	1,150
C. albicans	675,000	145,500	<100	<10	<10	<10
A. niger	535,000	385,000	103,000	162,000	187,000	173,000
Lot Number MCH1064-85						
Ca-Oxybate, pH 7.50, 500 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	425,000	121,000	1,650	<10	<10	<10
P. aeruginosa	420,000	22,000	300	<10	<10	<10
S. aureus	265,000	2,000	<100	<10	<10	<10
C. albicans	565,000	440,000	29,500	<1000	<10	<10
A. niger	1,310,000	965,000	370,000	640,000	690,000	675,000
Lot Number MCH1064-49						
GHB, pH 7.50, 500 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	615,000	6,500	<100	<10	<10	<10
P. aeruginosa	69,500	14,600	<100	<10	<10	<10
S. aureus	650,000	305,000	1,700	<10	<10	<10
C. albicans	720,000	107,000	<100	<10	<10	<10
A. niger	375,000	380,000	99,500	178,500	212,500	165,500

TABLE 19

Result Summary
Data from Dec. 30, 1997

GHB (pH 7.5) (n = 3) 750 mg/cc	Inoculu	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	470,000	160,000	64,500	4,300	420	<10	<10	<10
P. aeruginosa	437,500	152,000	3,500	10	<10	<10	<10	<10
S. aureus	447,500	330,000	24,500	42,000	8,050	1,935	15	10
C. albicans	375,000	234,500	28,000	1,950	<10	<10	10	<10
A. niger	475,500	395,000	395,000	229,000	101,500	161,500	101,000	202,000
750 mg/cc + 0.2% MP/PP, pH 7.50								
E. coli	470,000	127,000	<1,000	<10	<10	<10	<10	<10
P. aeruginosa	437,500	61,000	<1,000	<10	<10	<10	<10	<10
S. aureus	447,500	350,000	3,000	4,050	<10	<10	<10	<10
C. albicans	375,000	103,500	<1,000	<10	<10	<10	<10	<10
A. niger	457,500	315,000	415,000	35,500	79,500	38,500	87,500	6,400
750 mg/cc + 0.1% MP/PP, pH 7.5								
E. coli	470,000	157,000	7,000	<10	<10	<10	<10	<10
P. aeruginosa	437,500	90,000	<1,000	<10	<10	<10	<10	<10
S. aureus	447,500	239,000	5,500	16,950	600	<10	<10	<10
C. albicans	375,000	169,000	<1,000	<100	<10	<10	<10	<10
A. niger	457,500	335,000	425,000	34,500	168,500	90,500	95,500	99,000
750 mg/cc + 0.2% Potassium sorbate, pH 7.5								
E. coli	470,000	180,000	735,000	6,200	475	<10	<10	<10
P. aeruginosa	437,500	152,000	1,000	<10	<10	<10	<10	<10
S. aureus	447,500	264,000	27,500	49,800	14,550	2,370	<10	<10
C. albicans	375,000	300,000	41,500	3,800	<10	<10	<10	<100
A. niger	457,500	325,000	360,000	25,000	202,000	500,000	345,000	425,000

GHB (pH 6.0) 500 mg/cc	Inoculu	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Results
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10	
P. aeruginosa	437,500	172,000	3,000	<10	<10	<10	<10	<10	
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10	
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10	

TABLE 19-continued

Result Summary
Data from Dec. 30, 1997

A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600	
									PASS
500 mg/cc + 0.2% MP/PP, pH 6.0									
E. coli	470,000	163,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	60,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	243,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	150,500	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	400,000	38,000	<10	<10	<10	<10	<10	
									PASS
500 mg/cc + 0.1% MP/PP, pH 6.0									
E. coli	470,000	206,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	118,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	330,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	221,000	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	355,000	93,500	59,000	8,700	315	35	>10	
									PASS
500 mg/cc + 0.2% Potassium sorbate, pH 6.0									
E. coli	470,000	222,000	46,500	150	<10	<10	<10	<10	
P. aeruginosa	437,500	136,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	410,000	<1,000	130	<10	<10	<10	<10	
C. albicans	375,000	395,000	28,500	<100	<10	<10	<10	<10	
A. niger	475,500	405,000	270,000	63,000	51,000	49,500	39,000	11,150	
									PASS

TABLE 20

Result Summary

Data from Study Dated Dec. 30, 1997

GHB (pH 6.0) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10
P. aeruginosa	437,500	172,000	3,000	<10	<10	<10	<10	<10
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10
A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600

Data From Study Begun Mar. 12, 1998

GHB (pH 6.0) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	500,000	370,000	Nd	Nd	<100	<10	<10	<10
P. aeruginosa	350,000	198,500	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	480,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	340,000	Nd	Nd	<100	<10	<10	<10
A. niger	450,000	445,000	Nd	Nd	9,050	20,500	9,450	1,120
E. coli	500,000	199,000	Nd	Nd	<100	<10	<10	<10
P. acruginosa	350,000	192,500	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	300,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	370,000	Nd	nd	<100	<10	<10	<10
A. niger	450,000	445,000	Nd	Nd	10,100	22,750	3,800	4,050

Data From Study Begun Mar. 12, 1998

GHB (pH 9.0) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	500,000	320,000	Nd	Nd	<100	<10	<10	<10
P. aeruginosa	350,000	12,000	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	495,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	380,000	Nd	Nd	<100	<10	<10	<10
A. niger	450,000	355,000	Nd	Nd	12,550	157,500	365,000	365,000

TABLE 20-continued

Result Summary

GHB (pH 6.0 + Excipients) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	500,000	96,000	Nd	Nd	<100	<10	<10	<10
P. aeruginosa	350,000	26,000	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	155,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	205,000	Nd	Nd	<100	<10	<10	<10
A. niger	450,000	131,500	Nd	Nd	6,250	1,825	870	370

GHB (pH 6.0 + Excipients) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	500,000	93,000	Nd	Nd	<100	<10	<10	<10
P. aeruginosa	350,000	30,500	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	185,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	135,000	Nd	Nd	<100	<10	<10	<10
A. niger	450,000	121,500	Nd	Nd	5,400	1,785	795	505

TABLE 21

Result Summary

Jul. 2, 1998 Start Date

GHB (pH 7.50) 500 mg/cc	HCl Initial Cone	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	97000	82000	19200	Nd	1000	<10	<10	<10
P. aeruginosa	48500	29500	520	Nd	<10	<10	<10	<10
S. aureus	54500	58000	42350	Nd	4950	245	<10	<10
C. albicans	58500	38500	1060	Nd	<100	<10	<10	<10
A. niger	77500	48000	21450	Nd	46000	46000	38000	54000

GHB (pH 7.50) 500 mg/cc	Malic Acid Initial Cone	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	97000	83000	44450	Nd	3050	70	<10	<10
P. aeruginoas	48500	15650	545	Nd	<10	<10	<10	<10
S. aureus	54500	59500	48400	Nd	17400	6500	820	505
C. albicans	58500	44000	6200	Nd	500	<10	<10	<10
A. niger	77500	35500	24100	Nd	28000	49000	44500	44000

For Category IC Products:
Bacteria: Not less than 1 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days.
Yeast and Molds: No increase from the initial calculated count at 14 and 28 days.

Jul. 2, 1998 Start Date

GHB (pH 7.50) 500 mg/cc	HCl Initial Co	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	9.70E+04	8.20E+04	1.92E+04	nd	1.00E+03	<10	<10	<10
P. aeruginosa	4.85E+04	2.95E+04	5.20E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.80E+04	4.24E+04	nd	4.95E+03	2.45E+02	<10	<10
C. albicans	5.85E+04	3.85E+04	1.06E+03	nd	<100	<10	<10	<10
A. niger	7.75E+04	4.80E+04	2.15E+04	nd	4.60E+04	4.60E+04	3.80E+04	5.40E+04

GHB (pH 7.50) 500 mg/cc	Malic Acid Initial Co	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	9.70E+04	8.30E+04	4.45E+04	nd	3.05E+03	7.00E+01	<10	<10
P. aeruginosa	4.85E+04	1.57E+04	5.45E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.95E+04	4.84E+04	nd	1.74E+04	6.50E+03	8.20E+02	5.05E+02
C. albicans	5.85E+04	4.40E+04	6.20E+03	nd	5.00E+02	<10	<10	<10
A. niger	7.75E+04	3.55E+04	2.41E+04	nd	2.80E+04	4.90E+04	4.45E+04	4.40E+04

TABLE 22

pH Variable Result Summary

GHB, pH 7.5 750 mg/cc Dec. 30, 1997	Inoculum	0	Day 14	Day 28	GHB, pH 6.0 500 mg/cc Dec. 30, 1997	Inoculum	0	Day 14	Day 28
E. coli	470,000	160,000	<10	<10	*E. coli*	470,000	221,000	<10	<10
P. aeruginosa	437,500	152,000	<10	<10	*P. aeruginosa*	437,500	172,000	<10	<10
S. aureus	447,500	330,000	1,935	10	*S. aureus*	447,500	320,000	<10	<10
C. albicans	375,000	234,500	<10	<10	*C. albicans*	375,000	310,000	<10	<10
A. niger	475,500	395,000	161,500	202,000	*A. niger*	475,500	270,000	48,500	8,600
GHB, pH 7.5 750 mg/cc + 0.2% MP/PP Dec. 30, 1997					GHB, pH 6.0 500 mg/cc + 0.2% MP/PP Dec. 30, 1997				
E. coli	470,000	127,000	<10	<10	*E. coli*	470,000	163,000	<10	<10
P. aeruginosa	437,500	61,000	<10	<10	*P. aeruginosa*	437,500	60,000	<10	<10
S. aureus	447,500	350,000	<10	<10	*S. aureus*	447,500	243,000	<10	<10
C. albicans	375,000	103,500	<10	<10	*C. albicans*	375,000	150,500	<10	<10
A. niger	457,500	315,000	38,500	6,400	*A. niger*	475,500	400,000	<10	<10
GHB, pH 7.5 750 mg/cc + 0.1% MP/PP					GHB, pH 6.0 500 mg/cc + 0.1% MP/PP Dec. 30, 1997				
E. coli	470,000	157,000	<10	<10	*E. coli*	470,000	200,000	<10	<10
P. aeruginosa	437,500	90,000	<10	<10	*P. aeruginosa*	437,500	118,000	<10	<10
S. aureus	447,500	239,000	<10	<10	*S. aureus*	447,500	330,000	<10	<10
C. albicans	375,000	169,000	<10	<10	*C. albicans*	375,000	221,000	<10	<10
A. niger	457,500	335,000	90,500	99,000	*A. niger*	475,500	355,000	315	<10
GHB, pH 7.5 750 mg/cc + 0.2% Potassium sorbate	xxxxxx				GHB, pH 6.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coli					*E. coli*				
P. aeruginosa					*P. aeruginosa*				
S. aureus					*S. aureus*				
C. albicans					*C. albicans*				
A. niger					*A. niger*				
GHB, pH 6.0 500 mg/cc + 0.2% Potassium sorbate Dec. 30, 1997					GHB, pH 6.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coli	470,000	222,000	<10	<10	*E. coli*	500,000	199,000	<10	<10
P. aeruginosa	437,500	136,000	<10	<10	*P. aeruginosa*	350,000	192,500	<10	<10
S. aureus	447,500	410,000	<10	<10	*S. aureus*	280,000	300,000	<10	<10
C. albicans	375,000	395,000	<10	<10	*C. albicans*	450,000	370,000	<10	<10
A. niger	475,500	405,000	49,500	11,150	*A. niger*	450,000	445,000	22,750	4,050
GHB, pH 6.0 500 mg/cc + Excipients Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 6.0 500 mg/cc + Excipients Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	93,000	<10	<10	*E. coli*	500,000	96,000	<10	<10
P. aeruginosa	350,000	30,500	<10	<10	*P. aeruginosa*	350,000	26,000	<10	<10
S. aureus	280,000	185,000	<10	<10	*S. aureus*	280,000	155,000	<10	<10
C. albicans	450,000	135,000	<10	<10	*C. albicans*	450,000	205,000	<10	<10
A. niger	450,000	121,500	1,785	505	*A. niger*	450,000	131,500	1,825	370
GHB, pH 9.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 7.50 500 mg/cc HCl Jul. 2, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	320,000	<10	<10	*E. coli*	97000	82000	<10	<10
P. aeruginosa	350,000	12,000	<10	<10	*P. aeruginosa*	48500	29500	<10	<10
S. aureus	280,000	530,000	<10	<10	*S. aureus*	54500	58000	245	<10
C. albicans	450,000	510,000	<10	<10	*C. albicans*	58500	38500	<10	<10
A. niger	450,00	345,000	158,500	110,500	*A. niger*	77500	48000	46000	54,000

TABLE 22-continued

pH Variable Result Summary

GHB, pH 9.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 7.5 500 mg/cc, Malic Acid Jul. 2, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	305,000	<10	<10	*E. coli*	97000	83000	70	<10
P. aeruginosa	350,000	20,000	<10	<10	*P. aeruginosa*	48500	15650	<10	<10
S. aureus	280,000	495,000	<10	<10	*S. aureus*	54500	59500	6500	505
C. albicans	450,000	380,000	<10	<10	*C. albicans*	58500	44000	<10	<10
A. niger	450,000	355,000	157,500	365,000	*A. niger*	77500	35500	49000	44,000

Short term stability testing was carried out as described in Appendix A and results are summarized in—Results of Limited Stability Testing—XYREM® oral solution—are shown as follows:

TABLE 23-A

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333198

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	512 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.068%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.021%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.02%	NPLC-793D
		RRT 3.79: 0.007%	
PH	Report	7.6	USP <791>
Challenge Test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 1: 500 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328841

TABLE 23-B

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331347

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	510 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.36%	NPLC-793-D

TABLE 23-B-continued

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331347

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.23% RRT 4.31: 0.1%	NPLC-793-D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 days (25° C., 60% RH)
Formulation 1: 500 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.02%
RRT 3.93: 0.008%

TABLE 23-C

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333197

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	258 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.045%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.016% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.79: 0.009%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 2: 250 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328845

TABLE 23-D

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331346

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
(28 DAY CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	256 mg/ml (102%)	NPLC-793-D

TABLE 23-D-continued

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331346

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
(28 DAY CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Impurities total	≦2.0%	0.18%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.13% RRT 4.31: 0.03%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 days (25° C., 60% RH)
Formulation 2: 250 mg/cc; Malic acid; pH 7.5
*A: RRT 1.29: 0.007%
RRT 3.93: 0.008%

TABLE 23-E

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333196

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	360 mg/ml (103%)	NPLC-793
Impurities total	≦2.0%	0.050%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.017% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.006% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.7	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 3: 350 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328847

TABLE 23-F

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331345

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	363 mg/ml (104%)	NPLC-793-D
Impurities total	≦2.0%	0.21%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.14% RRT 4.31: 0.05%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	8.0	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)

Formulation 3: 350 mg/cc; Malic acid; pH 7.5

*A: RRT 1.29: 0.009%

RRT 3.93: 0.008%

TABLE 23-G

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333195

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE: 1741
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	461 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.065%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.018% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.02% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 4: 450 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328875

TABLE 23-H

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331343

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	454 mg/ml (101%)	NPLC-793-D
Impurities total	≦2.0%	0.40%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.26% RRT 4.31: 0.1%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)

Formulation 4: 450 mg/cc; Malic acid; pH 7.5

*A: RRT 1.30: 0.03%

RRT 3.93: 0.008%

TABLE 23-I

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333194

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	563 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.077%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.020% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.29: 0.03% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 5: 550 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328883

TABLE 23-J

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO.: 331341

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	561 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.56%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.31% RRT 4.31: 0.2%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 5: 550 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.04%
RRT 3.93: 0.007%

TABLE 23-K

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333193

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	666 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.10%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.025% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.05% RRT 3.78: 0.007%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 6: 650 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328885

TABLE 23-L

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331336

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	660 mg/ml (102%)	NPLC-764
Impurities total	≦2.0%	0.81%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.43% RRT 4.31: 0.3%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)

Formulation 6: 650 mg/cc; Malic acid; pH 7.5

*A: RRT 1.30: 0.07%

RRT 3.93: 0.007%

TABLE 23-M

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333192

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	518 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.065%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.018% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.79: 0.007% RRT 5.99: 0.02%	NPLC-793D
PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 7: 500 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 329033

TABLE 23-N

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331335

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	515 mg/ml (101%)	NPLC-793-D
Impurities total	≦2.0%	0.38%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.27% RRT 4.31: 0.1%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	3.93: 0.007%	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)

Formulation 7: 500 mg/cc; Malic acid; pH 7.5

TABLE 23-O

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 09 Feb. 1999
NO: 330721

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Challenge Test	Conforms to USP (0, 1, 7, 14, 21 and 28 days)	Conforms	USP 23 <51> S.8
Potency	Report	501 mg/ml (100%)	NPLC-793
Impurities total	≦2.0%	1.2%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone Report:	RRT 1.46: 0.013%	NPLC-793D
PH	Report	7.3	USP <791>
Solubility study	Report	*B	PR 98126 IIA

COMMENTS:

Initial test

500 mg/cc; Malic acid; pH 7.5

*A: RRT 1.31: 0.02% RRT 1.67: 0.008%

RRT 1.91: Interference with peak dilution solvent cannot calculate

RRT 3.47: 0.1% RRT 3.79: 0.009% RRT 3.84: 0.01%

RRT 4.18: 0.06% RRT 5.10: 0.008% RRT 5.35: 0.02%

RRT 6.74: 0.9% RRT 6.90: 0.08% RRT 7.41: 0.006%

*B: Maximum solubility: 700 mg/ml no pH adjustment.

TABLE 23-P

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Feb. 1999
NO: 331307

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM, LIQUID FORM.
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	508 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.70%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
Impurities specified	Gamma-Butyrolactone Report:	RRT 1.37: 0.054%	NPLC-793D
PH	Report	7.6	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
500 mg/ml cc; Malic acid; pH 7.5
*A: RRT 1.17: 0.03% RRT 3.47: 0.2%
RRT 5.46: 0.01% RRT 6.87: 0.3%
RRT 7.04: 0.007%
RRT 1.78: Can not calculate because it interfere with a dilution solvent peak.

This report summarizes the results of the above described study and provides a summary of previous development work which evaluated conditions other than those evaluated in this study. The purposes of this information is to define the scope and limitations of the self-preserving properties of Xyrem® oral solution for completion of patent application.

II. Summary of Results:

A. Preparation of various formulations of Sodium Oxybate and formulations using an alternative salt of GHB.

1. Various formulations of sodium oxybate were prepared as directed in the above Protocol. Sodium oxybate. 500 mg/cc with Malic Acid was not soluble at pH 5.0, and further evaluation of this solution was discontinued. All other solutions were successfully prepared as described.
2. The preparation of an alternative salt of gamma-hydroxybutyrare was described as the calcium salt, prepared at 500 mglcc (or maximum possible) with Malic Acid at pH 7.5.
   a. The calcium salt of gamma-hydroxybutyrate was prepared by Toronto Research and shipped to NeoPharm for determination of solubility and evaluation according to the Protocol. The absolute limit of solubility, without pH adjustment, was determined to be 700 mg/cc. The pH of this solution was 8.4. Solutions of lower pH were more difficult to prepare at 500 mg/cc using Malic acid, as acidulant. When pH was adjusted to 6.0 with Malic acid, the solubility of the calcium oxybate was limited (longer stirring required to solubilize). The desired solution of 500 mg/cc, pH 7.5 was prepared with Malic acid as acidulant without difficulty. Appearance of the final solution was slightly yellow in color. Copies of the laboratory record for preparation of these solutions is available.

B. Microbial Challenge Testing of the Various Formulations Prepared by MDS NeoPharm.

The microbial challenge testing was carried as specified in the Protocol and the following table summarizes the results of microbial challenge testing of various formulations of sodium oxybate and the single calcium oxybate formulation prepared.

TABLE 24

Testing of Sodium and Calcium GHB Salts

	pH of Solution	Microbial Challenge Result
Sodium Oxybate Concentration		
1. 500 mg/cc	7.5 (Malic acid)	Pass
2. 250 mg/cc	7.5 (Malic acid)	Pass
3. 350 mg/cc	7.5 (Malic acid)	Pass
4. 450 mg/cc	7.5 (Malic acid)	Pass
5. 550 mg/cc	7.5 (Malic acid)	Pass
6. 650 mg/cc	7.5 (Malic acid)	Pass
7. 500 mg/cc	7.5 (Citric acid)	Pass
Calcium Oxybate Conctration		
500 mg/cc	7.5	Pass

C. Short Term Stability Evaluation of Various Formulations of Sodium Oxybate and a Formulation of Calcium Oxybate.

Solutions were tested on day zero (preparation day) and day 28 according to the described Protocol. The results of the stability evaluation are summarized in Table 25 below:

TABLE 25

Sodium and Calcium GHB Evaluation

Sodium oxybate solution	Potency mg/cc (%)	Impurities (Total)	Impurities (Unspecified)	Impurities (Specified—GBL)	pH
500 mg/cc pH 7.5 Malic Acid Day 0	512 mg/cc (102%)	0.68%	0.041%	0.027%	7.6

TABLE 25-continued

Sodium and Calcium GHB Evaluation

Sodium oxybate solution	Potency mg/cc (%)	Impurities (Total)	Impurities (Unspecified)	Impurities (Specified—GBL)	pH
Day 28	510 mg/cc (103%)	0.36%	0.33%	0.028%	7.9
250 mg/cc pH 7.5 Malic Acid Day 0	258 mg/cc (103%)	0.045%	0.009%	0.026%	7.6
Day 28	256 mg/cc (102%)	0.18%	0.015%	0.16%	7.9
350 mg/cc pH 7.5 Malic Acid Day 0	360 mg/cc (103%)	0.050%	0.013%	0.037%	7.7
Day 28	363 mg/cc (104%)	0.21%	0.017%	0.19%	8.0
450 mg/cc pH 7.5 Malic Acid Day 0	461 mg/cc (102%)	0.065%	0.027%	0.038%	7.5
Day 28	454 mg/cc (101%)	0.40%	0.038%	0.36%	7.8
550 mg/cc pH 7.5 Malic Acid Day 0	563 mg/cc (102%)	0.077%	0.037%	0.040%	7.6
Day 28	561 mg/cc (102%)	0.56%	0.047%	0.51%	7.9
650 mg/cc pH 7.5 Malic Acid Day 0	666 mg/cc (102%)	0.10%	0.057%	0.045%	7.6
Day 28	660 mg/cc (102%)	0.81%	0.077%	0.73%	7.8
500 mg/cc pH 7.5 Citric Acid Day 0	518 mg/cc (104%)	0.065%	0.027%	0.038%	7.5
Day 28	515 mg/cc (103%)	0.38%	0.007%	0.37%	7.9
500 mg/cc pH 7.5 Malic Acid Day 0	501 mg/cc (100%)	1.2%	>0.1% (See C of A Attached)	0.013%	7.3
Day 28	508 mg/cc (102%)	0.70%	>0.1% (See C of A)	0.054%	7.6

D. Summary of Pertinent Solubility and Microbial Challenge Data are shown in Tables 26 and 27.

TABLE 26

Limits of Solubility

	pH of Solution	Comments
Sodium oxybate Maximum Solubility		
450 mg/cc	pH 4 (HCl)	25°
500 mg/cc	pH 5 (HCl)	25°
600 mg/cc	pH 6 (HCl)	25°
750 mg/cc	pH 6.8 (HCl)	25°
1000 mg/cc	pH (unadjusted)	65° Soluble, 25° gel
Calcium oxybate Maximum Solubility		
700 mg/cc	pH 8.4 (unadjusted)	25°
500 mg/cc	pH 6.0	25°

TABLE 27

Microbial Challenge Results

Sodium oxybate Concentration (Date)	pH of Solution	Microbial Challenge Results
750 mg/cc (December 1997)	7.5 (HCl)	pass
500 mg/cc (December 1997)	6.0 (HCl)	pass
500 mg/cc + Excipients (Xylitol) (March 1998)	6.0 (Malic Acid)	pass
500 mg/cc (March 1998)	9.0 (HCl)	pass (Borderline *aspergillus*)
150 mg/cc (BDL 1995)	5.0 (HCl)	fail (*aspergillus* only)
150 mg/cc (BDL 1995)	7.0 (HCl)	fail (*aspergillus* and *staph*)
150 mg/cc (BDL 1995)	3.0 (HCl)	fail (*aspergillus* only)
150 mg/cc (BDL 1995)	10.3 (HCl)	fail (*aspergillus* and *staph*)
500 mg/cc (May 1998)	6.0 (Malic Acid)	discontinued
500 mg/cc (May 1998)	7.5 (Malic Acid)	pass
500 mg/cc (May 1998)	9.0 (Malic Acid)	discontinued
500 mg/cc (May 1998)	7.5 (HCl)	pass
500 mg/cc	7.5 (Malic Acid)	pass

TABLE 27-continued

Microbial Challenge Results		
	pH of Solution	Microbial Challenge Results
250 mg/cc	7.5 (Malic Acid)	pass
350 mg/cc	7.5 (Malic Acid)	pass
450 mg/cc	7.5 (Malic Acid)	pass
550 mg/cc	7.5 (Malic Acid)	pass
650 mg/cc	7.5 (Malic Acid)	pass
500 mg/cc	7.5 (Citric Acid)	pass
Calcium oxybate Concentration (Date)		
500 mg/cc	7.5 (Malic Acid)	pass

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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U.S. Pat. No. 4,393,236

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EXHIBIT A

US006472431B2

(12) **United States Patent**
Cook et al.

(10) **Patent No.: US 6,472,431 B2**
(45) **Date of Patent: Oct. 29, 2002**

(54) **MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY**

(75) Inventors: **Harry Cook**, Eden Prairie; **Martha Hamilton**, St. Paul, both of MN (US); **Douglas Danielson**, Otsego, MI (US); **Colette Goderstad**, St. Paul; **Dayton Reardan**, Excelsior, both of MN (US)

(73) Assignee: **Orphan Medical, Inc.**, Minnetonka, MN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/470,570**

(22) Filed: **Dec. 22, 1999**

(65) **Prior Publication Data**

US 2002/0077334 A1 Jun. 20, 2002

Related U.S. Application Data

(60) Provisional application No. 60/113,745, filed on Dec. 23, 1998.

(51) **Int. Cl.**[7] **A61K 31/19**; A61K 31/235; A61K 31/34; A61K 31/215

(52) **U.S. Cl.** **514/557**; 514/473; 514/533; 514/529

(58) **Field of Search** 514/533, 923, 514/937, 944, 529, 557, 811, 812; 424/451, 464

(56) **References Cited**

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5,380,937	A	1/1995	Koehler et al.	562/579
5,840,331	A *	11/1998	Van Cauter et al.	424/464
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FOREIGN PATENT DOCUMENTS

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EP	0616804	3/1994	61/31
EP	0635265	7/1994	61/31
GB	922029	3/1963	61/81
WO	40105	12/1996	61/31

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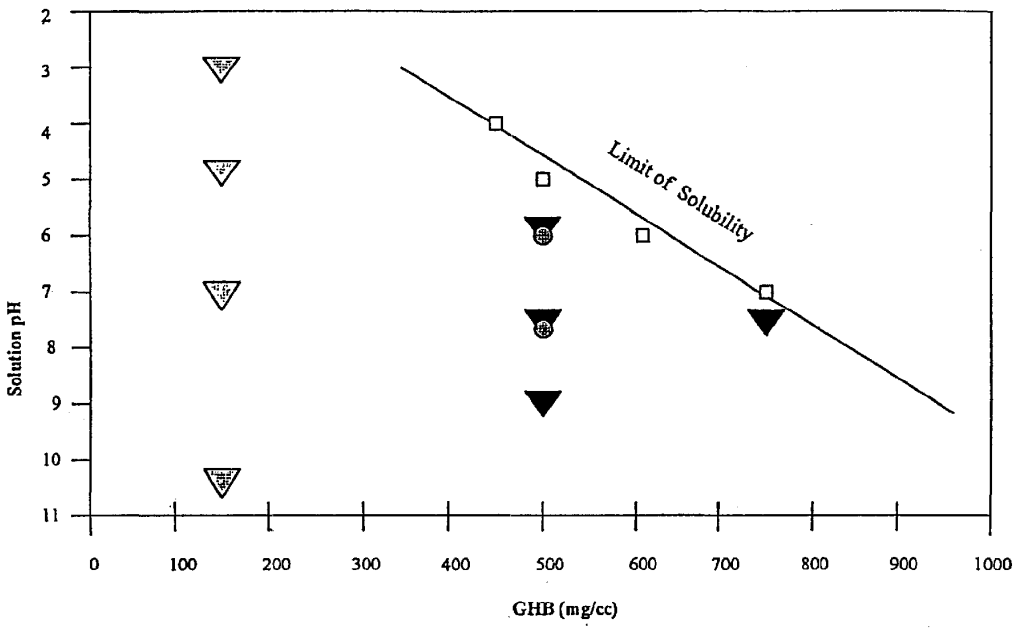
Primary Examiner—Zohreh Fay
Assistant Examiner—Brian-Yong S. Kwon
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg, Woessner & Kluth, P.A.

(57) **ABSTRACT**

Disclosed are formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial growth. Also disclosed are formulations of gamma-hydroxybutyrate that are also resistant to the conversion into GBL. Disclosed are methods to treat sleep disorders, including narcolepsy, with these stable formulations of GHB. The present invention also provides methods to treat alcohol and opiate withdrawal, reduced levels of growth hormone, increased intracranial pressure, and physical pain in a patient.

7 Claims, 1 Drawing Sheet

Figure 1.



□ Data points indicating limit of solubility of GHB as a function of concentration and pH, see Table 1.

Solutions susceptible to microbial growth, designated "Fail".
(All solutions demonstrated activity against Pseudomonas aeruginosa. Some reduction of aspergillus niger mold occurred in 7 days of contact time.)

Solutions resistant to microbial growth, designated "Pass". (Rate of reduction of microorganism counts was slightly higher at pH 7.5 and 6.0 than pH 9.0. The rate of reduction of formulations at 750mg/cc GHB were slightly lower than formulations at 500 mg/cc GHB.)

Solutions rresistant to microbial growth, designated "Pass". Results were similar for Malic Acid and HCl. Taste variations has implications for development of flavor systems.

Indicates pH adjustment with HCl.

Indicates pH adjustment with Malic Acid.

Note: Solutions with pH at 9.0 are not palatable or safe for oral consumption.

MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY

RELATED APPLICATIONS

This application claims priority from Provisional Application No. 60/113,745 filed Dec. 23, 1998, which is incorporated by reference herein.

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention relates generally to the fields of pharmaceutical compositions to be used in treatments, such as, sleeping disorders, such as, e.g., narcolepsy (particularly cataplexy), drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or for an increased level of intracranial pressure or the like. The present 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, e.g.

II. Description of Related Art

GHB is an endogenous compound with hypnotic properties that is found in many human body tissues. GHB is present, for example, in the mammalian brain and other tissues. In brain the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter (Snead and Morley, 1981). The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB is converted to succinate and then metabolized via the Krebs cycle. Clinical trials have shown that GHB increases delta sleep and improves the continuity of sleep (Ladinsky et al., 1983; Anden and Stock, 1973; Stock et al., 1973; Laborit, 1973; Lapierre et al., 1988; Lapierre et al., 1990; Yamda et al., 1967; Grove-White and Kelman, 1971; Scharf, 1985).

GHB has typically been administered in clinical trials as an oral solution (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993). GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e. daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency (Mamelak et al, 1973; Yamada et al., 1967; Bedard et al., 1989), reduces sleep apnea (Series et al, 1992; Scrima et al., 1987), and improves general anesthesia (Hasenbos and Gielen, 1985).

GHB has several clinical applications other than narcolepsy and sleep disorders. GHB has been reported to reduce alcohol craving, the number of daily drinks consumed, and the symptoms of alcohol withdrawal in patients (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992). GHB has been used to decrease the symptoms of opiate withdrawal. including both heroin and methadone withdrawal (Gallimberti et al, 1994; Gallimberti et al., 1993). It has analgesic effects that make it suitable as a pain reliever (U.S. Pat. No. 4,393,236). Intravenous administration of GHB has been reported to reduce intracranial pressure in patients (Strong, A. 1984). Also, administration of GHB was reported to increase growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970).

A good safety profile for GHB consumption, when used long term for treatment of narcolepsy, has been reported. Patients have been safely treated for many years with GHB without development of tolerance (Scharf, 1985). Clinical laboratory tests carried out periodically on many patients have not indicated organ or other toxicities (Lammers, 1993; Scrima, 1990; Scharf, 1985; Mamelack, 1977; Mamelak, 1979; Gallimberti, 1989; Gallimberti, 1992; Gessa, 1992). The side effects of GHB treatment have been minimal in incidence and degree of severity, though they include sleepwalking, enuresis, headache, nausea and dizziness (Broughton and Mamelak, 1979; Mamelak et al., 1981; Mamelak et al., 1977; Scrima et al., 1989; Scrima et al., 1990; Scharf et al., 1985).

The pharmacokinetics of GHB have been investigated in alcohol dependent patients (Ferrara et al., 1992) and in normal healthy males (Palatini et al., 1993) after oral administration. GHB possesses a rapid onset and short pharmacological effect (Ferrara et al., 1992; Palatine et al., 1993; Lee, C., 1977; van der Bogert; Gallimberti, 1989; Gallimberti, 1992; Lettieri and Fung, 1978; Arena and Fung, 1980; Roth and Giarman, 1966; Vickers, 1969; Lee, 1977). In alcohol dependent patients, GHB absorption into and elimination from the systemic circulation were fast processes. Virtually no unchanged drug could be recovered in the urine. There were preliminary indications that the pharmacokinetics of GHB might be non-linear or dose-dependent (Ferrara et al., 1992). In the healthy volunteers study, the pharmacokinetics of three rising GHB doses (12.5, 25, and 50 mg/kg) were investigated. These findings indicate that both the oral absorption and elimination processes of GHB were capacity-limited though the degree of dose dependency was moderate (Palatini et al., 1993).

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). 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.

SUMMARY OF THE INVENTION

The present invention overcomes deficiencies in the prior art by providing compositions of GHB in an aqueous medium that are resistant to microbial growth. These compositions are also resistant to the uncontrolled degradation of GHB into GBL or other substances. The compositions of the present invention are stable compositions of GHB that improve shelf-life, and provide a titratable formulation of GHB for easy dose measurement. In addition, the concentrated solutions embodied in this invention reduce shipping

and storage requirements and allow patients to carry more drugs for their convenience. The present invention provides methods to treat a number of conditions treatable by GHB, referred to herein as "therapeutic categories." Therapeutic categories for the present invention include, but are not limited to, sleeping disorders, drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders, such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or an increased level of intracranial pressure or other conditions treatable with GHB.

The invention first provides a pharmaceutical composition of GHB rendered chemically stable and/or resistant to microbial growth in an aqueous medium. Preferred GHB salts of the present invention include sodium, ammonium and calcium. As used herein in certain embodiments, "stable" may mean resistant to degradation of GHB into its known or unknown decomposition elements. The level of GBL that is acceptable can be up to 0.1% of the formulation as per the ICH guidelines for shelf-life determination, As used herein in certain embodiments, "resistant to microbial growth" or "resistant to microbial challenge" means that the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopocia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days. As used herein in certain embodiments, an "aqueous medium" may mean a liquid comprising more than about 50% water. In certain preferred embodiments, an "aqueous medium" may be a solution, suspension, gel or emulsion of GHB, with a solution of GHB being most preferred. Preferred gels are thixotropic gels. Compositions that are resistant to microbial growth are created by dissolving or mixing GHB in an aqueous medium to a concentration or content of greater than of about 150 mg/ml GHB to the maximal solubility of GHB. The solubility of GHB is up to about 750 mg/ml at room temperature (20° C. to about 25° C.), however, heating the aqueous medium during preparation up to 100° C. will increase GHB solubility to at least about 1000 mg/ml. A preferred concentration or content of GHB is about 500 mg/ml.

The amount of GHB that may be mixed or dissolved into an aqueous medium and still be resistant to microbial growth depends upon the pH of the aqueous medium. In certain embodiments the presence of a preservative may allow the amount of GHB contained in the compositions of the present invention to be increased and still maintain resistance to chemical degradation and/or microbial growth. In one embodiment of the present invention, the pH of the aqueous medium of the pharmaceutical composition is about 3 to about 10.

In a preferred embodiment, the pH of said aqueous medium is about 6 to about 7.5. The pH may be from about 3.0 to about 10.3, namely of about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0, about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, about 10.0, about 10.1, about 10.2, or about 10.3, and all pH values between each of the listed pH values, of the aqueous media. This will produce a GHB composition that is resistant to microbial growth as defined by the test described herein. As used herein, the term "about" generally means within about 10–20%.

These pH values will produce compositions resistant to microbial growth in an aqueous medium if the amount of GHB added, admixed, or dissolved is from above about 150 mg/ml to about 450 mg/ml, namely, above about 150 mg/ml, about 160 mg/ml, about 170 mg/ml, about 180 mg/ml, about 190 mg/ml, about 200 mg/ml, about 210 mg/ml, about 220 mg/ml, about 230 mg/ml, about 240 mg/ml, about 250 mg/ml, about 260 mg/ml, about 270 mg/ml, about 280 mg/ml, about 290 mg/ml, about 300 mg/ml, about 310 mg/ml, about 320 mg/ml, about 330 mg/ml, about 340 mg/ml, about 350 mg/ml, about 360 mg/ml, about 370 mg/ml, about 380 mg/ml, about 390 mg/ml, about 400 mg/ml, about 410 mg/ml, about 420 mg/ml, about 430 mg/ml, about 440 mg/ml, to about 450 mg/ml, and all amounts of GHB between the values listed.

At the medium to high end of the concentration or content of GHB that may be dissolved or mixed in the aqueous medium, the maximal pH that may be used is reduced at room temperature. This is shown in FIG. **1**, a graphical presentation of acceptable formulation ranges. At a concentration or content of about 450 mg/ml GHB, the pH may be of about 3.9 to about 10.3. At a concentration or content of about 500 mg/ml GHB, the pH may be of about 4.75 to about 10.3. At a concentration or content of about 600 mg/ml GHB, the pH may be of about 6.1 to about 10.3. At a concentration or content of about 750 mg/ml GHB, the pH may be of about 7.0 to about 10.3. Of course, all pH and concentration or content values in between each of the listed pH and concentration or content values are encompassed by the invention.

Certain embodiments may be selected as sub-ranges from these values of GHB content and aqueous medium pH. For example, a specific embodiment may be selected as a content of about 170 mg/ml to about 440 mg/ml GHB in an aqueous medium, at a pH range of about pH 5.5 to about pH 8.7. Another example of how a range may be selected in an embodiment would be the selection of a content of about 155 mg/ml of GHB, which is a value between the above listed values, to a content of about 350 mg/ml of GHB, and the selection of a pH range of the aqueous medium, such as a pH range of about 8.87, which is a value between the listed pH values, to a pH of about 8.93, which is another value between the listed values of pH. A third example of ranges that may be selected for a specific embodiment would be selection of a single content or concentration of GHB, such as about 200 mg/ml of GHB, and the selection of a pH range, such as a pH of about 3.5 to about 8.2. A fourth example of ranges that may be selected for a specific embodiment would be selection of a content or concentration of GHB over a range, such as about 300 mg/ml to about 400 mg/ml, and the selection of a single pII value for the aqueous medium, such as a pH of about 3. Another example of a range selected for an embodiment may be the selection of a single content or concentration of GHB, such as 400 mg/ml GHB, and a single pH value of the aqueous medium, such as pH 7.7.

Other examples of how a range of an embodiment of GHB content or concentration may be selected include a range of GHB content or concentration from about 200 mg/ml to

about 460 mg/ml GHB, encompassing the ranges for GHB described herein, and a range of pH for the aqueous medium may be from about pH 4.3 to about pH 7, encompassing ranges for GHB in an aqueous medium at room temperature described herein. Another example would be the selection of a range of GHB content or concentration from about 153 mg/ml to about 750 mg/ml, and a pH range of about 7 to about 9, encompassing ranges between the listed values of GHB content and pH described herein. An example may be the selection as a GHB concentration or content of about 170 mg/ml to about 640 mg/ml in an aqueous medium, at a pH range of about pH 6.5 to about pH 7.7. Another example of how a range may be selected in an embodiment would be a content or concentration of about 185 mg/ml of GHB, which is a value between the listed values, to a content or concentration of about 750 mg/ml of GHB, at a pH range of about 7.87, which is a value between the listed pH values, to a pH of about 8.91, which is another value between the listed values of pH. An additional example of ranges that may be selected for a specific embodiment would be a content or concentration of about 200 mg/ml of GHB at a pH of about 7 to about 8.2. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 750 mg/ml to about 400 mg/ml at a pH of about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 300 mg/ml to about 750 mg/ml at a pH of about 8.5 to about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 400 mg/ml to about 600 mg/ml at a pH of about 9 to about 5.8. And so forth. Thus, all ranges of pH and GHB concentration or content that can be selected from the values herein and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

The chemical stability of GHB is affected by pH, with compositions of GHB in an aqueous medium with a pH below about 6 being less effective in maintaining the chemical stability of GHB. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, all concentrations or content of GHB in an aqueous medium, as described herein, and as would be understood by those of ordinary skill in the art, may be selected to produce compositions of the present invention.

Additionally, the ranges described above are for a composition at room temperature, which is defined herein as from about about 20° C. to about 25° C., namely, about 20° C. about 21° C., about 22° C., about 23° C., about 24° C., to about 25° C. Within the values and ranges of pH described above, the ranges of concentration or content of GHB may increase at temperatures greater than room temperature. Thus, the maximal content or concentration of GHB in an aqueous medium at a temperature of from about 26° C. to about 100° C., namely about 26° C., about 27° C., about 28° C., about 29° C., about 30° C., about 31° C., about 32° C., about 33° C., about 34° C., about 35° C., about 36° C., about 37° C., about 38° C., about 39° C., about 40° C., about 41° C., about 42° C., about 43° C., about 44° C., about 45° C., about 46° C., about 47° C., about 48° C., about 49° C., about 50° C., about 51° C., about 52° C., about 53° C., about 54° C., about 55° C., about 56° C., about 57° C., about 58° C., about 59° C., about 60° C., about 61° C., about 62° C., about 63° C., about 64° C., about 65° C., about 66° C., about 67° C., about 68° C., about 69° C., about 70° C., about 71° C., about 72° C., about 73° C., about 74° C., about 75° C., about 76° C., about 77° C., about 78° C., about 79° C., about 80° C., about 81° C., about 82° C., about 83° C., about 84° C., about 85° C., about 86° C., about 87° C., about 88° C., about 89° C., about 90° C., about 91° C., about 92° C., about 93° C., about 94° C., about 95° C., about 96° C., about 97° C., about 98° C., about 99° C., to about 100° C., may be from about 750 to about 1 g/ml, namely to about 751 mg/ml, about 760 mg/ml, about 770 mg/ml, about 780 mg/ml, about 790 mg/ml, about 800 mg/ml, about 810 mg/ml, about 820 mg/ml, about 830 mg/ml, about 840 mg/ml, about 850 mg/ml, about 860 mg/ml, about 870 mg/ml, about 880 mg/ml, about 890 mg/ml, about 900 mg/ml, about 910 mg/ml, about 920 mg/ml, about 930 mg/ml, about 940 mg/ml, about 950 mg/ml, about 960 mg/ml, about 970 mg/ml, about 980 mg/ml, about 990 mg/ml, to about 1000 mg/ml. At temperatures below room temperature, the solubility of GHB may decrease, and compositions at lower temperature and solubility of GHB at the pH values and ranges described herein are also encompassed by the invention. Additionally, differences of atmospheric pressure may also increase or decrease the solubility of GHB within the ranges described, and embodiments of the invention with an increased or decreased content of GHB due to changes in pressure are also encompassed by the invention. Of course, it is understood that the present invention encompasses embodiments of GHB concentration or content in an aqueous medium at higher or lower temperature within the values described herein, such as about 980 mg/ml to about 200 mg/ml at 95° C. GHB at a pH of about 9 to about 7.5. Or about 150 mg/ml GHB at about 17° C. at about pH 6 to about pH 7. And so forth. Thus, all ranges of pH and GHB content that can be selected at various temperatures and pressures from the values above, and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

In certain other embodiments of the present invention, the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids, bases, or combinations thereof. In certain embodiments, the acid may be an organic acid, preferably a carboxylic acid or alphahydroxy carboxylic acid. In certain other embodiments, the acid is selected from the group including, but not limited to, acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like. In a preferred embodiment, the acid is malic or hydrochloric acid. In certain other embodiments, the pH adjusting agent may be a base selected from the group including, but not limited to, acetanilide, ammonia, apomorphine, atropine, benzocaine, caffeine, calcium hydroxide, cocaine, codeine, ephedrine, morphine, papaverine, physostigmine, pilocarpine, potassium bicarbonate, potassium hydroxide, procaine, quinine, reserpine, sodium bicarbonate, sodium dihydrogen phosphate, sodium citrate, sodium taitrate, sodium carbonate, sodium hydroxide, theobromine, thiourea or urea. 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.

In certain embodiments, the composition may contain one or more salts. A "salt" is understood herein to mean certain embodiments to mean a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base. Various salts, including salts of GHB, are also encompassed by the invention, particularly as pH adjusting or buffering agents. Pharmaceutically acceptable salts, include inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as malic, acetic, oxalic, tartaric, mandelic, and the like. Salts formed can also be derived from inorganic bases such as, for example, sodium, potassium, silicates, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Alkali met al salts, such as lithium, potassium, sodium, and the like may be used, preferably with an acid to form a pH adjusting agent. Other salts may comprise ammonium, calcium, magnesium and the like. In one embodiment, a salt of GHB comprising an alkali met al may be combined with an acid to create a composition that achieves the desired pH when admixed with an aqueous medium. In another embodiment, a weak base may be combined with GHB to create a composition that achieves the desired pH when admixed with an aqueous solution. Of course, other salts can be formed from compounds disclosed herein, or as would be known to one of ordinary skill in the art, and all such salts are encompassed by the invention.

In certain embodiments, excipients may be added to the invention. An "excipient" as used herein shall mean certain embodiments which are more or less inert substances added as diluents or vehicles or to give form or consistency when the remedy is in a solid form, though they may be contained in liquid form preparations, e.g. syrups, aromatic powders, honey, and various elixirs. Excipients may also enhance resistance to microbial growth, and thus act as a preservative. Such excipients include, but are not limited to, xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, cellulose derivatives, magnesium carbonate and the like.

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, propyl gallate BP, sorbic acid, chlorobutanol, dihydroacetic acid, monothioglycerol, potassium benzoate, propylparaben, benzoic acid, benzalkonium chloride, alcohol, benzoic acid, benzalkonium chloride, benzethonium chloride, benzyl alcohol, butylparaben, cetylpyridinium chloride, ethylenediamine, ethylpareben, ethyl vanillin, glycerin, hypophophorus acid, methylparaben, phenol, phenylethyl alcohol, phenymercuric nitrate, propylparaben, sassafras oil, sodium benzoate, sodium propionate, thimerosal and potassium sorbate. Preferred preservatives may be selected from the group comprising, but not limited to, xylitol, sodium benzoate, methylparaben, propylparaben and potassium sorbate. Xylitol is particularly preferred in certain compositions of the invention, because it acts as an preservative and a sweetener, is a caries preventative, is less laxative than other sweeteners, and is recommended for diabetics.

In certain embodiments, the pharmaceutical composition may also contain an antioxidant. An "antioxidant" is understood herein to mean certain embodiments which are substances that inhibits oxidation. Such antioxidants include, but are not limited to, asocrbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, potassium metabisulfite, sodium metabisulfite, anoxomer and maleic acid BP.

In certain embodiments, the pharmaceutical composition may also contain a flavoring agent. A "flavoring agent" is understood herein to mean certain embodiments which are substances that alters the flavor of the composition during oral consumption. A type of "flavoring agent" would be a sweetener. Preferred sweeteners or flavoring agents would be microbially non-metabolizable. Especially preferred sweeteners or flavoring agents would be carbohydrates such as xylitol and sorbitol. Such flavoring agents include, but are not limited to, acacia syrup, anethole, anise oil, aromatic elixir, benzaldehyde, benzaldehyde elixir-compound, caraway, caraway oil, cardamom oil, cardamom seed, cardamom spirit, cardamom tincture-compound, cherry juice, cherry syrup, cinnamon, cinnamon oil, cinnamon water, citric acid, citric acid syrup, clove oil, coca, coca syrup, coriander oil, dextrose, eriodictyon, eriodictyon fluidextract, eriodictyon syrup-aromatic, ethyl acetate, ethyl vanillin, fennel oil, ginger, ginger fluidextract, ginger oleoresin, glucose, glycerin, glycyrrhiza, glycyrrhiza elixir, glycyrrhiza extract, glycyrrhiza extract-pure, glycyrrhiza fluidextract, glycyrrhiza syrup, honey, non-alcoholic elixir, lavender oil, citrus extract or oil, lemon oil, lemon tincture, mannitol, methyl salicylate, nutmeg oil, orange-bitter-elixir, orange-bitter-oil, orange flower oil, orange flower water, orange oil, orange peel-bitter, orange-peel-sweet-tincture, orange spirit-compound, compound, orange syrup, peppermint, peppermint oil, peppermint spirit, peppermint water, phenylethyl alcohol, raspberry juice, raspberry syrup, rosemary oil, rose oil, rose water, saccharin, saccharin calcium, saccharin sodium, sarsaparilla syrup, sorbitol solution, spearmint, spearmint oil, sucrose, syrup, thyme oil, tolu balsam, tolu balsam syrup, vanilla, vanilla tincture, vanillin or wild cherry syrup.

Salts, excipients, pH adjusting agents such as acids, bases and buffering agents, flavoring agents, and other agents that may be combined with the compositions of the present invention, or may be used to prepare the compositions of the present invention, are well known in the art, (see for example, "Remington's Pharmaceutical Sciences" 8th and 15th Editions, and Nema et al., 1997, incorporated herein in their entirety), and are encompassed by the invention.

In certain other embodiments, the pharmaceutical composition comprises GHB, a pH adjusting or buffering agent, and an aqueous medium, wherein the components are admixed (sequentially or simultaneously) to prepare said pharmaceutical composition. The pH adjusting or buffering agent and aqueous medium may be any described herein.

The invention also provides a method of preparing a chemically stable and microbial growth-resistant pharmaceutical composition for the treatment of a condition responsive to GHB, comprising admixing GHB and a pH-adjusting or buffering agent in an aqueous medium. In certain embodiments, the method of preparing the pharmaceutical composition further comprises admixing a preservative with the pharmaceutical composition. Other components, such as flavoring agents, salts, and the like, may be added to the composition. The pH adjusting or buffering agent, aqueous medium, preservative, flavoring agents, salts, or other ingredient may be any described herein.

In certain other embodiments, the method of preparing the pharmaceutical composition comprises admixing GHB, a pH adjusting or buffering agent, and an aqueous medium soon before administration to a patient suspected of having a condition responsive to GHB.

The invention also provides a method of treating any therapeutic category of disorder responsive to GHB, comprising administering to a patient suspected of having such a condition a therapeutic amount of a pharmaceutical composition comprising chemically stable GHB (e.g. 1–10 gms.) in an aqueous medium resistant to microbial growth. In certain embodiments, the method of treating a condition responsive to GHB comprises a patient taking a first dosage of from about 0.1 g to about 10 g, namely about 0.1, about 0.2 about 0.3 about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0, about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, to about 10 grams of GHB, or as needed by the patient as would be recognized by one of skill in the art. Of course, it will be understood that all values in between those listed, such as 9.45 grams, 6.32 grams, etc. may be administered, and those values are encompassed well. In preferred embodiments, the first dose is administered within an hour of sleep. In preferred embodiments, a second dose of GHB within the values described above may be administered. This second dose is administered preferably within about 2.0 to about 5.0 hrs, namely about 2.0, about 2.1, about 2.2, about 2.3, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, to about 5.0 hours after the first dose, though it may be administered at a time outside of the preferred range.

In certain embodiments, a second pharmaceutical may be administered with the composition of GHB. Such a second pharmaceutical may be e.g., a stimulant administered within the same 24 hour period as the first dose of GHB. The stimulant may be, e.g., but not limited to, methylphenidate or pemoline to counter the residual effects of GHB treatment during periods of wakefulness. In certain embodiments, the method of treating a sleep disorder may include the discontinuation of other second pharmaceuticals used to control a sleep disorder. Such second pharmaceuticals may include, but are not limited to, a tricyclic antidepressant.

In certain embodiments, the invention provides a method of treating any appropriate therapeutic category of disorder, by administration of GHB compositions of the present invention as described above for the treatment of sleep disorders. When GHB is used in methods of treating any therapeutic category of disorder, the GHB composition of the present invention may be mixed with the aqueous medium, and optionally pH adjusting or buffering agent or other additives, by the patient or administrator soon before consumption. The patient may prepare the composition within a few minutes to hours before administration. Alternatively, one or more of the components may be premixed for ready use. The components of the GHB composition of the present invention, GHB, an aqueous medium, pH adjusting or buffering agent, excipients, preservatives, flavoring agents, and/or other components or additives may be stored in a container means suitable to aid preservation. Preferably, the container means is in the form of a set. A "set" as used herein certain embodiments is one or more components of the composition packaged in a container or other suitable storage means.

The present invention also provides a set for the treatment of a condition responsive to GHB comprising, in suitable storage means, GHB and a pH adjusting or buffering agent. In certain embodiments, the GHB and the pH adjusting or buffering agent are separately packaged. In certain other embodiments the GHB and the pH-adjusting or buffering agent may be mixed. The set may contain an aqueous medium. In certain other embodiments, at least one component selected from the group including, but not limited to, GHB, the pH-adjusting or buffering agent and/or an aqueous medium is separately packaged. In certain other embodiments, at least two of the components selected from the group comprising GHB, a pH adjusting or buffering agent and an aqueous medium are mixed together. In some embodiments, the set further contains a preservative. Such a set may have one, two, or more components from the group comprising GHB, a pH-adjusting or buffering agent, an aqueous medium or a preservative packaged separately. Such a set may have two or more components mixed together. Thus, both liquid and dry formulations of GHB and other components may be packaged in a set for mixing before administration, or one or more components may be premixed and packaged together with other components, or all the components may be premixed and packaged in a set.

It is understood that the compositions of the present invention, including those in a set, may be dispersed in a pharmaceutically acceptable carrier solution as described below. Such a solution would be sterile or aseptic and may include water, co-solvent vehicle buffers, isotonic agents, pharmuceutical aids or other ingredients known to those of skill in the art that would cause no allergic or other harmful reaction when administered to an animal or human subject. Therefore, the present invention may also be described as a pharmaceutical composition of GHB with increased stability in a pharmaceutically acceptable carrier solution.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also as used herein, the term "a" "an" or "the" is understood to include the meaning "one or more". Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. 1. The Range of Gamma-Hydroxybutyrate's Resistance to Microbial Growth and Chemical Stability in Aqueous Solution. The ordinate is the pH of solutions of GHB. The axis is the concentration (mg/ml) of GHB in aqueous solution. The region below the diagonal line [/] is the range

of GHB solubility at room temperature. Greater solubility can be achieved, up to 1 g/ml, by heating the solution up to 100° C. Three solutions were adjusted with HCl and were susceptible to microbial growth (Δ). Two solutions were pH adjusted with malic acid and were resistant to microbial growth (●). Of these two solutions, the one at pH 6 contained xylitol as an excipient. Three solutions were pH adjusted with hydrochloric acid and were resistant to microbial growth (▲). One solution was not pH adjusted and was susceptible to microbial growth (*).

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

I. Formualations of Gamma-Hydroxzybutyrate

A. Microbial Growth and Gamma-butyrolactone Formation

The present invention arises from the discovery of chemically stable and microorganism resistant formulations of GHB in an aqueous medium, preferably a solution, and the efficacy of these formulations in the treatment of therapeutic categories of disorders, such as narcolepsy and other sleep disorders. Specifically, GHB is prepared at a concentration greater than about 150 mg/ml in an aqueous medium, up to the limits of GHB's solubility or retention in an aqueous medium, to produce the compositions of the present invention.

The maximum solubility of GHB is affected by the pH of the aqueous medium. At about pH 4, the maximum amount of sodium-GHB that can be dissolved is about 450 mg/ml. The value of pH that is conducive to GHB solubility increases, as is shown at FIG. **1**, so that the minimal pH that will dissolve 750 mg/ml GHB was found to be about pH 6.8. This is shown in Table 1.

TABLE 1

Limits of Sodium Oxybate Solubility

ID	Sodium Oxybate Maximum Solubility	pH of Solution	Temperature
A			
B	450 mg/cc	pH 4 (HCl)	25°
C	500 mg/cc	pH 5 (HCl)	25°
D	600 mg/cc	pH 6 (HCl)	25°
E	750 mg/cc	pH 6.8 (HCl)	25°
F	750 mg/cc +	pH 10.3	25°
G	1000 mg/cc	pH unadjusted	65° Soluble, 25° Gel

The pH of the aqueous medium also affects the resistance of the composition to microbial growth at about 500 mg/ml GHB. GHB at this concentration in an aqueous medium that is between about pH 5 and pH 9 is resistant to microbial growth, with compositions at about pH 6 to about pH 7.5 being particularly resistant to microbial growth. However, at concentrations of GHB greater than about 750 mg/ml above about pH 7.5, the resistance to microbial growth is reduced. This is shown at Table 2.

TABLE 2

Microbial Challenge Data Summary

ID	Sodium Oxybate Concentration	pH of Solution	Microbial Challenge Result
H			
I	750 mg/cc	7.5 (HCl)	pass
J	500 mg/cc	6.0 (HCl)	pass
K	500 mg/cc + Excipients (Xylitol)	6.0 (Malic Acid)	pass
L	500 mg/cc	9.0 (HCl)	pass (borderline aspergillus)
M	150 mg/cc (BDL 1995)	5.0 (HCl)	fail (aspergillus only)
N	150 mg/cc (BDL 1995)	7.0 (HCl)	fail (aspergillus & staph)
O	150 mg/cc (BDL 1995)	3.0 (HCl)	fail (aspergillus only)
P	150 mg/cc (BDL 1995)	10.3 (unadjusted)	fail (aspergillus and staph)
Q	500 mg/cc	6.0 (Malic Acid)	discontinued
R	500 mg/cc	7.5 (Malic Acid)	pass
S	500 mg/cc (May '98)	9.0 (Malic Acid)	discontinued
T	500 mg/cc (May '98)	7.5 (HCl)	pass*
U	Others: 200 mg/cc–800 mg/cc	5.0–9.0	pending

*pass is generally defined as:

For Category 1C Products	
Bacteria:	Not less than 1.0 log reduction from the initial cout at 14 days, and no increase from the 14 days' count at 28 days.
Yeast and Molds:	No increase from the initial calculated count at 14 and 28 days.

The data from Table 1 and Table 2 are graphically shown in FIG. **1**. The concentration of GHB in the composition, when evaluated in relationship to the pH, affects the resistance of the GHB composition to microbial challenge. Compositions of GHB at or below 150 mg/ml are poorly resistant to microbial challenge from a pH range of about pH 3 to about pH 9. However, concentrations of GHB of greater than about 150 mg/ml, up to about 1000 mg/ml of GHB, are believed to be suitably resistant to microbial contamination at these pH ranges.

The chemical stability of GHB is affected by pH. Accordingly, the method for preparing GHB, as described herein, particularly as disclosed in the specific examples, varies with pH. GBL begins to form if the pH is about 6 or less. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, any pH or range of pH values where a clinically acceptable amount of GBL is produced is also contemplated as being preferred, and is encompassed by the present invention. The range of GBL could be regulatorily broadened with availability of sufficient toxicological data.

In certain embodiments of the invention, a pH-adjusting agent may be added to the composition. The choice of a pH adjusting agent may affect the resistance to microbial challenge and/or the stability of GHB, as measured by the reduction in assayable GHB. Compositions of GHB, pH adjusted with malic acid are resistant to both microbial growth and chemical degradation of GHB, and are preferred. Other pH adjusting or buffering agents may be selected. Agents that adjust pH that are selected on this basis will undergo a taste testing study. However, any pH adjusting agent disclosed herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the invention. Of course, any salt, flavoring agent, excipient, or other pharmaceutically acceptable addition described herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the inventions

Any of the above formulations may be prepared and/or packaged as a powdered or dry form for mixing with an

aqueous medium before oral administration, or they may be prepared in an aqueous medium and packaged. After mixing with an aqueous medium, preferrably to prepare a solution, these formulations are resistant to both microbial growth and chemical conversion of GHB to GBL, thereby increasing the shelf-life of therapeutic formulations of GHB in an aqueous medium. These formulations then provide an easily titratable liquid medium for measuring the dosage of GHB to be administered to a patient. Additional embodiments of the composition and methods of preparation are described below and in the examples.

B. Pharmaceutical Compositions

1. Pharmaceutically Acceptable Carriers

Aqueous compositions of the present invention comprise an effective amount of GHB dissolved or dispersed in a pharmaceutically acceptable carrier and/or an aqueous medium. The phrases "pharmaceutically or pharmacologically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is not appropriate. Supplementary compatible active ingredients can be incorporated into the compositions. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by the Food and Drug Administration (FDA).

The GHB may be lyophilized for more ready formulation into a desired vehicle where appropriate. The active compounds may be formulated for parenteral administration, e.g., formulated for injection via intravenous, intraarterial, intramuscular, sub-cutaneous, intralesional, intraperitoneal or other parenteral routes. The preparation of an aqueous composition that contains a GHB agent as an active component or ingredient will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for using to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including, e.g., aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

Solutions of the active compounds as free acid or pharmacologically acceptable salts can be prepared in water suitably mixed with hydroxypropylcellulose and/or a pharmacueutically acceptable surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof as well as in oils. Under ordinary conditions of storage and use, these preparation may best contain a preservative to further prevent the growth of microorganisms.

A GHB composition of the present invention can be formulated into a composition in a neutral or salt form. Such salts can be formed from any of the acids and bases described herein particularly depending on the particular GHB or GHB salt used, or as would be known to one of ordinary skill in the art.

The carrier can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, or the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a substance, such as lecithin (e.g. a coating), by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by any of the preservatives described herein, or as would be known to one of ordinary skill in the art, including various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The preparation of more, or highly, concentrated solutions for direct injection is also contemplated, where the use of DMSO as solvent (although DMSO may not now be a permitted human drug) is envisioned to result in extremely rapid penetration, delivering high concentrations of the active agents to a small area.

Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above, but drug release capsules and the like can also be employed.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035–1038 and 1570–1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The active GHB may be formulated within a therapeutic mixture to comprise about 100 to about 10,000 milligrams per dose. Multiple doses can also be administered.

In addition to the compounds formulated for parenteral administration, such as intravenous or intramuscular injection, other pharmaceutically acceptable forms include, e.g., tablets or other solids; liposomal formulations; time release capsules; and any other form currently used, including cremes, which then may be admixed with an aqueous medium for oral administration.

One may also use nasal solutions or sprays, aerosols or inhalants in the present invention. Nasal solutions are usually aqueous solutions designed to be administered to the nasal passages in drops or sprays. Nasal solutions are prepared so that they are similar in many respects to nasal secretions, so that normal ciliary action is maintained. Thus, the aqueous nasal solutions usually are isotonic and slightly buffered to maintain a pH of 5.5 to 6.5, though other pH ranges disclosed herein the specific examples, such as pH 3 to about pH 9, or pH 6 to about 7.5, are contemplated. In addition, preservatives, similar to those used in ophthalmic preparations, and appropriate drug stabilizers, if required, may be included in the formulation. Various commercial nasal preparations are known and include, for example, antibiotics and antihistamines and are used for asthma prophylaxis.

The perferred oral formulations may include such normally employed excipients, as, for example, pharmaceutical grades of xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate and the like. These compositions can take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders to be admixed with an aqueous medium. In certain defined embodiments, oral pharmaceutical compositions will comprise an inert diluent or assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsule, or they may be compressed into tablets, or the GHB may be packaged separately from or in combination with the excipients, salts, flavorings or any other components described herein, to be admixed with an aqueous medium for oral or injectable formulations, or they may be incorporated directly with the food (i.e. a beverage) of the diet.

For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of tablets, buccal tablets or tabs, troches, capsules, elixirs, suspensions, syrups, wafers, and the like, to be admixed with an aqueous medium. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 75% of the weight of the unit, or preferably between 25–60%. The amount of active compounds in such therapeutically useful compositions is such that a suitable dosage will be obtained.

The tablets, troches, pills, capsules and the like may also contain the following: a binder, nutural as gum tragacanth, acacia, cornstarch, or gelatin or synthetic as polyvinyl acetate; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a natural or synthetic flavoring agent. When the dosage unit form is a capsule for admixing with a specific volume of an aqueous medium, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with sugar, natural or synthetic polymers, or both. A syrup or elixir may contain the active compounds, sucrose as a sweetening agent, a preservative, a dye and/or a flavoring.

Additionally, any excipient, salt, acid, pH-mediating, adjusting or buffering compound or agent, flavoring, solution, solvent, dispersion, glycerol, glycol, oil, antibacterial and antifungal agents, antibiotics and antihistamines, binders, disintegrating agents, lubricants, sweetening agents, or any other additive or ingredient from those enumerated above or in the examples, or in any pharmaceutically acceptable composition or carrier described herein, or as would be known by one of skill in the art, is contemplated for use in aqueous mediums or solid forms of the GHB compositions of the invention. One or more of these compositions may be packaged with GHB or packaged separately from GHB prior to consumption. If packaged separately, useful compositions of GHB may be obtained by mixing GHB with the other components with an aqueous medium prior to consumption. Such components may be packaged in a set, described below.

2. Sets

Therapeutic sets of the present invention are sets comprising GHB. Such sets will generally contain, in suitable container, a pharmaceutically acceptable formulation of GHB. The set may have a single container, or it may have distinct container for each component, or distinct container for various combinations of components.

When the components of the set are provided in one or more liquid formulations, the liquid formulation is an aqueous medium, with a sterile aqueous solution being particularly preferred. The GHB compositions may also be formulated into a syringeable composition. In which case, the container means may itself be a syringe, pipette, vial, ampule or other such like apparatus, from which the formulation may be applied to an infected area of the body, injected into an animal, or even applied to and mixed with the other components of the set.

However, the components of the set may be provided as dried powder(s). When reagents or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent. It is envisioned that the solvent may also be provided in another container means.

The container means will generally include at least one vial, test tube, flask, bottle, pouch syringe or other container means, into which the GHB formulation or components thereof are placed, preferably, suitably allocated. The sets may also comprise a second container means for containing a sterile, pharmaceutically acceptable buffer or other diluent.

The sets of the present invention will also typically include a means for containing the vials in close confinement for commercial sale, such as, e.g., injection or blow-molded plastic containers into which the desired vials are retained.

Irrespective of the number or type of containers, the sets of the invention may also comprise, or be packaged with, an instrument for assisting with the injection/administration or placement of the GHB composition within the body of an animal. Such an instrument may be a drinking cup, syringe, pipette, or any such medically approved delivery vehicle.

II. Methods of Treatment With the GHB Compositions

Because GHB has been shown to be effective in treating narcolepsy and sleep disorders (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993), reducing alcohol craving and alcohol withdrawal symptoms, (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992), reducing opiate

withdrawal symptoms (Gallimberti et al, 1994; Gallimberti et al., 1993), reducing pain (U.S. Pat. No. 4,393,236), reducing intracranial pressure in patients (Strong, A. 1984), and increasing growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970), the formulations of the present invention are also contemplated to be useful in the treatment of any of these disorders or conditions in patients. GHB has also been used alone as a narcotic in patients with a terminal carcinomatous state. GHB has been used with other analgesics, neuroleptics, or with a subliminal barbiturate dose for use as an anesthesia. GHB has been used in closed cranio-cerebral trauma and as a soporific (U.S. Pat. No. 5,380,937). The inventors contemplate the use of the GHB compositions of the present invention as a narcotic, hypnotic, or as a soporific. The inventors also contemplate the use of the GHB compositions of the present invention in combination with analgesics, neuroleptics or barbiturates for use as an anesthesia. The GHB compositions of the present invention may be prepared and administered by any of the means described herein, particularly those described in the section "Pharmaceutical Compositions" and the examples, or by any means as would be known to those of skill in the art.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

Preferred Embodiments

XYREM™ CLINICAL TRIALS

The inventors developed a liquid formulation composed of GHB, xylitol, and preservative in water (XYREMTM). Subsequent instability of the preservative in this formulation and a desire to initiate clinical trials in a timely manner led to a change in the formulation to a foil pouch. One clinical trial utilized a twin-pouch dosage form, with one side (pouch 1) of the foil packet containing GHB and the other side (pouch 2) containing the flavoring agents (Xylitol, [NF]; Malic Acid, NF;

Patients were instructed to open the twin-pouch with a scissors, empty the contents into a dosing cup, add 2 ounces of water, snap the lid on the dosing cup, shake to dissolve, and drink the entire contents of the cup. Clinical trials conducted by the inventors have been performed using the twin-pouch dosage form.

However, the inventors have continued development of a liquid solution and have now overcome inherent problems with particular formulations and/or preservatives. The inventors have converted patients currently enrolled in a GHB open-label trial to a liquid solution composed of GHB, malic acid, and water—that is diluted with water immediately prior to oral administration.

The need for a liquid solution dosage form is further evidenced by the range of doses being used in a subsequent GHB open-label trial. Three sizes of pouches were prepared for the GHB open-label trial: 1.5 grams, 3.0 grams, and 4.5 grams. The initial dose for all patients in the GHB open-label trial was 6 grams of GHB nightly in divided doses. Dosage adjustments were permitted in the first two weeks of the trial as indicated for intolerance or lack of efficacy. The investigator was permitted to decrease the dose of GHB to 3 grams or 4.5 grams, or increase the dose to 7.5 grams or 9 grams nightly. After two weeks, further dosage adjustments were made if clinically indicated.

Thirty-five patients had their dose increased, and 16 patients had their dose decreased. Patients in the lowest dose group were disproportionately female and weighed 15 kg less than patients in the other two groups. Current dosing levels are noted below:

TABLE 3

	Dosing Levels in the GHB Open-Label Trial						
	Total	1.5 gram	3.0 gram	4.5 gram	6.0 gram	7.5 gram	9.0 gram
Number of Patients	95	0	4	10	39	12	30
Percent of Patients	100%	0%	4%	10%	41%	13%	32%

To achieve these individualized doses, it has been necessary to provide a combination of different dose strengths. This complexity would be very difficult to achieve with a marketed product. In addition, a month's supply of twin-pouches is quite bulky. A liquid formulation allows for ease in dosing adjustment with one dosage form. In addition "child-resistant" packaging has been developed with the liquid formulation.

A number of patients have also complained about the flavor with the twin-pouches. As follow-up the inventors sent questionnaires to participants in the inventors' clinical trial, and performed taste testing in normal volunteers. The questionnaire responses, taste testing results, and the clinical experience in narcolepsy patients of the study administrator have all confirmed that unflavored solutions were acceptable.

The concentration and volume of the GHB solution that the patient administers will be the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. This is illustrated in Chart 1 and Table 4:

Chart 1

Comparison of Liquid Solution to Twin-Pouch

Twin-Pouch - 3 g GHB (one pouch)	Liquid Solution - 3 g GHB (6 mL)
↓	↓
dissolve in water - 2 ounces	dilute with water to 2 ounces

-continued

Chart 1

Comparison of Liquid Solution to Twin-Pouch

↓	↓
administer solution 3 g in 60 mL	administer solution 3 g in 60 mL

TABLE 4

Comparison of Liquid Solution to Twin-Pouch

	Twin-Pouch	Liquid Solution
Amount of GHB	3 grams (1 pouch)	3 grams (6 mL)
Inactive Components	malic acid xylitol lemon/lime flavor orange flavor	malic acid
Final Concentration	50 mg/mL	50 mg/mL*
Final Volume	60 mL	60 mL

*Final concentration outside the range of the most stable formulation. This formulation strength may be only stable at short periods of time such as 48 hours. The twin pouch version could be solubilized at a a concentration within the preferred range of pH and GHB concentration for longer term storage.

Apart from the elimination of the sweetener (xylitol) and flavoring, the two formulations result in identical solutions.

Conclusions

The concentration and volume of the GHB solution that the patient administers is the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. Either method may be used to produce acceptably stable solutions of GHB.

EXAMPLE 2

Preferred Embodiments

SELF PRESERVING FORMULATIONS OF GAMMA-HYDROXYBUTYRATE SUMMARY OF FORMULATION STUDIES—LIQUID XYREM™

I. Maximum Solubility Range

As seen in FIG. **1** and Table 1, the solubility of GHB varies with pH levels at room temperature (25° C.). Additional amounts of GHB can be solubilized in a gel if heat is applied, in which case a 1000 mg/ml concentration can be achieved. The inventors contemplate that though the concentrations or contents of GHB shown in FIG. **1** and Table 1 are preferred for use, due to the ease of preparing and consuming unheated preparations, higher concentrations of GHB in aqueous medium may also be made, up to 1000 mg/ml.

II. Microbal Testing

The inventors used a three factor analysis involving pH, concentrations of GHB and the pH adjuster used. As seen in FIG. **1**, and Table 2, unacceptably low resistance to microbial challenge was seen at 150 mg/ml GHB at pH 3, 5, 7, and 9.0, using HCl as the pH adjusting agent. 150 mg/ml GHB at pH 10.3 without a pH adjusting agent also proved unacceptably resistant to microbial challenge. Borderline acceptable microbial preservativeness was seen in a solution pH adjusted with HCl at 500 mg/ml GHiB at pH 9. At a concentration of 500 mg/ml at pH 6.0 or 7.5, adjusted with either malic acid or HCl, and 500 mg/ml at pH 9.0 adjusted with HCl, the formulation is very effective in a microbial challenge test. The inventors contemplate that a concentration of greater than about 150 mg/ml of GHB, up to the maximal solubility in aqueous solution of GHB, will be suitably resistant to microbial challenge from about pH 3 to pH 10.3. Preferably, the aqueous medium will contain a pH-adjusting or buffering agent.

III. Gamma-Butyrolactone Degradation Range

GBL begins to form if the pH is about 6 or less with the formulation tested thus far.

A. Liquid Formulation Development

The objective of these experiments was to develop a commercial formulation for sodium gamma hydroxybutyric acid. The initial formulation for sodium gamma hydrobutyric acid (GHB) was intended to be an aqueous liquid formulation containing 150 mg/mL GHB, preservatives and flavoring agents. To develop this formulation, studies were conducted to establish the: solubility of the drug in water and as a function of pH, type and concentrations of suitable preservatives, type and concentrations of flavor ingredients, and stability of the formulations.

1. Solubility

The feasibility of preparing formulations containing 150 mg/mL of GHB at pH 3, 5 and 7 was established. Solutions containing 150 mg/mL GHB were prepared. The initial pH was greater than pH 7.5 and the final pH was adjusted to 3, 5 or 7 with hydrocloric acid. The solutions were observed for precipitation and assayed by HPLC for GHB content. The results showed that no precipitation was observed and the drug concentration was found to be 150 mg/mL by HPLC. This information was used as the basis for additional formulation development studies.

2. Preservatives

Preservative effectiveness studies were conducted to identify a suitable preservative for the GHB liquid formulation. The following formulations shown in Table 5 were prepared and tested using *Staphylococcus attreus* (ATCC #6538), *Pseudomonas aeruginosa* (ATCC #9027) and *Aspergillus niger* (ATCC #16404).

TABLE 5

Liquid Formulations Used in Preservative Effectiveness Testing

Formulation	pH	Sodium Benzoate	Methylparaben Propylparaben	Potassium Sorbate	Control
1	3	X			
2	5	X			
3	7	X			
4	3		X		
5	5		X		
6	7		X		
7	3			X	
8	5			X	
9	7			X	
10	3				X
11	5				X
12	7				X
13	no pH adjustment				X

The preservative used in each formulation is marked with an X. The results showed that formulations #3, 4, 6 and 9 reduced all three challenge microorganisms by >99.99% in 48 h of contact time. Formulations #1, 5 and 7 reduced all three challenge microorganism by >99.99% in 7 days of

contact time. Formulations #2, 8, 10, 11, 12 and 13 did not reduce *Aspergillus niger* mold to >99.99%, although some reduction occurred in 7 days of contact time. Controls #10, 11, 12 and 13 demonstrated activity against *Pseudomonas aeruginosa*.

3. Stability

Based on the results of the preservative effectiveness testing, five formulations were selected for stability testing. Table 6 shows the composition of the formulations.

TABLE 6

Liquid Formulations Used in Informal Stability Program

Chemical	1	2	3	4	5
Potassium Sorbate	0.4 gm	0.4 gm			
Sodium Benzoate		1.0 gm			
Methylparaben				0.36 gm	0.36 gm
Propyl-paraben				0.04 gm	0.04 gm
GHB	30 gm	30 gm	30 gm	30 gm	30 gm
Xylitol	40 gm	40 gm	40 gm	40 gm	40 gm
Water q.s.	200 mL	200 mL	200 mL	200 mL	200 mL
Initial pH	8.68	8.68	9.30	7.75	7.75
Formulation Adjusted pH	3.01	5.00	3.00	2.98	4.98

The formulations were packaged in 125 mL, amber PET bottles with safety lined child-resistant caps and stored upright and inverted at 60° C., 40° C./75% relative humidity (RH) and 25° C./60% relative humidity. Samples were removed from the stability chambers after 1, 2 and 3 months and assayed by high performance liquid chromatography (HPLC) for GHB content. Appearance and pH were also monitored.

Table 7 shows the results for the 3 month time point. Samples stored at 60° C. changed color but samples at all other conditions remained unchanged in color.

The pH of all formulations migrated upward over the three month stability period 60C. The percent increase in pH from initial to 3 months, was greater for the formulations which were initially adjusted to lower values.

For example, the migration of pH in formulations 1,3 and 4 (adjusted down to pH 3) were 21–30 percent across all conditions in three months. The migration of pH in formulations 2 and 5 (adjusted down to pH5) were 4.2–12 percent across all conditions in 3 months. Maintenance of pH becomes important for long term storage since preservatives are known to degrade in formulations having pH levels above approximately pH 6.

Additionally, development of flavor systems to mask the negative taste of perservatives is difficult.

TABLE 7

Table 7
Results of Liquid Formulation Informal Stability Study at Three Months

Formulation # (See Table 6)	Attribute	25° C./60% RH Upright	25° C./60% RH Inverted	40° C./75% RH Upright	40° C./75% RH Inverted	60° C. Upright
1	% t = 0	100.7	101.6	101.2	NA	NA
Potassium	pH	3.63	3.64	3.84	3.82	3.91
Sorbate (pH 3) at 3 months storage	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light yellow
2	% t = 0*	102.1	105.0	104.0	102.0	99.6
Potassium	pH	5.21	5.28	5.55	5.56	5.61
Sorbate (pH 5)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light brown
3	% t = 0	102.4	104.1	99.1	102.6	97.0
Sodium	pH	3.60	3.74	3.78	3.75	3.79
Benzoate (pH 3)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, colorless
4	% t = 0	101.5	102.7	100.6	101.2	93.7
4 Methyl &	pH	3.63	3.71	3.81	3.80	3.83
Propyl Parabense (pH 3)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, colorless
5	% t = 0	103.1	105.8	101.9	103.1	95.6
4 methyl &	pH	5.22	5.55	5.55	5.56	5.60
Propyl Prabens (pH 5)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light yellow

*% GHB at t = 0 percent of label claim
**initial time (t = 0)

4. Liquid Formulation Organoleptic Testing

Based on the above stability data and preservative effectiveness testing, a pH 5 formulation containing potassium sorbate was selected as the primary base formulation for flavor system development and organoleptic testing. A pH 3 formulation containing potassium sorbate was selected as the back-up formulation.

B. Dry Powder Formulation Development

Developing a flavor system for the primary and back-up liquid formulations proved to be difficult and a decision was made to develop a dry powder formulation for reconstitution with water before consumption. This approach removed the need for a preservative system, the requirement to adjust pH to levels below pH6, and allowed the development of a suitable flavor system.

1. Dry Powder Formulation Organoleptic Testing

To develop a flavor system for the powder formulation, several parameters were evaluated. The flavor attributes of a

GHB solution was characterized by a professional sensory panel. A mimic base containing similar sensory properties as a GHB solution for flavor system was developed. Generally Recognized As Safe (GRAS) excipients for flavor system development were selected. Different excipients (flavorings, sweeteners, acidulants and flow agents) in the mimic base were screened. Three flavor systems for the focus group test were selected. A preferred flavor system was optimized based on comments obtained from the focus group testing. This final formulation with GHB was optimized.

Based on the above activities, the following formulations in Table 8 were selected for stability studies:

TABLE 8

Composition of Prototype Dry Powder Formulation

Ingredient	Composition (grams)	Purpose
GHB	3	Active
Xylitol	5.5	non-cariogenic sweetener
Malic acid	0.2	Acidulant
Flavor 1	0.2	Flavor ingredient
Flavor 2	0.04	Flavor ingredient
Silicon Dioxide (Cab-O-Sil ®)	0.03	Flow enhancer

2. Dry Powder Formulation Stability

A study was initiated to evaluate the stability of the above prototype formulation in two types of foil packages (high and moderate moisture resistant) as well as the stability of GHB alone in one type of foil package (high moisture resistant). Table 9 shows the Lots that were placed on stability. The foil packages were a high moisture resistant pouch and a moderate moisture resistant pouch. The study protocol, Table 10, required the samples to be stored at 40±2° C./75±5% relative humidity for six months, and 25±2° C./60±5% relative humidity for 12 months. Table 11 shows the tests, methods, number of packets/test and specifications for the study.

TABLE 9

Dry Powder Informal Stability Study Package Composition

Lot Number	Manufacture Date	Package Configuration	Special Comments
SPO #8018 A	10/06/95	Foil Packet	Moderate moisture resistant pouch.
SPO #8018 B	10/06/95	Foil Packet	Highest moisture protection pouch.
SPO #8018 C	10/06/95	Foil Packet	Drug substance only. Highest moisture protection pouch.

TABLE 10

Dry Powder Informal Stability Study Protocol

Storage Conditions	Stability Time in Months 0	1	2	3	6	9	12
40 ± 2° C./75% ± 5% RH		X	X	X	X		
25 ± 2° C./60% ± 5% RH	X	X	C	C	R	R	R

X = Samples to be tested
C = Contingency Samples
R = Reduced testing; assay and H_2O only
RH = Relative Humidity

TABLE 11

Dry Powder Informal Stability Tests and Specifications

Test	Method	Packets/Test	Specification Limits
Appearance Dry Material	Visual	Use HPLC	White to off-white free flowing powder
Appearance Reconstituted Material	Visual	Use HPLC	Cloudy, off-white solution with visible particulates
Rate of Dissolution	Visual	Use HPLC	Material should dissolve completely in five min with mixing
Odor	Olfactory	Use HPLC	Characteristic Lemon/Lime odor
Assay: GHB	HPLC	3	90.0%–110.0%
Assay: Malic Acid	HPLC	Use HPLC	90.0%–110.0%
Impurities/ Degradants	HPLC	Use HPLC	Not more than 1% for any individual impurity/degradant and Not more than 3% total impurity/degradants
Vacuum Leak test	Visual	3	No Appearance of Leaking
pH	USP <791>	Use HPLC	For Information
Moisture	Karl Fisher	3	Report Value - to be determined

After two months at 40±2° C./75±5% relative humidity, the potency (% label claim) of Lots SPO 8018A and SPO 8018B was less than 94.0%, the lower limit of the specification, whereas Lot SPO 8018C showed no loss in potency. Lots 8018A and 8018B showed approximately 96% potencies after 2 months at 25° C.±2° C./65%±5% relative humidity. Lot SPO 8018C again showed no loss in potency at this lower storage condition.

3. Appearance

After 2 months at 40° C.±2° C./75%±5% relative humidity, Lots SPO 8018A and SPO 8018B showed significant melting, whereas Lot 8018C showed no melting. Lots SPO 8018A and SPO 8018B also showed partial melting after 2 months at 25° C.±2° C./65%±5% relative humidity. Lot SPO 8018C again showed no evidence of melting at this lower storage condition.

Based on the physical changes in state observed during the stability studies, it was apparent that a solid state interaction between GHB and the excipient blend had occurred. Since xylitol made up the majority of the excipient blend, it was assumed that xylitol was the primary source of the drug-excipient interaction. An alternative hypothesis was also proposed, based on the possibility that the package was mediating the interaction between GHB and xylitol. Three studies were initiated to test these hypotheses.

4. Stability of GHB Solids in a Set Container-System

In the first study, the samples that were stored at 25±2° C./60±5% relative humidity were transferred to glass vials and then stored at 40±2° C./7±5% relative humidity. In the second study, mixtures of GHB and xylitol were gently rubbed between sheets of different types of foil packaging. The mixtures were observed for changes in physical appearance. In the third study, different mixtures of GHB and xylitol were prepared. Differential Scanning Calorimetry (DSC) thermograms were then done to look for changes in the thermograms. The results of these studies are summarized below.

Transfer to Glass: Samples of Lot 8018A and Lot 8018C that were previously stored at 25±2° C./60±5% relative humidity were transferred to amber screw cap vials and stored at 40±2° C./75±5% relative humidity. Analyses similar to those shown in Table 6 were done. After 1 month, the

potency of Lot 8018A was 94.6% whereas the potency of Lot 8018C (GHB only) was 100%. In addition, Lot 8018A also showed evidence of melting. The results supported the hypothesis that GHB and xylitol were interacting in the solid state and the interaction appeared to be independent of packaging.

Foil Study: Mixtures of GHB and xylitol were placed between folded sheets of several different foil packaging materials. Slight adhesion of the mixed granules with the foil lining was observed for all of the foils examined. No direct evidence of melting was observed, however, even when excessive force was applied to the outer foil surfaces. This data suggests that the packaging material was not responsible for the solid state interaction observed during the stability studies.

DSC thermographs were obtained for samples of GHB/xylitol containing GHB:xylitol mixtures of 33:66, 45:55 and 55 percent 45 respectively. The scans were conducted at a scan rate of 10° C./min. The thermograms showed that the sample containing GHB:xylitol 33:66 showed a broad endothermic transition starting at 35° C.–40° C. Samples with higher ratios of GHB:xylitol also showed broad endothermic transitions that started at temperatures of 45° C.–50° C. The changes seen in the thermograms supported the hypothesis that a solid state interaction may be occurring between GHB and xylitol that resulted in low potencies for formulations containing mixtures of these two agents.

As a result of the changes seen in the DSC thermograms for different mixtures of GHB:xylitol, a study was initiated to investigate the stability of a formulation containing GHB:xylitol excipient blend 55:45. A formulation containing GHB:xylitol excipient blend 33:66 was used as a control sample. The formulations were packaged in glass vials and stored at 50° C., 40±2° C./75±5% relative humidity and 25±2° C./60±5% relative humidity. The appearance and potency of the formulations were monitored through analyses of stability samples. The stability study also showed potency losses after 1 month at 40° C.±2° C./75±5% relative humidity with both the 50/50 GHB:xylitol ratio as well as the original 33/66 ratio formulation. Partial evidence of melting was also observed in both formulations.

Studies with mixtures of GHB:xylitol excipient blend indicated that the mixture was incompatible in the solid state. However, when prepared as an aqueous solution, these mixtures were chemically compatible. Using this information, a decision was made to package the GHB formulation in dual pouches; one pouch containing GHB alone and the other containing a mixture of xylitol and the other flavor ingredients. The formulation will contain equal amounts of GHB and the excipient blend. This product will be prepared, packaged, and may be checked for stability.

EXAMPLE 3

THE PHARMACOKINETICS OF GAMMA-HYDROXYBUTYRATE

I. Study Objectives

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; patients generally ingested the first dose of this medication prior to bedtime and the second dose from 2.5 to 4.0 h later) to narcoleptic patients who are maintained on a chronic regimen of GHB.

II. Study Design

This pharmacokinetic study was conducted as an open-label, single-center investigation in 6 narcoleptic patients. The study design is summarized as follows:

TABLE 12

Screening/Washout →	Treatment/Blood Sampling →	Follow-up
(1 or more days to dosing; washout, at least 8 h	(Two 2 g GHB oral doses, 4 h apart; 21 blood samples)	(Within 48 h after last blood sample)

Narcoleptic patients, 18 years of age or older, who volunteered for this study were screened at least one day prior to the treatment phase. Each patient was determined to be in stable health and evaluated for the presence of narcolepsy, defined for the purposes of this example as one or more years of medical history of narcolepsy as evidenced by a recent nocturnal polysomnogram (PSG) and a valid score from a Multiple Sleep Latency Test (MSLT).

Patients maintained on GHB were allowed to participate. These patients had been weaned from antidepressants, hypnotics, sedatives, antihistamines, clonidine, and anticonvulsants though a stable regimen of methylphenidate (immediate release or sustained release) was allowed. Each patient passed a pre-study physical examination (which included hematology, blood chemistry, urinalysis, and vital signs measurements) prior to the commencement of the treatment phase.

Before oral administration of the first GHB dose, an indwelling catheter was placed in an arm vein and a baseline blood sample was collected. Each patient then ingested a 3 g dose of GHB before bedtime. Another 3 g GHB dose was administered 4 h after the first dose. Twenty-one sequential blood samples were collected over 12 h (starting at 10 min after the first dose and ending at 8 h after the second dose). Upon completion of the treatment phase, a follow-up physical examination which included the measurement of vital signs was performed on each patient within 48 h after the last blood sample. A detailed description of the trial methodology is presented in Section IV.

III. Inclusion Criteria

Patients were included in the study if they: had signed an informed consent prior to beginning protocol required procedures; had not participated in such a study at an earlier date; were willing and able to complete the entire study as described in the protocol; were 18 years of age or older at study entry; had not taken any investigational therapy other than GHB within the 30-day period prior to screening for this study; had an established diagnosis of narcolepsy for at least one year with documentation from a qualified laboratory by a nocturnal polysomnogram (PSG) and a Multiple Sleep Latency Test (MSLT) which demonstrated mean sleep latency to be less than 5 min and REM onset in at least 2 of 5 naps; had not been diagnosed with uncontrolled sleep apnea syndrome, defined as a sleep Apnea Index of 5 or an Apnea Hypopnea Index (AHI) greater than 10 per hour or any other cause of daytime sleepiness; and were free of any medication for their narcolepsy (including hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants) other than GHB and methylphenidate (IR or SR). Patients admitted to this study if they were not experiencing unstable cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, metabolic, neurological, pulmonary, and/or renal disease which would place them at risk during the study or compromise the protocol objective; did not have neurological or psychiatric disorders (including transient ischemic attacks,

epilepsy, or multiple sclerosis) which, in the investigator's opinion, would preclude the patients' participation and completion of this study; did not have a current or recent (within one year) history of alcohol or drug abuse; did not have a serum creatinine greater than 2.0 mg/dL, abnormal liver function tests (SGOT or SGPT more than twice the upper limit of normal, or serum bilirubin more than 1.5 times normal). Female patients were entered into the study if they were either post-menopausal (i.e. no menstrual period for a minimum of 6 months), surgically sterilized or provided evidence of effective birth control. Females of childbearing potential must agree to continue to use an IUD, diaphragm, or take their oral contraceptives for the duration of the study. Female patients of childbearing potential must have a negative pregnancy test upon entry into the study.

IV. Trial Methodology

A time and events schedule is presented in Table 12.

A. Screening Period/Washout

Six narcoleptic patients who were chronically being treated with GHB were recruited to participate in this pharmacokinetic study. The screening period was at least one day prior to the treatment phase. During the screening period each patient completed the following procedures for the assessment of their physical condition: medical history evaluation; physical examination evaluation; clinical laboratory evaluation; inclusion criteria review. Each patient's GHB and methylphenidate regimen also were recorded on an appropriate case report form (CRF). The investigator also ensured that there was at least an 8-hour washout period for GHB prior to the treatment.

B. Treatment Period/Blood Samples Collection

All patients were hospitalized from approximately four hours prior to first GHB dosing (around 6 p.m.) until the end of the treatment period (around 10 a.m. the next morning). Patients ate their dinner at the clinical research unit soon after arrival and fasted until breakfast next morning. At least three hours elapsed between the completion of dinner and the administration of the first GHB dose. An indwelling catheter was placed in an arm vein of each patient for blood sampling at approximately 30 min and 1 h before the first GHB dose and a baseline blood sample (5 mL) was collected.

The first GHB dose (3 g) was administered at around 10 p.m. Dosing of individual patients were staggered. The second GHB dose was administered at 4 h after the first GHB dose (i.e. immediately after the 4 h blood sample). The exact dosing times in each patient were recorded on appropriate CRF pages. Blood samples (5 mL each) were collected through the indwelling catheter into heparinized tubes at 0.2, 0.4, 0.6, 0.8, 1, 1.5, 2, 3, 4, 4.2, 4.4, 4.6, 4,8, 5, 5.5, 5, 7, 8, 10, and 12 h after the first GHB dose. Blood samples were processed according to the procedures described herein. Patients were monitored for adverse experiences throughout the study according to the specific procedures.

C. Follow-up

Follow-up occurred within 48 h after the last blood sample had been collected. An abbreviated physical examination which included vital signs measurement was performed. Adverse experiences and concomitant medication use, if any, were assessed. Any ongoing adverse experiences and clinically important findings in a patient were followed to the investigator's and/or sponsor's satisfaction before the patient was discharged from the study.

D. Methods of Assessment

1. Medical History

The medical history was recorded during the screening period. The history included gender, age, race, height, prior reaction to drugs, use of alcohol and tobacco, history and treatment, if any, of cardiovascular pulmonary, gastrointestinal, hepatic, renal, immunologic, neurological, or psychiatric diseases and confirmation of inclusion criteria.

2. Physical Examination

Physical Examination included body system review as well as measurement of body weight and vital signs and a neurological examination.

3. Vital Signs

Vital signs measurements included recording of blood pressure, heart rate, respiration, and body temperature.

4. Clinical Laboratory

All clinical laboratory tests were performed at a local laboratory. The laboratory tests and analysis were required of each patient included: hematology, including hemoglobin, hematocrit, red blood cell count, white blood cell count and differential; fasting blood chemistries included blood urea nitrogen (BUN), uric acid, glucose, creatinine, calcium, phosphorus, total protein, albumin, sodium, potassium, SCOT (AST), SGPT (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), and total bilirubin; midstream catch urinalysis included specific gravity, pH, protein, occult blood, ketones and glucose by dipstick determination as well as a microscopic examination of urine sediment for RBC, WBC, epithelial cells or casts or crystals; and a urine pregnancy test, if applicable. Any laboratory parameter that was out of range and considered clinically significant excluded the patient from participation in this study. The investigator would provide an explanation of all observations that were significantly outside the reference range.

5. Concomitant Medication

The continued use of a fixed dose of methylphenidate immediate release or sustained release (IR or SR) is acceptable. The methylphenidate regimen was recorded on the appropriate case report form.

6. Adverse Experiences

An adverse experience are any undesirable event experienced by a patient or volunteer whether or not considered drug-related by the investigator. An undesirable event can be, but is not limited to, subjective symptoms experienced by a patient or, objective findings such as significant clinical laboratory abnormalities. Adverse experience is considered synonymous with the term "adverse event".

The investigators report in detail all adverse experiences and symptoms that occurred during or following the course of trial drug administration for up to 2 days. Included in the description was the nature of the sign or symptom; the date of onset; date or resolution (duration); the severity; the relationship to trial treatment or other therapy; the action taken, if any; and the outcome.

A serious adverse experience is defined as one that is fatal, life threatening, permanently disabling, or which results in or prolongs hospitalization. In addition, overdose, congenital anomaly and occurrences of malignancy are always considered to be serious adverse experiences. An unexpected adverse experience is one not previously reported.

Any serious or unexpected adverse experience (including death) due to any cause which occurs during the course of this investigation, whether or not it is related to the investigational drug, was reported within 24 h by telephone or facsimile. Appropriate authorities were to be informed if the serious or unexpected adverse experience, in the opinion of inventors, was likely to affect the safety of other patients or volunteers or the conduct of the trial.

7. Clinical Supplies-Study Medication

Formulation: Unit 3 g GHB doses (Lot PKI) were obtained from Orphan Medical. Each unit dose comprised twin foil pouches: one pouch containing GHB and the other containing a flavor excipient blend. (Table 8 formulation) Labeling: The clinical supplies for individual patients were packaged in separate containers. Each container included two unit doses, i.e. two twin-pouches. Clinical supplies for eight patients (including those for two replacement patients) were delivered to the investigator. Foil twin-pouches were identified with a two-part label.

Dose Administration: The investigator or designee prepared the oral solution for dosing within 30 min prior to the first oral administration to individual patients. The contents of one twin-pouch was emptied into a dosing cup to which two ounces of water were added. After replacing the lid of the dosing cup, it 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 ingesting in its entirety at 4 h after the first GHB dose.

Investigational Drug Accountability: At the conclusion of the study, all clinical supplies were accounted for on the drug accountability form and unused drug supplies were returned for proper disposition.

8. Determination of Plasma GHB Concentrations

Plasma samples were analyzed for GHB by the Department of Bioanalytical Chemistry (Covance (previously known as Hazelton Corning), Madison, Wis.) A gas chromatographic method with mass selective detection (GC-MSD) was used in the analysis.

9. Data Management and Analysis

Data Base: An EXCEL data base (spreadsheet) was constructed from data recorded on Case Report Forms (CFR) and plasma GHB concentration data sets received from Covance (Corning Hazleton). Each entry in the EXCEL spreadsheet was checked against the CRFs and any data entry error found was corrected.

Pharmacokinetic Analysis: Pharmacokinetic parameters were determined for individual sets of plasma GHB concentration vs. time data using the non-compartmental routine in WinNonlin Version 1.1. The peak GHB concentrations (C_{max}) and the times of their respectively occurrences (t_{max}) were observed values. Terminal half-life ($T_{1/2}$) was obtained by log-linear regression analysis of the terminal phase of concentration vs. time curves. The area under the curve (AUC_{inf}) and the area under the first moment curve ($AUMC_{inf}$) were calculated by the linear trapezoidal rule up to the last determined concentration and included extrapolated areas to time infinity. Apparent oral clearance (CL/F) was calculated as Dose/AUC_{inf}. Volume of distribution (Vz/F) was determined by taking the ratio between CL/F and λ_z (elimination rate constant). Mean residence time (MRT) was estimated from the ratio between $AUMC_{inf}$ and AUC_{inf}.

Safety Analyses: Results of physical examinations, vital signs, clinical laboratory data were summarized in tabular form and presented by patient number. Adverse events also were tabulated in a similar fashion.

10. Results

Patient and Study Accountability: Six narcoleptic patients were enrolled and all six completed the study in its entirety.

Protocol Compliance: There were no inclusion criteria violations. All patients admitted into the study met the study entrance requirements and completed the screening phase at least one day before the treatment phase.

All six patients took non-study medications in addition to methylphenidate and GHB doses because none of their concomitant medications (Synthyroid, Premarin, Lovastatin, Flovastatin, furosemide, potassium, hydrochlorothiazide, lansoprazole, and verapamil) were on the exclusion list (which included hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants). Adverse experience probes, vital sign measurements, and essentially all pharmacokinetic blood samples were performed at protocol specified times; the few deviations in blood sampling times should not have any impact on the outcome of the study since actual blood sampling times were used in the pharmacokinetic analysis.

The diagnosis of narcolepsy for at least one year in each patient was verified by a nocturnal polysomnogram (NSC) and a Multiple Sleep Latency Test (MSLT) conducted at a qualified laboratory. Five patients have been maintained on GHB nightly for over 10 years and one patient has been receiving GHB nightly for two years. One patient (Subject 101) also had multiple sclerosis; however, the attending physician, judged that it would not interfere with the objective of this study. A few of the screening clinical laboratory results marginally fell outside the reference range but none was considered by the attending physician to be clinically significant.

Exposure to Study Drug: All patients ingested the two GHB doses as scheduled (immediately prior to bedtime). The GHB doses per kg body weight ranged from 26.4 to 52.4 mg/kg.

Plasma GHB Concentration Profiles: It was noted that, in certain cases, (Patients #103, and #106), plasma GHB concentrations did not decline from the first C_{max} to zero concentration at h 4. Upon achievement of the second C_{max}, the semi-logarithmic plots of concentration versus time data in Patients #102, #103, and #105 exhibited a convex decline profile. Such a decline pattern suggested non-linear pharmacokinetics. The highest plasma GHB concentration observed in the study was 125.0 lg/mL which occurred in Subject 101 after the second 3 g GHB dose.

Pharmacokinetic Parameter Estimates: The mean (±SD) showed that maximum GHB concentrations (C_{max}) were 62.8±27.4 μg/mL and 91.2±25.6 μg/mL for the first and second GHB doses, respectively. The corresponding mean observed times to maximum concentrations were 40±6 and 36±7 min after the first and second GHB doses, respectively. The mean AUC_{inf} was 17732±4603 μg/mL.h. The mean CL/F was 4.2±1 mL/min/kg and the mean V_z/F was 307±96 mL/kg. The mean MRT_{inf} was 249±56 min. The mean GHB $T_{1/2}$, estimated by linear regression of log[C] vs. time data of the terminal phase of the second GHB dose was 53±19 min.

Adverse Experiences: No adverse experiences were reported in the study.

Follow-up Safety Assessments: Inspection of screen and follow-up physical examination results per individual patient did not identify any changes attributable to GHB.

11. Discussion

To the inventors' knowledge, the level of GHB in human systemic circulation has not been reported in the literature. Hence, baseline (0 h) plasma samples were analyzed for GHB concentrations. The GC-MSD method used in the present study had a limit of quantification (LOQ) of 7.02 μg/mL and analysis of the baseline plasma samples showed the endogenous levels of GHB are below this sensitivity limit. This finding was confirmed by adding known amounts of GHB (5, 10, and 25 μg per mL of plasma) to blank human plasma samples and subjected these samples to GC-MSD analysis. This method of standard addition allowed an estimation of the endogenous GHB level in human plasma

which was found to average about 2.02 μg/mL, (i.e. approximately 2/7 of the Limit Of Quantitation (LOQ) for a validated assay. Hence, the endogenous GHB level was not subtracted from exogenous GHB concentrations prior to pharmacokinetic analysis.

Values of mean t_{max} (~40 min after dosing) and $t_{1/2}$ (~35 min) suggest that the GHB solution administered to narcoleptic patients in this study was readily absorbed and rapidly eliminated. In 3 out of 6 patients the drug was essentially gone from the systemic circulation by h 4 after the first GHB dose whereas in the remaining three patients residual GHB levels of 15 μg/mL was still detected at h 4.

The convex nature of the decline of plasma GHB concentrations in three patients after achievement of the second C_{max} indicated that elimination of GHB from the systemic circulation in these three patients is capacity limited. Nevertheless, it should be noted that plasma GHB concentrations were no longer detectable by h 6 after the second GHB dose (10 h after the first GHB dose). The mean apparent oral clearance found in this study was 4.2±1.0 mL/min/kg and appeared to be comparable to the apparent oral clearance of 5.3±2.2 mL/min/kg reported in the literature for a group of alcohol dependent patients who were administered a dose of 50 mg/kg (Ferrara, 1992). While it appeared that the GHB dose (ranging from 26.4 to 52.4 mg/kg with a mean of 36.5 mg/kg) in the present study was lower than the comparison GHB dose (50 mg/kg) administered to the alcohol dependent patients (Ferrara, 1992), it should be noted that each patient in the present study was administered two consecutive GHB doses at four-hour interval and residual GHB levels were detected in three out of six patients immediately prior to the second GHB dose. The GHB pharmacokinetic non-linearity in alcohol dependent patients easily can be observed from the apparent oral clearance which increased to 8.1±4.8 mL/min/kg when the GHB dose is reduced to 25 mg/kg dose (Ferrara, 1992). In the present study, the non-linearity was less obvious because each narcoleptic patient received two consecutive fixed 3 g doses regardless of body weight.

The mean elimination half-life of GHB in the six narcoleptic patients was determined to be 53±19 min, longer than that in alcohol dependent patients after a 50 mg/kg GHB dose (Ferrara, 1992). The lengthening of GHB elimination half-life observed in this study partially was caused by the wider spacing in sampling time points. However, capacity limited elimination of this drug in some of the narcoleptic patients also could have contributed to this prolongation.

GHB appears to have a shortcoming in that its elimination from the body is capacity limited in some patients when the drug is administered at a fixed regimen of 3 g twice nightly at four-hour interval. However, from a therapeutic perspective, GHB offers an advantage in the treatment of narcolepsy because by the time a patient wakes up in the morning (i.e. 8 to 10 h after the first GHB dose), all GHB, including that from the second dose, will have been eliminated from the systemic circulation. GHB was also well tolerated by narcoleptic patients in this study. No adverse experience was reported.

12. Conclusions

The capacity limited elimination kinetics was observed in three out of six patients who had been administered two consecutive 3 g oral doses of GHB, 4 h apart. From a pharmacokinetic perspective, dividing the nightly GHB dose into two portions and administering the two portions to narcoleptic patients at a 2.5- to 4-h interval was rational because the elimination half-life of GHB was short (<1 h). The pharmacokinetic profiles of GHB in narcoleptic patients who had been receiving this agent nightly for years appeared to be comparable to those in alcohol dependent patients (Ferrara, 1992).

EXAMPLE 4

SODIUM OXYBATE FORMULATION STUDY

I. Study Objectives

This example described ways that sodium oxybate may be prepared and tested for stability to determine preferred formulations. Various formulations of sodium oxybate in water were prepared under different conditions of mixing and with addition of selected acidulents at multiple pH levels (Neo-Pharm Laboratories, Blainville, Quebec). Selected formulations were placed on real time and accelerated stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Therefore several acidulents across a range of 6.0–9.0 were evaluated.

II. Study Design-Part I

The following experimental work is designed to be performed in two stages. Initial studies were conducted to evaluate the impact of conditions of formulation, pH and acidulent on the resultant levels of impurities, specified and unspecified, and potency of sodium oxybate. Sodium oxybate was prepared (MDS Neo-Pharm Laboratories, Quebec Canada), under different conditions of mixing and with addition of selected acidulents at multiple pH levels. These formulations of sodium oxybate acidulent were then tested.

A. Preliminary studies

1. Formulations description

All formulations were prepared at a concentration of 500 mg/cc of sodium oxybate in water. Three acidulents (HCl, malic acid, and phosphoric acid), were selected and tested at pH 6.0, 7.5 and 9.0.

2. Method of formulation

Solutions, were prepared using the described methods:

a. Rapid mix method

Sodium oxybate was dissolved in water and concentrated acidulent was added immediately without temperature control. Temperature of solution was monitored and recorded prior to and during addition of acidulent. The time of equiliberation to room temperature was also recorded. After the solution reached ambient room temperature, it was filtered through a 10 Mm filter.

b. Cool mix method:

Sodium oxybate was dissolved in water. Acidulent was diluted to 10% and slowly added. The solution was cooled by water with jacket or ice bath. Monitor and record the temperature of the solution was monitored and recorded during addition of acidulent. The time of equilibrium from room temperature was also recorded. The preferred maximum temperature should be maintained at less than 40° C. The solution was filtered through a 10 μm filter.

c. Reverse order of addition:

Acidulent was added to water and cooled to room temperature. The sodium oxybate was dissolved in the diluted acidulent solution. The temperature of solution was monitored and recorded during addition of sodium oxybate. The solution was filtered through a 10 μm filter.

d. Sodium oxybate control

Sodium oxybate was dissolved in water to a concentration of 500 mg/cc with no added acidulent. The final pH was recorded and the solution was filtered through a 10 μm (micron or micrometer) filter.

3. Solution data:

Data was recorded for each solution which included: 1) date of preparation 2) date of analysis, 3) amount of acidulent required to achieve target pH, 4) length of time for dissolution of sodium oxybate, 5) temperature profile of solution over time of solution preparation to be recorded at 15 minute intervals, 6) final pH of solution.

4. Testing requirements:

The following methods were used to test the prepared solutions: pH, HPLC (High Pressure Liquid Chromotography) for potency (sodium oxybate), and for impurities. Time 0 analysis was performed immediately (within 24 h). RRT=(relative retention time).

B. Summary of Part I:

1. Preliminary Evaluation of Sodium Oxybate Formulations

Tables 13, 14 and 15 provide test results for the three methods of preparation of sodium oxybate formulations.

TABLE 13

Formulation Study/PR98068
Results of Formulation Study - Time Zero determinations of Sodium Oxybate, GBL and Unspecified Impurities
Preparation Method A

Addition of Concentrated Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/cc % [95–105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (4/23/98)	pH 9.0	9.0	509 mg/cc	0.009%	RRT 4.88 = 0.01%
(10 drops over 2 minutes)			101%		
(2.5 ml/4 minutes)	pH 7.5	7.5	507 mg/cc	0.01%	RRT 4.89 = 0.02%
			101%		
(45 ml/34 minutes)	pH 6.0	6.0	504 mg/cc	0.033%	RRT 4.89 = 0.33%
			101%		
Malic Acid (4/24/98)	pH 9.0	9.1	498 mg/cc	0.009%	RRT 4.89 = 0.01%
(0.12 gm)			99.6%		
(1.6 gm)	pH 7.5	7.6	506 mg/cc	0.009%	RRT 4.89 = 0.01%
			101%		
(25 gm)	pH 6.0	6.2	493 mg/cc	0.011%	RRT 4.89 = 0.01%
			98.6%		
H_3PO_4 (4/24/98)	pH 9.0	9.0	493 mg/cc	0.009%	RRT 4.89 = 0.01%
(2 drops)			98.6%		
(1.0 ml)	pH 7.5	7.5	493 mg/cc	0.009%	RRT 4.89 = 0.02%
			98.6%		
(17.3 ml)	pH 6.0	6.1	497 mg/cc	0.063%	RRT 4.89 = 0.02%
			99.4%		
Sodium Oxybate Control	n.a.	9.8	500 mg/cc	0.009%	RRT 4.89 = 0.04%
No Acidulent			100%		

*Method A = Mix Method with Concentrated Acidulent and Temperature Monitoring

TABLE 14

Preparation Method B

Addition of Diluted Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95–105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (25%) (4/28/98)	pH 9.0	9.1	500 mg/cc	0.009%	RRT 4.88 = 0.01%
(20 drops)			100%		
(8.0 ml)	pH 7.5	7.6	499 mg/cc	0.009%	RRT 4.88 = 0.01%
			99.8%		
(175 ml)	pH 6.0	6.0	502 mg/cc	0.016%	RRT 4.88 = 0.02%
			101%		
H_3PO_4 (25%) (4/29/98)	pH 9.0	8.9	499 mg/cc	0.007%	RRT 4.92 = 0.02%
(0.3 ml)			99.8%		
(4.0 ml)	pH 7.5	7.5	497 mg/cc	0.008%	RRT 4.89 = 0.02%
			99.4%		
(120 ml)	pH 6.0	6.0	499 mg/cc	0.019%	RRT 4.89 = 0.01%
			99.8%		
Malic Acid (500 mg/cc) (4/30/98)	pH 9.0	9.0	495 mg/cc	0.008%	RRT 4.92 = 0.02%
(0.115 gm/0.23 ml)			99%		
(1.75 mg/3.5 ml)	pH 7.5	7.4	488 mg/cc	0.009%	RRT 4.92 = 0.01%
			97.5%		
(35 gm/70 ml)	pH 6.0	6.0	487 mg/cc	0.013%	RRT 4.92 = 0.01%
			97.0%		

*Acidulent added slowly at the rate of 2–3 drops/second

TABLE 15

Preparation Method C

Reverse Order of Addition* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95–105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (5/1/98)	pH 9.0	9.0	497 mg/cc	0.006%	RRT 4.92 = 0.03%
(20 drops)			99.4%		
(2.4 ml)	pH 7.5	7.6	504 mg/cc	0.004%	RRT 4.92 = 0.04%
			101%		
(45 ml)	pH 6.0	6.0	493 mg/cc	0.044%	RRT 4.92 = 0.04%
			98.6%		
H_3PO_4 (5/4/98)	pH 9.0	8.9	496 mg/cc	0.005%	RRT 4.91 = 0.03%
(0.08 ml)			99.2%		
(1.0 ml)	pH 7.5	7.6	496 mg/cc	0.004%	RRT 4.91 = 0.04%
			99.2%		
(30 ml)	pH 6.0	6.1	489 mg/cc	0.023%	RRT 4.91 = 0.04%
			97.8%		
Malic Acid (5/5/98)	pH 9.0	9.0	495 mg/cc	0.006%	RRT 4.93 = 0.02%
(0.12 gm)			99%		
(1.6 gm)	pH 7.5	7.6	497 mg/cc	0.004%	RRT 4.93 = 0.04%
			99.4%		
(35 gm)	pH 6.0	6.2	495 mg/cc	0.044%	RRT 4.93 = 0.04%
			99%		

*Acidulent added to water first, GHB added second.

Review of the data indicated that the optimum method for preparation of sodium oxybate with minimal impurity levels is Method B: Controlled mixing with diluted acidulent. Method 2b resulted in formulations with lowest levels of GBL.

2. Conclusions.

Additional evaluations were carried out on selected formulations: 1) sodium oxybate with HCl as acidulent, at pH 7.5, and 2) sodium oxybate with malic acid as acidulent, pH 6.0, 7.5, and 9.0.

III. Study Design-Part II

Microbial Challenge and Stability Tested to determine the most preferred embodiments, the number of formulations was limited to three based on the data prepared from the above experiments.

A. Kinetic Stability Study with Selected Formulations

Samples of formulations are stored in tightly closed containers. Storage Conditions were 25° C., 40° C., and 60° C. Time points in brackets were tested at the inventor's discretion. The samples were tested according to the following schedule: at 25° C. storage temperature, the assay points will be 0, 14, 28, 45, 60 days and 120 days; at 40° C. storage temperature, the assay points will be 0, 7, 14, 28, 45, 60 days; at 60° C. storage temperature, the assay points will be at 0, 3, 7, 14, 28, 45 days, and, 60 days.

The testing requirements included pH, HPLC for sodium oxybate (duplicate injections of single sample preparation), and impurities, specified and unspecified.

B. Preservative Effectiveness Testing of selected formulations

Microbial challenge testing of formulations was preformed according to USP XXIII, <51>, Eighth Supplement. Solutions are determined to "Pass or Fail" based upon the USP criteria for perservative effectivuess which states: For Bacteria, "Not less than 1 log reduction from the initial microbial count at 14 days and no increase from the 14 days count at 28 days;" and for yeast and molds, "No increase from the initial calculated count at 14 and 28 days." Solutions which met these criteria were designated as "Pass" and those that did not meet these criteria were designated as "Fail".

C. Summary Stability Results:

1. Formulations prepared with Malic Acid as acidulents:

a. Malic Acid, pH 6.0 formulation (25°), GBL and impurity A levels were very low on Day 0, however, by Day 45 GBL levels had reached 2.8%. Impurity A increased from 0.01 to 1.0%, and pH increased from 6.0 to 6.3 by day 45. This formulation stored at 40° C. and 60° C. showed GBL levels up to 5.4%, impurity A levels increased to 2.3%, and pH increased to 6.3 by Day 14.

b. Malic Acid, pII 7.5 formulation (25° C.), GBL levels were 0.009% on Day 0, and increased to 0.17% by day 45. Impurity A increased from 0.01% to 0.1% and pH increased from 7.5 to 7.9. Malic acid, pH 7.5 GBL levels are reached (40° C.) and 60° C. a maximum of 0.22%. Impurity A levels reached 0.1% and pH increased to 8.0. Under accelerated conditions, all parameters reached an apparent maximum by Day 7 and did not increase significantly thereafter.

c. Malic Acid, pH 9.0 formulation (25° C.,) GBL levels measure 0.008% on Day 0, and increased slightly to 0.013% on Day 45. Impurity A did not increase nor did pH increase. Under accelerated conditions, GBL increased from 0.008% to a maximum of 0.018% by Day 14. Impurity A increased slightly from 0.10 to 0.014% by Day 14.

2. Formulations prepared with HCl as acidulents.

HCl, pH 6.0 formulation (25°) GBL levels measured 2.8% by Day 30, and impurity A 0.004%, and pH 6.0. Accelerated storage conditions (40° C.) GBL levels were measured at 6.6%, and impurity A measured 3.1% by Day 30.

HCl, pH 7.5 formulation (25%) GBL levels measured 0 041% on Day 0, Impurity A measured 0.02%, and by Day 18 GBL measured to 0.12% and impurity A to 0.07%. Under accelerated conditious (40° C. and 60° C.), GBL increased to a maximum of 0.21%, impurity A increased from 0.02% to 0.1%, and pH increased from 7.5 to 8.0. As with Malic Acid at pH 7.5, the measured parameters reached maximum by Day 7 and did not increase significantly thereafter.

HCl, pH 9.0 formulation (25° C.) GBL levels reached 0.022% by Day 18. Impurity A stayed constant at 0.01% for 18 days. Under accelerated conditions (40° C.) GBL levels

were equivalent to 25° C. storage (0.21%). Impurity A showed no increase over 25° C. conditions.

3. Conclusions.

Formulations selected for microbial challenge testing were the following: HCl, pH 7.5, and malic acid, pH 7.5. The rationale for this decision was twofold. First, the formulations were selected based on minimal formation of GBL and impurity A. Second, the formulations were selected to maintain a pH in the neutral range.

EXAMPLE 5

FURTHER EVALUATION OF SODIUM OXYBATE FORMULATIONS

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of garnma-hydroxybutyrate.

Scope: Various formnlations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple pH levels. Solutions were prepared and tested at Neo-Pharm Laboratories, Blainville, Quebec. All formulations successfully prepared were placed on limited stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Conditions of varying pH and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Procedures: Solutions were prepared as summarized and microbial challenge testing carried out as follows:

I. Evaluation of Sodium Oxybate Formulations

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of gamma-hydroxybutyrate.

Scope: Various formulations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple pH levels. Selected formulations were studied for limited stability. Earlier studies demonstrated that degradation prodncts are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Conditions of varying pH and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Responsibility: It was the responsibility of Neo-Pharm Laboratories to prepare selected formulations and perform testing per this protocol. Orphan Medical, New Medicine Development and Quality Assurance were responsible for reviewing raw data at the decision point, defining which formulations will be included in stability testing. Orphan Medical was also responsible for reviewing final results (raw data) and the final report.

Procedure: The following formulations were prepared by scientists at Neo-Pharm following the steps listed below and dispensed into containers (amber PET 240 ml bottle OMI CS-460) and closures (Clic-Loc 111, 24–400, OMI CS-470) to a volnme of 200 ml each bottle. The bottles were tested by 28-day microbial challenge and by limited stability testing at 25° C. including, appearance, pH, potency, and impurity profile on day 1 (day of preparation) and day 28.

Formulations Prepared and Evaluated Using Sodium Oxybate:

TABLE 16

Formulations Prepared and Evaluated Using Sodium Oxybate

Formulation ID No.	Sodium Oxybate Concentration	Acidulent	Final pH
1	500 mg/cc	Malic Acid	7.5
2	250 mg/cc	Malic Acid	7.5
3	350 mg/cc	Malic Acid	7.5
4	450 mg/cc	Malic Acid	7.5
5	550 mg/cc	Malic Acid	7.5
6	650 mg/cc	Malic Acid	7.5
7	500 mg/cc	Citric Acid	7.5
8	500 mg/cc	Malic Acid	5.0

1. Preparation: Method for preparation of various formulations: As previously determined in PR98068, the method of choice for preparation of liquid formulations of sodium oxybate was the following:

a. For a one liter quantity of product, add the sodium oxybate in 500 ml of purified and stir until dissolved. Prepare a 10% solution of the acid (Malic or Citric) and add slowly to the solution of sodium oxybate. The solution should be monitored for pH and temperature and both variables recorded at reasonable intervals (every 10 or 15 minutes). When the target pH is attained, the solution will be Q. S. to 1 liter, and pH rechecked and recorded.

b. The final solutions will be filtered through 10 μm filters and 200 mL dispensed into 5 amber PET bottles with closures (provided by Orphan Medical, Inc.). Two bottles will be used for microbial challenge studies and the remaining three bottles will be placed on limited stability.

2. Testing: Formulations were tested by two methods of evaluation:

a. Limited stability evaluation:
(1) Storage Conditions: 25° C.
(2) Pull Points: Day 0 (day of preparation), and day 28
(3) Testing Requirements:

Test	Method
Appearance	Visual
Potency	HPLC Neopharm 764
Impurities	HPLC Neopharm 793DT
pH	USP <791>

b. Microbial challenge:
(1) Storage Conditions: Microbial challenge studies of above formulations were set up with 5 microorganisms and stored for 28 days at 20–25° C., per USP<51>Eighth Supplement.
(2) Microorganisms: After a sufficient quantity of each formulation is prepared, aliquots were inoculated with 5 microorganisms at a concentration of at least 10^5 microorganisms/cc:
(a) *Escherichia coli*, ATCC 8739
(b) *Pseudomonas aeruginosa*, ATCC 9027
(c) *Staphylococcus aureus*, ATCC 6538
(d) *Aspergillus niger*, ATCC 18404
(e) *Candida albicans*, ATCC 10231
(3) Time Points: A determination of the viable cell concentration in each inoculated container was performed after 0, 1, 3, 7, 14, 21 and 28 days.

B. Formulations To Be Prepared From Alternative Salts of Gamma-Hydroxybutyrate: This work may be staged to take place at a later time than the work described above.

TABLE 17

Formulation ID No.	Formulation Detail: Salt of GHB	Concentration of Salt of GHB	Acidultent	Final pH
9	Calcium salt	500 mg/cc (Or maximum possible*)	Malic Acid (If compatible)	7.5

1. Solubility determination: Little information is available about the solubility of this alternative salt of gamma-hydroxybutyrate and a determination of solubility was done in advance of efforts to prepare formulations for evaluation by stability and microbial challenge. Maximum solubility is evaluated for pH unadjusted soluations and within the pH range desired for this formulation (pH 6.0–8.0). If solubility is limited, the formulation will be changed to accommodate the solubility limitations. The preferred acidulent for this work is Malic acid. If acid is not compatible with the salt, then an alternative acid can be selected.

2. Preparation: Method for preparation of alternative salt formulations:

a. The previously described method (Part A) is used for preparation of formulations of calcium gamma-hydroxybutyrate at the concentrations and specified pH determined by solubility experiments.

b. The final solutions were filtered through 10 μm filters and dispensed into 5 amber PET bottles with closures (provided by Orphan Medical, Inc.). Two bottles are used for microbial challenge studies and two bottles are placed on limited stability. The remaining bottles are retained for any additional studies at a future time.

3. Testing: Formulations are tested as described above.

C. Reporting of Results: The results will be reported for the Stability and Microbial Challenge results in standard format as defined by the described Orphan Medical Development. Copies of HPLC chromatograms and any raw data from these studies will be provided with results.

D. Acceptance Criteria: Specific acceptance criteria for this study can be described analogous to those for sodium oxybate.

Results: Summarized as follows in Tables 18, 19 and 20 for various studies.

TABLE 18

Result Summary
Results of Protocol 98126 Microbial Challenge Study

	0	Day 1	Day 7	Day 14	Day 21	Day 28
			Lot Number MCH1064-33			
GHB, pH 7.50, 500 mg/cc Malic Acid						
E. coli	490,000	5,500	<100	<10	<10	<10
P. aeruginosa	141,000	21,600	<100	<10	<10	<10
S. aureus	1,035,000	405,000	79,500	8,300	1,645	375
C. albicans	835,000	147,000	<100	<10	<10	<10
A. niger	370,000	285,000	120,500	246,500	148,500	183,000
			Lot Number MCH1064-35			
GHB, pH 7.50, 250 mg/cc Malic Acid						
E. coli	705,000	229,500	<100	<10	<10	<10
P. aeruginosa	224,500	5,200	<100	<10	<10	<10
S. aureus	1,135,000	390,000	262,500	31,500	4,250	155
C. albicans	705,000	435,000	52,000	850	<10	<10
A. niger	510,000	515,000	155,500	176,000	147,500	184,000
			Lot Number MCH1064-37			
GHB, pH 7.50, 350 mg/cc Malic Acid						
E. coli	365,000	310,000	13,400	<10	<10	<10
P. aeruginosa	205,000	15,600	50	<10	<10	<10
S. aureus	1,170,500	605,000	67,500	<60	60	<10
C. albicans	870,000	355,000	8,300	<10	<10	<10
A. niger	540,000	525,000	172,000	155,500	155,500	163,500
			Lot Number MCH1064-43			
GHB, pH 7.50, 550 mg/cc Malic Acid						
E. coli	425,000	63,500	700	<10	<10	<10
P. aeruginosa	171,500	211,500	250	<10	<10	<10
S. aureus	1,020,000	520,000	41,500	1,050	180	10
C. albicans	880,000	157,500	800	<10	<10	<10
A. niger	545,000	505,000	131,000	156,500	205,000	187,500
			Lot Number MCH1064-45			
GHB, pH 7.50, 550						

TABLE 18-continued

Result Summary
Results of Protocol 98126 Microbial Challenge Study

	0	Day 1	Day 7	Day 14	Day 21	Day 28
mg/cc Malic Acid						
E. coli	660,000	58,500	450	<10	<10	<10
P. aeruginosa	896,000	14,450	900	<10	<10	<10
S. aureus	860,000	132,000	19,750	935	110	45
C. albicans	1,125,000	166,000	<100	<10	<10	<10
A. niger	530,000	530,000	105,500	153,000	157,500	177,000
Lot Number MCH1064-47						
GHB, pH 7.50, 650 mg/cc Malic Acid						
E. coli	630,000	119,000	1,350	<10	<10	<10
P. aeruginosa	183,500	5,900	50	<10	<10	<10
S. aureus	890,000	650,000	76,000	14,550	510	1,150
C. albicans	675,000	145,500	<100	<10	<10	<10
A. niger	535,000	385,000	103,000	162,000	187,000	173,000
Lot Number MCH1064-85						
Ca-Oxybate, pH 7.50, 500 mg/cc Malic Acid						
E. coli	425,000	121,000	1,650	<10	<10	<10
P. aeruginosa	420,000	22,000	300	<10	<10	<10
S. aureus	265,000	2,000	<100	<10	<10	<10
C. albicans	565,000	440,000	29,500	<1000	<10	<10
A. niger	1,310,000	965,000	370,000	640,000	690,000	675,000
Lot Number MCH1064-49						
GHB, pH 7.50, 500 mg/cc Citric Acid						
E. coli	615,000	6,500	<100	<10	<10	<10
P. aeruginosa	69,500	14,600	<100	<10	<10	<10
S. aureus	650,000	305,000	1,700	<10	<10	<10
C. albicans	720,000	107,000	<100	<10	<10	<10
A. niger	375,000	380,000	99,500	178,500	212,500	165,500

TABLE 19

Result Summary
Data from December 30, 1997

	(n = 3) Inoculu	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Results
GHB (7.5) 750 mg/cc									
E. coli	470,000	160,000	64,500	4,300	420	<10	<10	<10	
P. aeruginosa	437,500	152,000	3,500	10	<10	<10	<10	<10	
S. aureus	447,500	330,000	24,500	42,000	8,050	1,935	15	10	
C. albicans	375,000	234,500	28,000	1,950	<10	<10	10	<10	
A. niger	475,500	395,000	395,000	229,000	101,500	161,500	101,000	202,000	
750 mg/cc + 0.2% MP/PP, pH 7.50									
E. coli	470,000	127,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	61,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	350,000	3,000	4,050	<10	<10	<10	<10	
C. albicans	375,000	103,500	<1,000	<10	<10	<10	<10	<10	
A. niger	457,500	315,000	415,000	35,500	79,500	38,500	87,500	6,400	
750 mg/cc + 0.1% MP/PP, pH 7.5									
E. coli	470,000	157,000	7,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	90,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	239,000	5,500	16,950	600	<10	<10	<10	
C. albicans	375,000	169,000	<1,000	<100	<10	<10	<10	<10	
A. niger	457,500	335,000	425,000	34,500	168,500	90,500	95,500	99,000	

TABLE 19-continued

Result Summary
Data from December 30, 1997

	(n = 3) Inoculu	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Results
750 mg/cc + 0.2% Potassium sorbate, pH 7.5									
E. coli	470,000	180,000	735,000	6,200	475	<10	<10	<10	
P. aeruginosa	437,500	152,000	1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	264,000	27,500	49,800	14,550	2,370	<10	<10	
C. albicans	375,000	300,000	41,500	3,800	<10	<10	<10	<100	
A. niger	457,500	325,000	360,000	25,000	202,000	500,000	345,000	425,000	
GHB (pH 6.0) 500 mg/cc									
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10	
P. aeruginosa	437,500	172,000	3,000	<10	<10	<10	<10	<10	
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10	
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10	
A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600	
									PASS
500 mg/cc + 0.2% MP/PP, pH 6.0									
E. coli	470,000	163,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	60,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	243,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	150,500	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	400,000	38,000	<10	<10	<10	<10	<10	
									PASS
500 mg/cc + 0.1% MP/PP, pH 6.0									
E. coli	470,000	206,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	118,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	330,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	221,000	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	355,000	93,500	59,000	8,700	315	35	<10	
									PASS
500 mg/cc + 0.2% Potassium sorbate, pH 6.0									
E. coli	470,000	222,000	46,500	150	<10	<10	<10	<10	
P. aeruginosa	437,500	136,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	410,000	<1,000	130	<10	<10	<10	<10	
C. albicans	375,000	395,000	28,500	<100	<10	<10	<10	<10	
A. niger	475,500	405,000	270,000	63,000	51,000	49,500	39,000	11,150	
									PASS

TABLE 20

Result Summary

	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
Data from Study Dated December 30, 1997								
GHB (pH 6.0) 500 mg/cc								
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10
P. aeruginosa	437,500	172,000	3,000	<10	<10	<10	<10	<10
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10
A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600
Data From Study Begun March 12, 1998								
GHB (pH 6.0) 500 mg/cc								
E. coli	500,000	370,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	198,500	nd	nd	<100	<10	<10	<10
S. aureus	280,000	480,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	340,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	445,000	nd	nd	9,050	20,500	9,450	1,120
GHB (pH 6.0)								

TABLE 20-continued

	Result Summary							
	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
500 mg/cc								
E. coli	500,000	199,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	192,500	nd	nd	<100	<10	<10	<10
S. aureus	280,000	300,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	370,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	445,000	nd	nd	10,100	22,750	3,800	4,050
GHB (pH 9.0) 500 mg/cc								
E. coli	500,000	320,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	12,000	nd	nd	<100	<10	<10	<10
S. aureus	280,000	530,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	510,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	345,000	nd	nd	13,800	158,500	315,000	110,500
GHB (pH 9.0) 500 mg/cc								
E. coli	500,000	305,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	20,000	nd	nd	<100	<10	<10	<10
S. aureus	280,000	495,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	380,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	355,000	nd	nd	12,550	157,500	365,000	365,000
GHB (pH 6.0 + Excipients) 500 mg/cc								
E. coli	500,000	96,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	26,000	nd	nd	<100	<10	<10	<10
S. aureus	280,000	155,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	205,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	131,500	nd	nd	6,250	1,825	870	370
GHB (pH 6.0 + Excipients) 500 mg/cc								
E. coli	500,000	93,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	30,500	nd	nd	<100	<10	<10	<10
S. aureus	280,000	185,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	135,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	121,500	nd	nd	5,400	1,785	795	505

TABLE 21

		Result Summary						
GHB (pH 7.50)	HCl	July 2, 1998 Start Date						
500 mg/cc	Initial Conc	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	97000	82000	19200	nd	1000	<10	<10	<10
P. aeruginosa	48500	29500	520	nd	<10	<10	<10	<10
S. aureus	54500	58000	42350	nd	4950	245	<10	<10
C. albicans	58500	38500	1060	nd	<100	<10	<10	<10
A. niger	77500	48000	21450	nd	46000	46000	38000	54000
GHB (pH 7.50) 500 mg/cc	Malic Acid Initial Conc	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	97000	83000	44450	nd	3050	70	<10	<10
P. aeruginosa	48500	15650	545	nd	<10	<10	<10	<10
S. aureus	54500	59500	48400	nd	17400	6500	820	505
C. albicans	58500	44000	6200	nd	500	<10	<10	<10
A. niger	77500	35500	24100	nd	28000	49000	44500	44000

For Category 1C Products:
Bacteria: Not less that 1 log reduction from the initial count at 14 days, and no increase from the 14 days count at
28 days.
Yeast and Molds: No increase from the initial calculated count at 14 and 28 days.

GHB (pH 7.50)	HCl	July 2, 1998 Start Date						
500 mg/cc	Initial Co	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28

TABLE 21-continued

Result Summary								
E. coli	9.70E+04	8.20E+04	1.92E+04	nd	1.00E+03	<10	<10	<10
P. aeruginosa	4.85E+04	2.95E+04	5.20E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.80E+04	4.24E+04	nd	4.95E+03	2.45E+02	<10	<10
C. albicans	5.85E+04	3.95E+04	1.06E+03	nd	<100	<10	<10	<10
A. niger	7.75E+04	4.80E+04	2.15E+04	nd	4.60E+04	4.60E+04	3.80E+04	5.40E+04
GHB (pH 7.50) 500 mg/cc	Malic Acid Initial Co	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	9.70E+04	8.30E+04	4.45E+04	nd	3.05E+03	7.00E+01	<10	<10
P. aeruginosa	4.85E+04	1.57E+04	5.45E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.95E+04	4.84E+04	nd	1.74E+04	6.50E+03	8.20E+02	5.05E+02
C. albicans	5.85E+04	4.40E+04	6.20E+03	nd	5.00E+02	<10	<10	<10
A. niger	7.75E+04	3.55E+04	2.41E+04	nd	2.80E+04	4.90E+04	4.45E+04	4.40E+04

TABLE 22

pH Variable Result Summary

	Inoculum	0	Day 14	Day 28
GHB, pH 7.5 750 mg/cc 12/30/97				
E. coli	470,000	160,000	<10	<10
P. aeruginosa	437,500	152,000	<10	<10
S. aureus	447,500	330,000	1,935	10
C. albicans	375,000	234,500	<10	<10
A. niger	475,500	395,000	161,500	202,000
GHB, pH 7.5 750 mg/cc + 0.2% MP/PP 12/30/97				
E. coli	470,000	127,000	<10	<10
P. aeruginosa	437,500	61,000	<10	<10
S. aureus	447,500	350,000	<10	<10
C. albicans	375,000	103,500	<10	<10
A. niger	457,500	315,000	38,500	6,400
GHB, pH 7.5 750 mg/cc + 0.1% MP/PP				
E. coli	470,000	157,000	<10	<10
P. aeruginosa	437,500	90,000	<10	<10
S. aureus	447,500	239,000	<10	<10
C. albicans	375,000	169,000	<10	<10
A. niger	457,500	335,000	90,500	99,000
GHB, pH 7.5 750 mg/cc + 0.2% Potassium sorbate	XXXXXX			
E. coli				
P. aeruginosa				
S. aureus				
C. albicans				
A. niger				
GHB, pH 6.0 500 mg/cc + 0.2% Potassium sorbate 12/30/97				
E. coli	470,000	222,000	<10	<10
P. aeruginosa	437,500	136,000	<10	<10
S. aureus	447,500	410,000	<10	<10
C. albicans	375,000	395,000	<10	<10
A. niger	475,500	405,000	49,500	11,150
GHB, pH 6.0 500 mg/cc + Excipients 3/12/98				
E. coli	500,000	93,000	<10	<10
P. aeruginosa	350,000	30,500	<10	<10
S. aureus	280,000	185,000	<10	<10
C. albicans	450,000	135,000	<10	<10
A. niger	450,000	121,500	1,785	505

TABLE 22-continued

pH Variable Result Summary

	Inoculum	0	Day 14	Day 28
GHB, pH 9.0 500 mg/cc 3/12/98				
E. coli	500,000	320,000	<10	<10
P. aeruginosa	350,000	12,000	<10	<10
S. aureus	280,000	530,000	<10	<10
C. albicans	450,000	510,000	<10	<10
A. niger	450,000	345,000	158,500	110,500
GHB, pH 9.0 500 mg/cc 3/12/98				
E. coli	500,000	305,000	<10	<10
P. aeruginosa	350,000	20,000	<10	<10
S. aureus	280,000	495,000	<10	<10
C. albicans	450,000	380,000	<10	<10
A. niger	450,000	355,000	157,500	365,000
GHB, pH 6.0 500 mg/cc 12/30/97				
E. coli	470,000	221,000	<10	<10
P. aeruginosa	437,500	172,000	<10	<10
S. aureus	447,500	320,000	<10	<10
C. albicans	375,000	310,000	<10	<10
A. niger	475,500	270,000	48,500	8,600
GHB, pH 6.0 500 mg/cc + 0.2% MP/PP 12/30/97				
E. coli	470,000	163,000	<10	<10
P. aeruginosa	437,500	60,000	<10	<10
S. aureus	447,500	243,000	<10	<10
C. albicans	375,000	150,500	<10	<10
A. niger	475,500	400,000	<10	<10
GHB, pH 6.0 500 mg/cc + 0.1% MP/PP 12/30/97				
E. coli	470,000	206,000	<10	<10
P. aeruginosa	437,500	118,000	<10	<10
S. aureus	447,500	330,000	<10	<10
C. albicans	375,000	221,000	<10	<10
A. niger	475,500	355,000	315	<10
GHB, pH 6.0 500 mg/cc 3/12/98				
E. coli				
P. aeruginosa				
S. aureus				

TABLE 22-continued

pH Variable Result Summary

	Inoculum	0	Day 14	Day 28
C. albicans				
A. niger				
GHB, pH 6.0				
500 mg/cc				
3/12/98				
E. coli	500,000	199,000	<10	<10
P. aeruginosa	350,000	192,500	<10	<10
S. aureus	280,000	300,000	<10	<10
C. albicans	450,000	370,000	<10	<10
A. niger	450,000	445,000	22,750	4,050
GHB, pH 6.0				
500 mg/cc + Excipients				
3/12/98				
E. coli	500,000	96,000	<10	<10
P. aeruginosa	350,000	26,000	<10	<10
S. aureus	280,000	155,000	<10	<10
C. albicans	450,000	205,000	<10	<10
A. niger	450,000	131,500	1,825	370
GHB, pH 7.50				
500 mg/cc, HCl 7/2/98				
E. coli	97000	82000	<10	<10
P. aeruginosa	48500	29500	<10	<10
S. aureus	54500	58000	245	<10
C. albicans	58500	38500	<10	<10
A. niger	77500	48000	46000	54,000
GHB, pH 7.5				
500 mg/cc, Malic Acid				
7/2/98				
E. coli	97000	83000	70	<10
P. aeruginosa	48500	15650	<10	<10
S. aureus	54500	59500	6500	505
C. albicans	58500	44000	<10	<10
A. niger	77500	35500	49000	44,000

Short term stability testing was carried out as described in Appendix A and results are summarized in—Results of Limited Stability Testing—Xyrem oral solution—are show as follows:

TABLE 23-A

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26/01/1999

NO.: 333198

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PRO-CEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	d512 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.068%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6) ≦0.5%	RRT 1.45:0.021%	NPLC-793D
GBL-RRT 1.6	Impurity A (RRT 4.3) : ≦0.5%	RRT 4.17:0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28:0.02% RRT 3.79:0.007%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge Test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test
Formulation 1: 500 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328841

TABLE 23-B

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21/01/1999

NO.: 331347

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PRO-CEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	510 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.36%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6):≦0.5%	RRT 1.46:0.23%	NPLC-793D
	Impurity A (RRT 4.3): ≦ 0.5%	RRT 4.31:0.1%	
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:

28 days (25° C., 60% RH)
Formulation 1: 500 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.02%
RRT 3.93 : 0.008%

TABLE 23-C

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26/01/1999

NO.: 333197

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PRO-CEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	258 mg/ml (103%)	NPLC-793-D
Impurities total	≦2.0%	0.045%	NPLC-793D
Impurities specified	Gamma-	RRT 1.45:0.016%	NPLC-793D
GBL-RRT 1.6	Butyrolactone (RRT=1.6): ≦0.5%		

TABLE 23-C-continued

	Impurity A (RRT 4.3) : ≦0.5%	RRT 4.17:0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.79:0.009%	NPLC-793D
PH	Report	7.6	USP <791>

TABLE 23-C-continued

Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test
Formulation 2: 250 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328845

TABLE 23-D

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21/01/1999

NO.: 331346

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	256 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.18%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.46: 0.13%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.31: 0.03%	
Impurities unspecified	Ind. imp. <0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)
Formulation 2: 250 mg/cc; Malic acid; pH 7.5
*A: RRT 1.29: 0.007%
RRT 3.93: 0.008%

TABLE 23-E

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26/01/1999

NO.: 333196

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	360 mg/ml (103%)	NPLC-793
Impurities total	<2.0%	0.050%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): <0.5%	RRT 1.45: 0.017%	NPLC-793D
	Impurity A (RRT 4.3): <0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. <0.1%	RRT 1.28: 0.006% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.7	USP <791>

TABLE 23-E-continued

Challenge test	Conforms to USP (0,1,7,14,21,28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test
Formulation 3: 350 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328847

TABLE 23-F

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21/01/1999

NO.: 331345

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULTAT/RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	363 mg/ml (104%)	NPLC-793-D
Impurities total	≦2.0%	0.21%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.46: 0.14%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.31: 0.05%	
Impurities unspecified	Ind. imp. <0.1%	*A	NPLC-793D
PH	Report	8.0	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)
Formulation 3: 350 mg/cc; Malic acid; pH 7.5
*A: RRT 1.29: 0.009%
RRT 3.93: 0.008%

TABLE 23-G

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26/01/1999

NO.: 333195

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE: 1741
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	461 mg/ml (102%)	NPLC-793
Impurities total	<2.0%	0.065%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): <0.5%	RRT 1.45: 0.018%	NPLC-793D
	Impurity A (RRT 4.3): <0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. <0.1%	RRT 1.28: 0.006% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0,1,7,14,21,28 days)	Conforms	USP 23 <51> S.8

TABLE 23-G-continued

COMMENTS:

Initial test

Formulation 4: 450 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328875

TABLE 23-H

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21/01/1999

NO.: 331343

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	454 mg/ml (101%)	NPLC-793-D
Impurities total	≦2.0%	0.40%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.46: 0.26%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.31: 0.1%	
Impurities unspecified	Ind. imp. <0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)
Formulation 4: 450 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.03%
RRT 3.93: 0.008%

TABLE 23-I

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26/01/1999

NO.: 333194

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	563 mg/ml (102%)	NPLC-793
Impurities total	<2.0%	0.077%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): <0.5%	RRT 1.45: 0.020%	NPLC-793D
	Impurity A (RRT 4.3): <0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. <0.1%	RRT 1.29: 0.03% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0,1,7,14,21,28 days)	Conforms	USP 23 <51> S.8

TABLE 23-I-continued

COMMENTS:

Initial test

Formulation 5: 550 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328883

TABLE 23-J

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21/01/1999

NO.: 331341

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	561 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.56%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.46: 0.31%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.31: 0.2%	
Impurities unspecified	Ind. imp. <0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)
Formulation 2: 250 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.04%
RRT 3.93: 0.007%

TABLE 23-K

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26/01/1999

NO.: 333193

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	666 mg/ml (102%)	NPLC-793
Impurities total	<2.0%	0.10%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): <0.5%	RRT 1.45: 0.025%	NPLC-793D
	Impurity A (RRT 4.3): <0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. <0.1%	RRT 1.28: 0.05% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0,1,7,14,21,28 days)	Conforms	USP 23 <51> S.8

TABLE 23-K-continued

COMMENTS:

Initial test

Formulation 6: 650 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328885

TABLE 23-L

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21/01/1999

NO.: 331336

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	660 mg/ml (102%)	NPLC-764
Impurities total	≦2.0%	0.81%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.46: 0.43%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.31: 0.3%	
Impurities unspecified	Ind. imp. <0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)
Formulation 6: 650 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.07%
RRT 3.93: 0.007%

TABLE 23-M

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26/01/1999

NO.: 333192

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	518 mg/ml (104%)	NPLC-793
Impurities total	<2.0%	0.065%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): <0.5%	RRT 1.45: 0.018%	NPLC-793D
	Impurity A (RRT 4.3): <0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. <0.1%	RRT 3.79: 0.007% RRT 5.99: 0.02%	NPLC-793D
PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0,1,7,14,21,28 days)	Conforms	USP 23 <51> S.8

TABLE 23-M-continued

COMMENTS:

Initial test
Formulation 7: 500 mg/cc; Citric acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 329033

TABLE 23-N

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21/01/1999

NO.: 331335

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	515 mg/ml (103%)	NPLC-793-D
Impurities total	≦2.0%	0.38%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.46: 0.27%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.31: 0.1%	
Impurities unspecified	Ind. imp. <0.1%	RRT 3.93: 0.007%	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)
Formulation 7: 500 mg/cc; Citric acid; pH 7.5

TABLE 23-O

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 09/01/1999

NO.: 330721

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Challenge Test	Conforms to USP (0,1,7,14,21 and 28 days)	Conforms	USP 23 <51> S.8
Potency	Report	501 mg/ml (100%)	NPLC-793
Impurities total	<2.0%	1.2%	NPLC-793D
Impurities unspecified	Ind. imp. <0.1%	*A	NPLC-793D
Impurities specified	Gamma-Butyrolactone Report:	RRT 1.46: 0.013%	NPLC-793D
PH	Report	7.3	USP <791>
Solubility study	Report	*B	PR 98126 IIA

COMMENTS:

Initial test
500 mg/ml cc; Malic acid; pH 7.5
*A: RRT 1.31: 0.02% RRT 1.67: 0.008%
RRT 1.91: Interference with peak of dilution solvent cannot calculate.
RRT 3.47: 0.1% RRT 3.79: 0.009% RRT 3.84: 0.01%
RRT 4.18: 0.06% RRT 5.10: 0.008% RRT 5.35: 0.02%

TABLE 23-O-continued

RRT 6.74: 0.9% RRT 6.90: 0.08% RRT 7.41: 0.006%
*B: Maximum solubility: 700 mg/ml no pH adjustment.

TABLE 23-P

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26/02/1999

NO.: 331307

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM LIQUID FORM.
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	508 mg/ml (102%)	NPLC-793
Impurities total	<2.0%	0.70%	NPLC-793D
Impurities unspecified	Ind. imp. <0.1%	*A	NPLC-793D
Impurities specified	Gamma-Butyrolactone Report:	RRT 1.37: 0.054%	NPLC-793D
PH	Report	7.6	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)
500 mg/ml cc; Malic acid; pH 7.5
*A: RRT 1.17: 0.03% RRT 3.47: 0.2%
RRT 5.46: 0.01% RRT 6.87: 0.3%
RRT 7.04: 0.007%
RRT 1.78: Can not calculate because it interfere with a dilution solvant peak.

II. Summary of Results

A. Preparation of various formulations of Sodium Oxybate and formulations using an alternative salt of GHB.

1. Various formulations of sodium oxybate were prepared as directed in the above Protocol. Sodium oxybate, 500 mg/cc with Malic Acid was not soluble at pH 5.0, and further evaluation of this solution was discontinued. All other solutions were successfully prepared as described.

2. The preparation of an alternative salt of gamma-hydroxybutyrate was described as the calcium salt, prepared at 500 mg/cc (or maximum possible) with Malic Acid at pH 7.5.

a. The calcium salt of gamma-hydroxybutyrate was prepared by Toronto Research and shipped to NeoPharm for determination of solubility and evaluation according to the Protocol. The absolute limit of solubility, without p14 adjustment, was determined to be 700 mg/cc. The pH of this solution was 8.4. Solutions of lower pH were more difficult to prepare at 500 mg/cc using Malic acid as acidulant. When pH was adjusted to 6.0 with Malic acid, the solubility of the calcium oxybate was limited (longer stirring required to solubilize). The desired solution of 500 mg/cc, pH 7.5 was prepared with Malic acid as acidulant without difficulty. Appearance of the final solution was slightly yellow in color. Copies of the laboratory record for preparation of these solutions is available.

B. Microbial Challenge Testing of the various formulations prepared by MDS NeoPharm.

The microbial challenge testing was carried as specified in the Protocol and the following table summarizes the results of microbial challenge testing of various formulations of sodium oxybate and the single calcium oxybate formulation prepared.

TABLE 24

Testing of Sodium and Calcium GHB Salts

	pH of Solution	Microbial Challenge Result
Sodium Oxybate Concentration		
1. 500 mg/cc	7.5 (Malic acid)	Pass
2. 250 mg/cc	7.5 (Malic acid)	Pass
3. 350 mg/cc	7.5 (Malic acid)	Pass
4. 450 mg/cc	7.5 (Malic acid)	Pass
5. 550 mg/cc	7.5 (Malic acid)	Pass
6. 650 mg/cc	7.5 (Malic acid)	Pass
7. 500 mg/cc	7.5 (Citric acid)	Pass
Calcium Oxybate Conctration		
500 mg/cc	7.5	Pass

C. Short term stability evaluation of various formulations of sodium oxybate and a formulation of calcium oxybate.

Solutions were tested on day zero (preparation day) and day 28 according to the described Protocol. The results of the stability evaluation are summarized in Table 25 below:

TABLE 25

Sodium and Calcium GHB Evaluation

Sodium oxybate solution	Potency mg/cc (%)	Impurities (Total)	Impurities (Unspecified)	Impurities (Specified-GLB)	pH
500 mg/cc pH 7.5 Malic Acid Day 0	512 mg/cc (102%)	0.68%	0.041%	0.027%	7.6
Day 28	510 mg/cc (103%)	0.36%	0.33%	0.028%	7.9
250 mg/cc pH 7.5 Malic Acid Day 0	258 mg/cc (103%)	0.045%	0.009%	0.026%	7.6
Day 28	256 mg/cc (102%)	0.18%	0.015%	0.16%	7.9
350 mg/cc pII 7.5 Malic Acid Day 0	360 mg/cc (103%)	0.050%	0.013%	0.037%	7.7
Day 28	363 mg/cc (104%)	0.21%	0.017%	0.19%	8.0
450 mg/cc pH 7.5 Malic Acid Day 0	461 mg/cc (102%)	0.065%	0.027%	0.038%	7.5
Day 28	454 mg/cc (101%)	0.40%	0.038%	0.36%	7.8
550 mg/cc pH 7.5 Malic Acid Day 0	563 mg/cc (102%)	0.077%	0.037%	0.040%	7.6
Day 28	561 mg/cc (102%)	0.56%	0.047%	0.51%	7.9
650 mg/cc pH 7.5 Malic Acid Day 0	666 mg/cc (102%)	0.10%	0.057%	0.045%	7.6
Day 28	660 mg/cc (102%)	0.81%	0.077%	0.73%	7.8
500 mg/cc pH 7.5 Citric Acid Day 0	518 mg/cc (104%)	0.065%	0.027%	0.038%	7.5
Day 28	515 mg/cc (103%)	0.38%	0.007%	0.37%	7.9

Calcium oxybate solution	Potency	Impurities (Total)	Impurities (Specified)	Impurities (Unspecified)	pH
500 mg/cc pH 7.5 Malic Acid Day 0	501 mg/cc (100%)	1.2%	>0.1% (See C of A Attached)	0.013%	7.3
Day 28	508 mg/cc (102%)	0.70%	>0.1% (See C of A)	0.054%	7.6

D. Summary of Pertinent Solubility and Microbial Challenge Data are shown in Tables 26 and 27.

TABLE 26

Limits of Solubility

	pH of Solution	Comments
Sodium oxybate Maximum Solubility		
450 mg/cc	pH 4 (HCl)	25°
500 mg/cc	pH 5 (HCl)	25°
600 mg/cc	pH 6 (HCl)	25°
750 mg/cc	pH 6.8 (HCl)	25°
750 mg/cc +	pH 10.3	25°
1000 mg/cc	pH (unadjusted)	65° Soluble, 25° Gel
Calcium oxybate Maximum Solubility		
700 mg/cc	pH 8.4 (unadjusted)	25°
500 mg/cc	pH 6.0	25°

TABLE 27

Microbial Challenge Results

	pH of Solution	Microbial Challenge Result
Sodium oxybate Concentration (Date)		
750 mg/cc (Dec. '97)	7.5 (HCl)	pass
500 mg/cc (Dec. '97)	6.0 (HCl)	pass
500 mg/cc + Excipients (Xylitol) (March '98)	6.0 (Malic Acid)	pass
500 mg/cc (March '98)	9.0 (HCl)	pass (Borderline aspergillus)
150 mg/cc (BDL 1995)	5.0 (HCl)	fail (aspergillus only)
150 mg/cc (BDL 1995)	7.0 (HCl)	fail (aspergillus and staph)
150 mg/cc (BDL 1995)	3.0 (HCl)	fail (aspergillus only)
150 mg/cc (BDL 1995)	10.3 (unadjusted)	fail (aspergillus and staph)
500 mg/cc (May '98)	6.0 (Malic Acid)	discontinued
500 mg/cc (May '98)	7.5 (Malic Acid)	pass
500 mg/cc (May '98)	9.0 (Malic Acid)	discontinued
500 mg/cc (May '98)	7.5 (HCl)	pass
500 mg/cc	7.5 (Malic Acid)	pass
250 mg/cc	7.5 (Malic Acid)	pass
350 mg/cc	7.5 (Malic Acid)	pass
450 mg/cc	7.5 (Malic Acid)	pass
550 mg/cc	7.5 (Malic Acid)	pass
650 mg/cc	7.5 (Malic Acid)	pass
500 mg/cc	7.5 (Citric Acid)	pass
Calcium oxybate Concentration (Date)		
500 mg/cc	7.5 (Malic Acid)	pass

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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What is claimed is:

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.

2. The method of claim **1** wherein the salt is sodium gamma-hydroxybutyrate.

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 9.

4. The method of claim **1**, **2**, or **3** wherein the medium does not contain a preservative.

5. The method of claim **1**, wherein the concentration of said gamma-hydroxybutyrate is from about 250 to about 750 mg/ml.

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

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.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

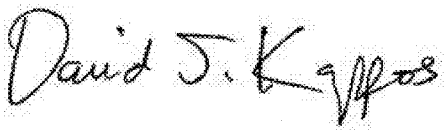
CERTIFICATE OF CORRECTION

PATENT NO. : 6,472,431 B2
APPLICATION NO. : 09/470570
DATED : October 29, 2002
INVENTOR(S) : Harry Cook et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 70, lines 18-19, in Claim 4, delete "4. The method of claim 1, 2, or 3 wherein the medium does not contain a preservative." and
insert -- 4. The method of claim 1 or 2 wherein the medium does not contain a preservative. --, therefor.

Signed and Sealed this
Sixteenth Day of August, 2011



David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT B

US006780889B2

(12) **United States Patent**
Cook et al.

(10) **Patent No.: US 6,780,889 B2**
(45) **Date of Patent: Aug. 24, 2004**

(54) **MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY**

(75) Inventors: **Harry Cook**, Eden Prairie, MN (US); **Martha Hamilton**, St. Paul, MN (US); **Douglas Danielson**, Otsego, MI (US); **Colette Goderstad**, St. Paul, MN (US); **Dayton Reardan**, Excelsior, MN (US)

(73) Assignee: **Orphan Medical, Inc.**, Minnetonka, MN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 195 days.

(21) Appl. No.: **10/194,021**

(22) Filed: **Jul. 11, 2002**

(65) **Prior Publication Data**

US 2003/0125385 A1 Jul. 3, 2003

Related U.S. Application Data

(62) Division of application No. 09/470,570, filed on Dec. 22, 1999, now Pat. No. 6,472,431.
(60) Provisional application No. 60/113,745, filed on Dec. 23, 1998.

(51) **Int. Cl.**[7] **A61K 31/19**; A61K 31/235; A61K 31/34; A61K 31/215

(52) **U.S. Cl.** **514/557**; 514/473; 514/533; 514/529

(58) **Field of Search** 514/557, 473, 514/533, 529

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(List continued on next page.)

Primary Examiner—Zohreh Fay
Assistant Examiner—Brian-Yong S. Kwon
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg, Woessner & Kluth, P.A.

(57) **ABSTRACT**

Disclosed are formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial growth. Also disclosed are formulations of gamma-hydroxybutyrate that are also resistant to the conversion into GBL. Disclosed are methods to treat sleep disorders, including narcolepsy, with these stable formulations of GHB. The present invention also provides methods to treat alcohol and opiate withdrawal, reduced levels of growth hormone, increased intracranial pressure, and physical pain in a patient.

1 Claim, 1 Drawing Sheet

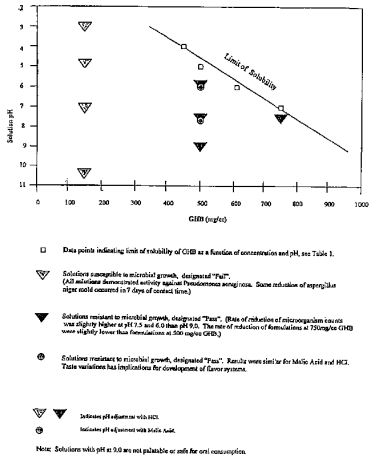

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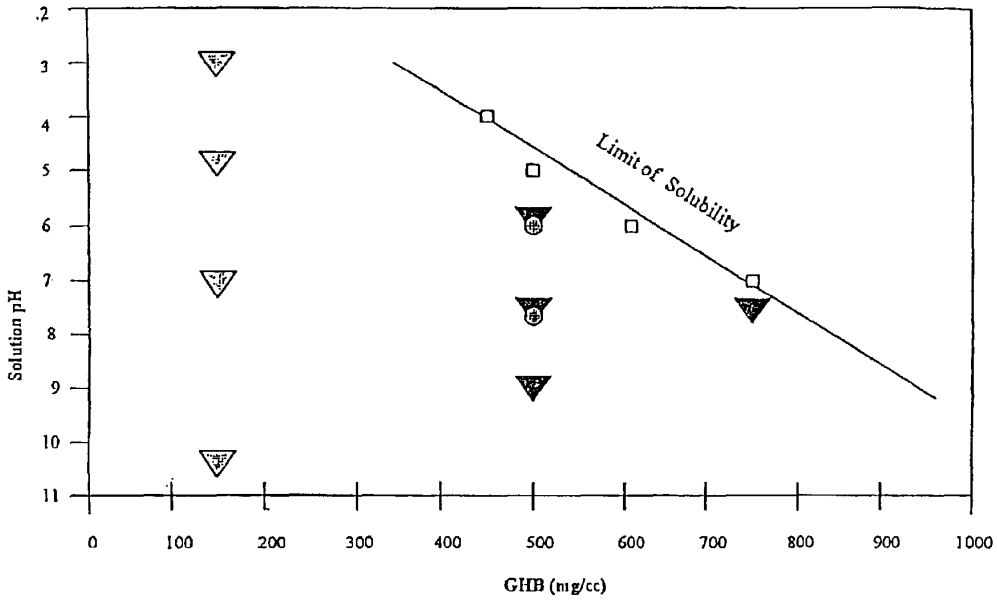
Figure 1.



□ Data points indicating limit of solubility of GHB as a function of concentration and pH, see Table 1.

Solutions susceptible to microbial growth, designated "Fail".
(All solutions demonstrated activity against Pseudomonas aeruginosa. Some reduction of aspergillus niger mold occurred in 7 days of contact time.)

Solutions resistant to microbial growth, designated "Pass". (Rate of reduction of microorganism counts was slightly higher at pH 7.5 and 6.0 than pH 9.0. The rate of reduction of formulations at 750mg/cc GHB were slightly lower than formulations at 500 mg/cc GHB.)

Solutions rresistant to microbial growth, designated "Pass". Results were similar for Malic Acid and HCl. Taste variations has implications for development of flavor systems.

Indicates pH adjustment with HCl.

Indicates pH adjustment with Malic Acid.

Note: Solutions with pH at 9.0 are not palatable or safe for oral consumption.

MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY

RELATED APPLICATIONS

This application is a divisional of U.S. patent application Ser. No. 09/470,570, filed Dec. 22, 1999, now U.S. Pat. No. 6,472,431 which claims priority from U.S. Provisional Patent Application Serial No. 60/113,745, filed Dec. 23, 1998, both of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention relates generally to the fields of pharmaceutical compositions to be used in treatments, such as, sleeping disorders, such as, e.g., narcolepsy (particularly cataplexy), drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or for an increased level of intracranial pressure or the like. The present 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, e.g.

II. Description of Related Art

GHB is an endogenous compound with hypnotic properties that is found in many human body tissues. GHB is present, for example, in the mammalian brain and other tissues. In brain the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter (Snead and Morley, 1981). The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB is converted to succinate and then metabolized via the Krebs cycle. Clinical trials have shown that GHB increases delta sleep and improves the continuity of sleep (Ladinsky et al., 1983; Anden and Stock, 1973; Stock et al., 1973; Laborit, 1973; Lapierre et al., 1988; Lapierre et al., 1990; Yamda et al., 1967; Grove-White and Kelman, 1971; Scharf, 1985).

GHB has typically been administered in clinical trials as an oral solution (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993). GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e. daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency (Mamelak et al, 1973; Yamada et al., 1967; Bedard et al., 1989), reduces sleep apnea (Series el al, 1992; Scrima et al., 1987), and improves general anesthesia (Hasenbos and Gielen, 1985).

GHB has several clinical applications other than narcolepsy and sleep disorders. GHB has been reported to reduce alcohol craving, the number of daily drinks consumed, and the symptoms of alcohol withdrawal in patients (Gallimberti et a., 1989; Gallimberti et al., 1992; Gessa et al., 1992). GHB has been used to decrease the symptoms of opiate withdrawal, including both heroin and methadone withdrawal (Gallimberti et al, 1994; Gallimberti et al., 1993). It has analgesic effects that make it suitable as a pain reliever (U.S. Pat. No. 4,393,236). Intravenous administration of GHB has been reported to reduce intracranial pressure in patients (Strong, A. 1984). Also, administration of GHB was reported to increase growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970).

A good safety profile for GHB consumption, when used long term for treatment of narcolepsy, has been reported. Patients have been safely treated for many years with GHB without development of tolerance (Scharf, 1985). Clinical laboratory tests carried out periodically on many patients have not indicated organ or other toxicities (Lammers, 1993; Scrima, 1990; Scharf, 1985; Mamelack, 1977; Mamelak, 1979; Gallimberti, 1989; Gallimberti, 1992; Gessa, 1992). The side effects of GHB treatment have been minimal in incidence and degree of severity, though they include sleepwalking, enuresis, headache, nausea and dizziness (Broughton and Mamelak, 1979; Mamelak et al., 1981; Mamelak et al., 1977; Scrima et al., 1989; Scrima et al., 1990; Scharf et al., 1985).

The pharmacokinetics of GHB have been investigated in alcohol dependent patients (Ferrara et al., 1992) and in normal healthy males (Palatini et al., 1993) after oral administration. GHB possesses a rapid onset and short pharmacological effect (Ferrara et al., 1992; Palatine et al., 1993; Lee, C., 1977; van der Bogert; Gallimberti, 1989; Gallimberti, 1992; Lettieri and Fung, 1978; Arena and Fung, 1980; Roth and Giarman, 1966; Vickers, 1969; Lee, 1977). In alcohol dependent patients, GHB absorption into and elimination from the systemic circulation were fast processes. Virtually no unchanged drug could be recovered in the urine. There were preliminary indications that the pharmacokinetics of GHB might be non-linear or dose-dependent (Ferrara et al., 1992). In the healthy volunteers study, the pharmacokinetics of three rising GHB doses (12.5, 25, and 50 mg/kg) were investigated. These findings indicate that both the oral absorption and elimination processes of GHB were capacity-limited though the degree of dose dependency was moderate (Palatini et al., 1993).

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). 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.

SUMMARY OF THE INVENTION

The present invention overcomes deficiencies in the prior art by providing compositions of GHB in an aqueous medium that are resistant to microbial growth. These compositions are also resistant to the uncontrolled degradation of GHB into GBL or other substances. The compositions of the present invention are stable compositions of GHB that improve shelf-life, and provide a titratable formulation of

GHB for easy dose measurement. In addition, the concentrated solutions embodied in this invention reduce shipping and storage requirements and allow patients to carry more drugs for their convenience. The present invention provides methods to treat a number of conditions treatable by GHB, referred to herein as "therapeutic categories." Therapeutic categories for the present invention include, but are not limited to, sleeping disorders, drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders, such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or an increased level of intracranial pressure or other conditions treatable with GHB.

The invention first provides a pharmaceutical composition of GHB rendered chemically stable and/or resistant to microbial growth in an aqueous medium. Preferred GHB salts of the present invention include sodium, ammonium and calcium. As used herein in certain embodiments, "stable" may mean resistant to degradation of GHB into its known or unknown decomposition elements. The level of GBL that is acceptable can be up to 0.1% of the formulation as per the ICH guidelines for shelf-life determination, As used herein in certain embodiments, "resistant to microbial growth" or "resistant to microbial challenge" means that the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days. As used herein in certain embodiments, an "aqueous medium" may mean a liquid comprising more than about 50% water. In certain preferred embodiments, an "aqueous medium" may be a solution, suspension, gel or emulsion of GHB, with a solution of GHB being most preferred. Preferred gels are thixotropic gels. Compositions that are resistant to microbial growth are created by dissolving or mixing GHB in an aqueous medium to a concentration or content of greater than of about 150 mg/ml GHB to the maximal solubility of GHB. The solubility of GHB is up to about 750 mg/ml at room temperature (20° C. to about 25° C.), however, heating the aqueous medium during preparation tip to 100° C. will increase GHB solubility to at least about 1000 mg/ml. A preferred concentration or content of GHB is about 500 mg/ml.

The amount of GHB that may be mixed or dissolved into an aqueous medium and still be resistant to microbial growth depends upon the pH of the aqueous medium. In certain embodiments the presence of a preservative may allow the amount of GLIB contained in the compositions of the present invention to be increased and still maintain resistance to chemical degradation and/or microbial growth. In one embodiment of the present invention, the pH of the aqueous medium of the pharmaceutical composition is about 3 to about 10.

In a preferred embodiment, the pH of said aqueous medium is about 6 to about 7.5. The pH may be from about 3.0 to about 10.3, namely of about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0, about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, about 10.0, about 10.1, about 10.2, or about 10.3, and all pH values between each of the listed pH values, of the aqueous media. This will produce a GHB composition that is resistant to microbial growth as defined by the test described herein. As used herein, the term "about" generally means within about 10–20%.

These pH values will produce compositions resistant to microbial growth in an aqueous medium if the amount of GHB added, admixed, or dissolved is from above about 150 mg/ml to about 450 mg/ml, namely, above about 150 mg/ml, about 160 mg/ml, about 170 mg/ml, about 180 mg/ml, about 190 mg/ml, about 200 mg/ml, about 210 mg/ml, about 220 mg/ml, about 230 mg/ml, about 240 mg/ml, about 250 mg/ml, about 260 mg/ml, about 270 mg/ml, about 280 mg/ml, about 290 mg/mi, about 300 mg/ml, about 310 mg/ml, about 320 mg/ml, about 330 mg/ml, about 340 mg/ml, about 350 mg/ml, about 360 mg/ml, about 370 mg/ml, about 380 mg/ml, about 390 mg/ml, about 400 mg/ml, about 410 mg/ml, about 420 mg/ml, about 430 mg/ml, about 440 mg/ml, to about 450 mg/ml, and all amounts of GHB between the values listed.

At the medium to high end of the concentration or content of GHB that may be dissolved or mixed in the aqueous medium, the maximal pH that may be used is reduced at room temperature. This is shown in FIG. **1**, a graphical presentation of acceptable formulation ranges. At a concentration or content of about 450 mg/ml GHB, the pH may be of about 3.9 to about 10.3. At a concentration or content of about 500 mg/ml GHB, the pH may be of about 4.75 to about 10.3. At a concentration or content of about 600 mg/ml GHB, the pH may be of about 6.1 to about 10.3. At a concentration or content of about 750 mg/ml GHB, the pH may be of about 7.0 to about 10.3. Of course, all pH and concentration or content values in between each of the listed pH and concentration or content values are encompassed by the invention.

Certain embodiments may be selected as sub-ranges from these values of GHB content and aqueous medium pH. For example, a specific embodiment may be selected as a content of about 170 mg/ml to about 440 mg/ml GHB in an aqueous medium, at a pH range of about pH 5.5 to about pH 8.7. Another example of how a range may be selected in an embodiment would be the selection of a content of about 155 mg/ml of GHB, which is a value between the above listed values, to a content of about 350 mg/ml of GHB, and the selection of a pH range of the aqueous medium, such as a pH range of about 8.87, which is a value between the listed pH values, to a pH of about 8.93, which is another value between the listed values of pH. A third example of ranges that may be selected for a specific embodiment would be selection of a single content or concentration of GHB, such as about 200 mg/ml of GHB, and the selection of a pH range, such as a pH of about 3.5 to about 8.2. A fourth example of ranges that may be selected for a specific embodiment would be selection of a content or concentration of GHB over a range, such as about 300 mg/ml to about 400 mg/ml, and the selection of a single pH value for the aqueous medium, such as a pH of about 3. Another example of a range selected for an embodiment may be the selection of a single content or concentration of GHB, such as 400 mg/ml GHB, and a single pH value of the aqueous medium, such as pH 7.7.

Other examples of how a range of an embodiment of GHB content or concentration may be selected include a range of

GHB content or concentration from about 200 mg/ml to about 460 mg/ml GHB, encompassing the ranges for GHB described herein, and a range of pH for the aqueous medium may be from about pH 4.3 to about pH 7, encompassing ranges for GHB in an aqueous medium at room temperature described herein. Another example would be the selection of a range of GHB content or concentration from about 153 mg/ml to about 750 mg/ml, and a pH range of about 7 to about 9, encompassing ranges between the listed values of GHB content and pH described herein. An example may be the selection as a GHB concentration or content of about 170 mg/ml to about 640 mg/ml in an aqueous medium, at a pH range of about pH 6.5 to about pH 7.7. Another example of how a range may be selected in an embodiment would be a content or concentration of about 185 mg/ml of GHB, which is a value between the listed values, to a content or concentration of about 750 mg/ml of GHB, at a pH range of about 7.87, which is a value between the listed pH values, to a pH of about 8.91, which is another value between the listed values of pH. An additional example of ranges that may be selected for a specific embodiment would be a content or concentration of about 200 mg/ml of GHB at a pH of about 7 to about 8.2. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 750 mg/ml to about 400 mg/ml at a pH of about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 300 mg/ml to about 750 mg/ml at a pH of about 8.5 to about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 400 mg/ml to about 600 mg/ml at a pH of about 9 to about 5.8. And so forth. Thus, all ranges of pH and GHB concentration or content that can be selected from the values herein and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

The chemical stability of GHB is affected by pH, with compositions of GHB in an aqueous medium with a pH below about 6 being less effective in maintaining the chemical stability of GHB. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, all concentrations or content of GHB in an aqueous medium, as described herein, and as would be understood by those of ordinary skill in the art, may be selected to produce compositions of the present invention.

Additionally, the ranges described above are for a composition at room temperature, which is defined herein as from about about 20° C. to about 25° C., namely, about 20° C. about 21° C., about 22° C., about 23° C., about 24° C., to about 25° C. Within the values and ranges of pH described above, the ranges of concentration or content of GHB may increase at temperatures greater than room temperature. Thus, the maximal content or concentration of GHB in an aqueous medium at a temperature of from about 26° C. to about 100° C., namely about 26° C., about 27° C., about 28° C., about 29° C., about 30° C., about 31° C., about 32° C., about 33° C., about 34° C., about 35° C., about 36° C., about 37° C., about 38° C., about 39° C., about 40° C., about 41° C., about 42° C., about 43° C., about 44° C., about 45° C., about 46° C., about 47° C., about 48° C., about 49° C., about 50° C., about 51° C., about 52° C., about 53° C., about 54° C., about 55° C., about 56° C., about 57° C., about 58° C., about 59° C., about 60° C., about 61° C., about 62° C., about 63° C., about 64° C., about 65° C., about 66° C., about 67° C., about 68° C., about 69° C., about 70° C., about 71° C., about 72° C., about 73° C., about 74° C., about 75° C., about 76° C., about 77° C., about 78° C., about 79° C., about 80° C., about 81° C., about 82° C., about 83° C., about 84° C., about 85° C., about 86° C., about 87° C., about 88° C., about 89° C., about 90° C., about 91° C., about 92° C., about 93° C., about 94° C., about 95° C., about 96° C., about 97° C., about 98° C., about 99° C., to about 100° C. may be from about 750 to about mg/ml, namely to about 751 mg/ml, about 760 mg/ml, about 770 mg/ml, about 780 mg/ml, about 790 mg/ml, about 800 mg/ml, about 810 mg/ml, about 820 mg/ml, about 830 mg/ml, about 840 mg/ml, about 850 mg/ml, about 860 mg/ml, about 870 mg/ml, about 880 mg/ml, about 890 mg/ml, about 900 mg/ml, about 910 mg/ml, about 920 mg/ml, about 930 mg/ml, about 940 mg/ml, about 950 mg/ml, about 960 mg/ml, about 970 mg/ml, about 980 mg/ml, about 990 mg/ml, to about 1000 mg/ml. At temperatures below room temperature, the solubility of GHB may decrease, and compositions at lower temperature and solubility of GHB at the pH values and ranges described herein are also encompassed by the invention. Additionally, differences of atmospheric pressure may also increase or decrease the solubility of GHB within the ranges described, and embodiments of the invention with an increased or decreased content of GHB due to changes in pressure are also encompassed by the invention. Of course, it is understood that the present invention encompasses embodiments of GHB concentration or content in an aqueous medium at higher or lower temperature within the values described herein, such as about 980 mg/ml to about 200 mg/ml at 95° C. GHB at a pH of about 9 to about 7.5. Or about 150 mg/ml GHB at about 17° C. at about pH 6 to about pH 7. And so forth. Thus, all ranges of pH and GHB content that can be selected at various temperatures and pressures from the values above, and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

In certain other embodiments of the present invention, the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids, bases, or combinations thereof. In certain embodiments, the acid may be an organic acid, preferably a carboxylic acid or alphahydroxy carboxylic acid. In certain other embodiments, the acid is selected from the group including, but not limited to, acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like. In a preferred embodiment, the acid is malic or hydrochloric acid. In certain other embodiments, the pH adjusting agent may be a base selected from the group including, but not limited to, acetanilide, ammonia, apomorphine, atropine, benzocaine, caffeine, calcium hydroxide, cocaine, codeine, ephedrine, morphine, papaverine, physostigmine, pilocarpine, potassium bicarbonate, potassium hydroxide, procaine, quinine, reserpine, sodium bicarbonate, sodium dihydrogen phosphate, sodium citrate, sodium taitrate, sodium carbonate, sodium hydroxide, theobromine, thiourea or urea. 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.

In certain embodiments, the composition may contain one or more salts. A "salt" is understood herein to mean certain embodiments to mean a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base. Various salts, including salts of GHB, are also encompassed by the invention, particularly as pH adjusting or buffering agents. Pharmaceutically acceptable salts, include inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as malic, acetic, oxalic, tartaric, mandelic, and the like. Salts formed can also be derived from inorganic bases such as, for example, sodium, potassium, silicates, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Alkali metal salts, such as lithium, potassium, sodium, and the like may be used, preferably with an acid to form a pH adjusting agent. Other salts may comprise ammonium, calcium, magnesium and the like. In one embodiment, a salt of GHB comprising an alkali metal may be combined with an acid to create a composition that achieves the desired pH when admixed with an aqueous medium. In another embodiment, a weak base may be combined with GHB to create a composition that achieves' the desired pH when admixed with an aqueous solution. Of course, other salts can be formed from compounds disclosed herein, or as would be known to one of ordinary skill in the art, and all such salts are encompassed by the invention.

In certain embodiments, excipients may be added to the invention. An "excipient" as used herein shall mean certain embodiments which are more or less inert substances added as diluents or vehicles or to give form or consistency when the remedy is in a solid form, though they may be contained in liquid form preparations, e.g. syrups, aromatic powders, honey, and various elixirs. Excipients may also enhance resistance to microbial growth, and thus act as a preservative. Such excipients include, but are not limited to, xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, cellulose derivatives, magnesium carbonate and the like.

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, propyl gallate BP, sorbic acid, chlorobutanol, dihydroacetic acid, monothioglycerol, potassium benzoate, propylparaben, benzoic acid, benzalkonium chloride, alcohol, benzoic acid, benzalkonium chloride, benzethonium chloride, benzyl alcohol, butylparaben, cetylpyridinium chloride, ethylenediamine, ethylpareben, ethyl vanillin, glycerin, hypophophorus acid, methylparaben, phenol, phenylethyl alcohol, phenymercuric nitrate, propylparaben, sassafras oil, sodium benzoate, sodium propionate, thimerosal and potassium sorbate. Preferred preservatives may be selected from the group comprising, but not limited to, xylitol, sodium benzoate, methylparaben, propylparaben and potassium sorbate. Xylitol is particularly preferred in certain compositions of the invention, because it acts as an preservative and a sweetener, is a caries preventative, is less laxative than other sweeteners, and is recommended for diabetics.

In certain embodiments, the pharmaceutical composition may also contain an antioxidant. An "antioxidant" is understood herein to mean certain embodiments which are substances that inhibits oxidation. Such antioxidants include, but are not limited to, asocrbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, potassium metabisulfite, sodium metabisulfite, anoxomer and maleic acid BP.

In certain embodiments, the pharmaceutical composition may also contain a flavoring agent. A "flavoring agent" is understood herein to mean certain embodiments which are substances that alters the flavor of the composition during oral consumption. A type of "flavoring agent" would be a sweetener. Preferred sweeteners or flavoring agents would be microbially non-metabolizable. Especially preferred sweeteners or flavoring agents would be carbohydrates such as xylitol and sorbitol. Such flavoring agents include, but are not limited to, acacia syrup, anethole, anise oil, aromatic elixir, benzaldehyde, benzaldehyde elixir-compound, caraway, caraway oil, cardamom oil, cardamom seed, cardamom spirit, cardamom tincture-compound, cherry juice, cherry syrup, cinnamon, cinnamon oil, cinnamon water, citric acid, citric acid syrup, clove oil, coca, coca syrup, coriander oil, dextrose, eriodictyon, eriodictyon fluidextract, eriodictyon syrup-aromatic, ethyl acetate, ethyl vanillin, fennel oil, ginger, ginger fluidextract, ginger oleoresin, glucose, glycerin, glycyrrhiza, glycyrrhiza elixir, glycyrrhiza extract, glycyrrhiza extract-pure, glycyrrhiza fluidextract, glycyrrhiza syrup, honey, non-alcoholic elixir, lavender oil, citrus extract or oil, lemon oil, lemon tincture, mannitol, methyl salicylate, nutmeg oil, orange-bitter-elixir, orange-bitter-oil, orange flower oil, orange flower water, orange oil, orange peel-bitter, orange-peel-sweet-tincture, orange spirit-compound, compound, orange syrup, peppermint, peppermint oil, peppermint spirit, peppermint water, phenylethyl alcohol, raspberry juice, raspberry syrup, rosemary oil, rose oil, rose water, saccharin, saccharin calcium, saccharin sodium, sarsaparilla syrup, sorbitol solution, spearmint, spearmint oil, sucrose, syrup, thyme oil, tolu balsam, tolu balsam syrup, vanilla, vanilla tincture, vanillin or wild cherry syrup.

Salts, excipients, pH adjusting agents such as acids, bases and buffering agents, flavoring agents, and other agents that may be combined with the compositions of the present invention, or may be used to prepare the compositions of the present invention, are well known in the art, (see for example, "Remington's Pharmaceutical Sciences" 8th and 15th Editions, and Nema et al., 1997, incorporated herein in their entirety), and are encompassed by the invention.

In certain other embodiments, the pharmaceutical composition comprises GHB, a pH adjusting or buffering agent, and an aqueous medium, wherein the components are admixed (sequentially or simultaneously) to prepare said pharmaceutical composition. The pH adjusting or buffering agent and aqueous medium may be any described herein.

The invention also provides a method of preparing a chemically stable and microbial growth-resistant pharmaceutical composition for the treatment of a condition responsive to GHB, comprising admixing GHB and a pH-adjusting or buffering agent in an aqueous medium. In certain embodiments, the method of preparing the pharmaceutical composition further comprises admixing a preservative with the pharmaceutical composition. Other components, such as flavoring agents, salts, and the like, may be added to the composition. The pH adjusting or buffering agent, aqueous medium, preservative, flavoring agents, salts, or other ingredient may be any described herein.

In certain other embodiments, the method of preparing the pharmaceutical composition comprises admixing GHB, a pH adjusting or buffering agent, and an aqueous medium soon before administration to a patient suspected of having a condition responsive to GHB.

The invention also provides a method of treating any therapeutic category of disorder responsive to GHB, comprising administering to a patient suspected of having such a condition a therapeutic amount of a pharmaceutical composition comprising chemically stable GHB (e.g. 1–10 gms.) in an aqueous medium resistant to microbial growth. In certain embodiments, the method of treating a condition responsive to GHB comprises a patient taking a first dosage of from about 0.1 g to about 10 g, namely about 0.1, about 0.2 about 0.3 about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0, about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, to about 10 grams of GHB, or as needed by the patient as would be recognized by one of skill in the art. Of course, it will be understood that all values in between those listed, such as 9.45 grams, 6.32 grams, etc. may be administered, and those values are encompassed well. In preferred embodiments, the first dose is administered within an hour of sleep. In preferred embodiments, a second dose of GHB within the values described above may be administered. This second dose is administered preferably within about 2.0 to about 5.0 hrs, namely about 2.0, about 2.1, about 2.2, about 2.3, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, to about 5.0 hours after the first dose, though it may be administered at a time outside of the preferred range.

In certain embodiments, a second pharmaceutical may be administered with the composition of GHB. Such a second pharmaceutical may be e.g., a stimulant administered within the same 24 hour period as the first dose of GHB. The stimulant may be, e.g., but not limited to, methylphenidate or pemoline to counter the residual effects of GHB treatment during periods of wakefulness. In certain embodiments, the method of treating a sleep disorder may include the discontinuation of other second pharmaceuticals used to control a sleep disorder. Such second pharmaceuticals may include, but are not limited to, a tricyclic antidepressant.

In certain embodiments, the invention provides a method of treating any appropriate therapeutic category of disorder, by administration of GHB compositions of the present invention as described above for the treatment of sleep disorders. When GHB is used in methods of treating any therapeutic category of disorder, the GHB composition of the present invention may be mixed with the aqueous medium, and optionally pH adjusting or buffering agent or other additives, by the patient or administrator soon before consumption. The patient may prepare the composition within a few minutes to hours before administration. Alternatively, one or more of the components may be premixed for ready use. The components of the GHB composition of the present invention, GHB, an aqueous medium, pH adjusting or buffering agent, excipients, preservatives, flavoring agents, and/or other components or additives may be stored in a container means suitable to aid preservation. Preferably, the container means is in the form of a set. A "set" as used herein certain embodiments is one or more components of the composition packaged in a container or other suitable storage means.

The present invention also provides a set for the treatment of a condition responsive to GHB comprising, in suitable storage means, GHB and a pH adjusting or buffering agent. In certain embodiments, the GHB and the pH adjusting or buffering agent are separately packaged. In certain other embodiments the GHB and the pH-adjusting or buffering agent may be mixed. The set may contain an aqueous medium. In certain other embodiments, at least one component selected from the group including, but not limited to, GHB, the pH-adjusting or buffering agent and/or an aqueous medium is separately packaged. In certain other embodiments, at least two of the components selected from the group comprising GHB, a pH, adjusting or buffering agent and an aqueous medium are mixed together. In some embodiments, the set further contains a preservative. Such a set may have one, two, or more components from the group comprising GHB, a pH-adjusting or buffering agent, an aqueous medium or a preservative packaged separately. Such a set may have two or more components mixed together. Thus, both liquid and dry formulations of GHB and other components may be packaged in a set for mixing before administration, or one or more components may be premixed and packaged together with other components, or all the components may be premixed and packaged in a set.

It is understood that the compositions of the present invention, including those in a set, may be dispersed in a pharmaceutically acceptable carrier solution as described below. Such a solution would be sterile or aseptic and may include water, co-solvent vehicle buffers, isotonic agents, pharmaceutical aids or other ingredients known to those of skill in the art that would cause no allergic or other harmful reaction when administered to an animal or human subject. Therefore, the present invention may also be described as a pharmaceutical composition of GHB with increased stability in a pharmaceutically acceptable carrier solution.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also as used herein, the term "a" "an" or "the" is understood to include the meaning "one or more". Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. **1**. The Range of Gamma-Hydroxybutyrate's Resistance to Microbial Growth and Chemical Stability in Aqueous Solution. The ordinate is the pH of solutions of GHB. The axis is the concentration (mg/ml) of GHB in aqueous solution. The region below the diagonal line [/] is the range

of GHB solubility at room temperature. Greater solubility can be achieved, up to 1 g/ml, by heating the solution up to 100° C. Three solutions were adjusted with HCl and were susceptible to microbial growth (Δ). Two solutions were pH adjusted with malic acid and were resistant to microbial growth (●). Of these two solutions, the one at pH 6 contained xylitol as an excipient. Three solutions were pH adjusted with hydrochloric acid and were resistant to microbial growth (▲). One solution was not pH adjusted and was susceptible to microbial growth (*).

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

1. Formulations of Gamma-Hydroxybutyrate

A. Microbial Growth and Gamma-butyrolactone Formation

The present invention arises from the discovery of chemically stable and microorganism resistant formulations of GHB in an aqueous medium, preferably a solution, and the efficacy of these formulations in the treatment of therapeutic categories of disorders, such as narcolepsy and other sleep disorders. Specifically, GHB is prepared at a concentration greater than about 150 mg/ml in an aqueous medium, up to the limits of GHB's solubility or retention in an aqueous medium, to produce the compositions of the present invention.

The maximum solubility of GHB is affected by the pH of the aqueous medium. At about pH 4, the maximum amount of sodium-GHB that can be dissolved is about 450 mg/ml. The value of pH that is conducive to GHB solubility increases, as is shown at FIG. **1**, so that the minimal pH that will dissolve 750 mg/ml GHB was found to be about pH 6.8. This is shown in Table 1.

TABLE 1

	Limits of Sodium Oxybate Solubility		
ID A	Sodium Oxybate Maximum Solubility	pH of Solution	Temperature
B	450 mg/cc	pH 4 (HCl)	25°
C	500 mg/cc	pH 5 (HCl)	25°
D	600 mg/cc	pH 6 (HCl)	25°
E	750 mg/cc	pH 6.8 (HCl)	25°
F	750 mg/cc+	pH 10.3	25°
G	1000 mg/cc	pH unadjusted	65° Soluble, 25° Gel

The pH of the aqueous medium also affects the resistance of the composition to microbial growth at about 500 mg/ml GHB. GHB at this concentration in an aqueous medium that is between about pH 5 and pH 9 is resistant to microbial growth, with compositions at about pH 6 to about pH 7.5 being particularly resistant to microbial growth. However, at concentrations of GHB greater than about 750 mg/ml above about pH 7.5, the resistance to microbial growth is reduced. This is shown at Table 2.

TABLE 2

	Microbial Challenge Data Summary		
ID H	Sodium Oxybate Concentration	pH of Solution	Microbial Challenge Result
I	750 mg/cc	7.5 (HCl)	pass
J	500 mg/cc	6.0 (HCl)	pass
K	500 mg/cc + Excipients (Xylitol)	6.0 (Malic Acid)	pass
L	500 mg/cc	9.0 (HCl)	pass (borderline *aspergillus*)
M	150 mg/cc (BDL 1995)	5.0 (HCl)	fail (*aspergillus* only)
N	150 mg/cc (BDL 1995)	7.0 (HCl)	fail (*aspergillus* & *staph*)
O	150 mg/cc (BDL 1995)	3.0 (HCl)	fail (*aspergillus* only)
P	150 mg/cc (BDL 1995)	10.3 (unadjusted)	fail (*aspergillus* and *staph*)
Q	500 mg/cc	6.0 (Malic Acid)	discontinued
R	500 mg/cc	7.5 (Malic Acid)	pass
S	500 mg/cc (May 1998)	9.0 (Malic Acid)	discontinued
T	500 mg/cc (May 1998)	7.5 (HCl)	pass*
U	Others: 200 mg/cc–800 mg/cc	5.0–9.0	pending

*pass is generally defined as:

For Category IC Products

Bacteria:	Not less than 1.0 log reduction from the initial cout at 14 days, and no increase from the 14 days' count at 28 days.
Yeast and Molds:	No increase from the initial calculated count at 14 and 28 days.

The data from Table 1 and Table 2 are graphically shown in FIG. **1**. The concentration of GHB in the composition, when evaluated in relationship to the pH, affects the resistance of the GHB composition to microbial challenge. Compositions of GHB at or below 150 mg/ml are poorly resistant to microbial challenge from a pH range of about pH 3 to about pH 9. However, concentrations of GHB of greater than about 150 mg/ml, up to about 1000 mg/ml of GHB, are believed to be suitably resistant to microbial contamination at these pH ranges.

The chemical stability of GHB is affected by pH. Accordingly, the method for preparing GHB, as described herein, particularly as disclosed in the specific examples, varies with pH. GBL begins to form if the pH is about 6 or less. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, any pH or range of pH values where a clinically acceptable amount of GBL is produced is also contemplated as being preferred, and is encompassed by the present invention. The range of GBL could be regulatorily broadened with availability of sufficient toxicological data.

In certain embodiments of the invention, a pH-adjusting agent may be added to the composition. The choice of a pH adjusting agent may affect the resistance to microbial challenge and/or the stability of GHB, as measured by the reduction in assayable GHB. Compositions of GHB, pH adjusted with malic acid are resistant to both microbial growth and chemical degradation of GHB, and are preferred. Other pH adjusting or buffering agents may be selected. Agents that adjust pH that are selected on this basis will undergo a taste testing study. However, any pH adjusting agent disclosed herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the invention. Of course, any salt, flavoring agent, excipient, or other pharmaceutically acceptable addition described herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the invention.

Any of the above formulations may be prepared and/or packaged as a powdered or dry form for mixing with an aqueous medium before oral administration, or they may be prepared in an aqueous medium and packaged. After mixing

with an aqueous medium, preferrably to prepare a solution, these formulations are resistant to both microbial growth and chemical conversion of GHB to GBL, thereby increasing the shelf-life of therapeutic formulations of GHB in an aqueous medium. These formulations then provide an easily titratable liquid medium for measuring the dosage of GHB to be administered to a patient. Additional embodiments of the composition and methods of preparation are described below and in the examples.

B. Pharmaceutical Compositions

1. Pharmaceutically Acceptable Carriers

Aqueous compositions of the present invention comprise an effective amount of GHB dissolved or dispersed in a pharmaceutically acceptable carrier and/or an aqueous medium. The phrases "pharmaceutically or pharmacologically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is not appropriate. Supplementary compatible active ingredients can be incorporated into the compositions. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by the Food and Drug Administration (FDA).

The GHB may be lyophilized for more ready formulation into a desired vehicle where appropriate. The active compounds may be formulated for parenteral administration, e.g., formulated for injection via intravenous, intraarterial, intramuscular, sub-cutaneous, intralesional, intraperitoneal or other parenteral routes. The preparation of an aqueous composition that contains a GHB agent as an active component or ingredient will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for using to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including, e.g., aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

Solutions of the active compounds as free acid or pharmacologically acceptable salts can be prepared in water suitably mixed with hydroxypropylcellulose and/or a pharmacueutically acceptable surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof as well as in oils. Under ordinary conditions of storage and use, these preparation may best contain a preservative to further prevent the growth of microorganisms.

A GHB composition of the present invention can be formulated into a composition in a neutral or salt form. Such salts can be formed from any of the acids and bases described herein particularly depending on the particular GHB or GHB salt used, or as would be known to one of ordinary skill in the art.

The carrier can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, or the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a substance, such as lecithin (e.g. a coating), by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by any of the preservatives desribed herein, or as would be known to one of ordinary skill in the art, including various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The preparation of more, or highly, concentrated solutions for direct injection is also contemplated, where the use of DMSO as solvent (although DMSO may not now be a permitted human drug) is envisioned to result in extremely rapid penetration, delivering high concentrations of the active agents to a small area.

Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above, but drug release capsules and the like can also be employed.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035–1038 and 1570–1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The active GHB may be formulated within a therapeutic mixture to comprise about 100 to about 10,000 milligrams per dose. Multiple doses can also be administered.

In addition to the compounds formulated for parenteral administration, such as intravenous or intramuscular injection, other pharmaceutically acceptable forms include, e.g., tablets or other solids; liposomal formulations; time release capsules; and any other form currently used, including cremes, which then may be admixed with an aqueous medium for oral administration.

One may also use nasal solutions or sprays, aerosols or inhalants in the present invention. Nasal solutions are usually aqueous solutions designed to be administered to the nasal passages in drops or sprays. Nasal solutions are prepared so that they are similar in many respects to nasal secretions, so that normal ciliary action is maintained. Thus, the aqueous nasal solutions usually are isotonic and slightly buffered to maintain a pH of 5.5 to 6.5, though other pH ranges disclosed herein the specific examples, such as pH 3 to about pH 9, or pH 6 to about 7.5, are contemplated. In addition, preservatives, similar to those used in ophthalmic preparations, and appropriate drug stabilizers, if required, may be included in the formulation. Various commercial nasal preparations are known and include, for example, antibiotics and antihistamines and are used for asthma prophylaxis.

The perferred oral formulations may include such normally employed excipients, as, for example, pharmaceutical grades of xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate and the like. These compositions can take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders to be admixed with an aqueous medium. In certain defined embodiments, oral pharmaceutical compositions will comprise an inert diluent or assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsule, or they may be compressed into tablets, or the GHB may be packaged separately from or in combination with the excipients, salts, flavorings or any other components described herein, to be admixed with an aqueous medium for oral or injectable formulations, or they may be incorporated directly with the food (i.e. a beverage) of the diet.

For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of tablets, buccal tablets or tabs, troches, capsules, elixirs, suspensions, syrups, wafers, and the like, to be admixed with an aqueous medium. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 75% of the weight of the unit, or preferably between 25–60%. The amount of active compounds in such therapeutically useful compositions is such that a suitable dosage will be obtained.

The tablets, troches, pills, capsules and the like may also contain the following: a binder, nutural as gum tragacanth, acacia, cornstarch, or gelatin or synthetic as polyvinyl acetate; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a natural or synthetic flavoring agent. When the dosage unit form is a capsule for admixing with a specific volume of an aqueous medium, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with sugar, natural or synthetic polymers, or both. A syrup or elixir may contain the active compounds, sucrose as a sweetening agent, a preservative, a dye and/or a flavoring.

Additionally, any excipient, salt, acid, pH-mediating, adjusting or buffering compound or agent, flavoring, solution, solvent, dispersion, glycerol, glycol, oil, antibacterial and antifungal agents, antibiotics and antihistamines, binders, disintegrating agents, lubricants, sweetening agents, or any other additive or ingredient from those enumerated above or in the examples, or in any pharmaceutically acceptable composition or carrier described herein, or as would be known by one of skill in the art, is contemplated for use in aqueous mediums or solid forms of the GHB compositions of the invention. One or more of these compositions may be packaged with GHB or packaged separately from GHB prior to consumption. If packaged separately, useful compositions of GHB may be obtained by mixing GHB with the other components with an aqueous medium prior to consumption. Such components may be packaged in a set, described below.

2. Sets

Therapeutic sets of the present invention are sets comprising GHB. Such sets will generally contain, in suitable container, a pharmaceutically acceptable formulation of GHB. The set may have a single container, or it may have distinct container for each component, or distinct container for various combinations of components.

When the components of the set are provided in one or more liquid formulations, the liquid formulation is an aqueous medium, with a sterile aqueous solution being particularly preferred. The GHB compositions may also be formulated into a syringeable composition. In which case, the container means may itself be a syringe, pipette, vial, ampule or other such like apparatus, from which the formulation may be applied to an infected area of the body, injected into an animal, or even applied to and mixed with the other components of the set.

However, the components of the set may be provided as dried powder(s). When reagents or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent. It is envisioned that the solvent may also be provided in another container means.

The container means will generally include at least one vial, test tube, flask, bottle, pouch syringe or other container means, into which the GHB formulation or components thereof are placed, preferably, suitably allocated. The sets may also comprise a second container means for containing a sterile, pharmaceutically acceptable buffer or other diluent.

The sets of the present invention will also typically include a means for containing the vials in close confinement for commercial sale, such as, e.g., injection or blow-molded plastic containers into which the desired vials are retained.

Irrespective of the number or type of containers, the sets of the invention may also comprise, or be packaged with, an instrument for assisting with the injection/administration or placement of the GHB composition within the body of an animal. Such an instrument may be a drinking cup, syringe, pipette, or any such medically approved delivery vehicle.

II. Methods of Treatment with the GHB Compositions

Because GHB has been shown to be effective in treating narcolepsy and sleep disorders (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993), reducing alcohol craving and alcohol withdrawal symptoms, (Gallimberti et al., 1989;

Gallimberti et al., 1992; Gessa et al., 1992), reducing opiate withdrawal symptoms (Gallimberti et al, 1994; Gallimberti et al., 1993), reducing pain (U.S. Pat. No. 4,393,236), reducing intracranial pressure in patients (Strong, A. 1984), and increasing growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970), the formulations of the present invention are also contemplated to be useful in the treatment of any of these disorders or conditions in patients. GHB has also been used alone as a narcotic in patients with a terminal carcinomatous state. GHB has been used with other analgesics, neuroleptics, or with a subliminal barbiturate dose for use as an anesthesia. GHB has been used in closed cranio-cerebral trauma and as a soporific (U.S. Pat. No. 5,380,937). The inventors contemplate the use of the GHB compositions of the present invention as a narcotic, hypnotic, or as a soporific. The inventors also contemplate the use of the GHB compositions of the present invention in combination with analgesics, neuroleptics or barbiturates for use as an anesthesia. The GHB compositions of the present invention may be prepared and administered by any of the means described herein, particularly those described in the section "Pharmaceutical Compositions" and the examples, or by any means as would be known to those of skill in the art.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

Preferred Embodiments

Xyrem™ Clinical Trials

The inventors developed a liquid formulation composed of GHB, xylitol, and preservative in water (XYREM™). Subsequent instability of the preservative in this formulation and a desire to initiate clinical trials in a timely manner led to a change in the formulation to a foil pouch. One clinical trial utilized a twin-pouch dosage form, with one side (pouch 1) of the foil packet containing GHB and the other side (pouch 2) containing the flavoring agents (Xylitol, [NF]; Malic Acid, NF;

Patients were instructed to open the twin-pouch with a scissors, empty the contents into a dosing cup, add 2 ounces of water, snap the lid on the dosing cup, shake to dissolve, and drink the entire contents of the cup. Clinical trials conducted by the inventors have been performed using the twin-pouch dosage form.

However, the inventors have continued development of a liquid solution and have now overcome inherent problems with particular formulations and/or preservatives. The inventors have converted patients currently enrolled in a GHB open-label trial to a liquid solution composed of GHB, malic acid, and water—that is diluted with water immediately prior to oral administration.

The need for a liquid solution dosage form is further evidenced by the range of doses being used in a subsequent GHB open-label trial. Three sizes of pouches were prepared for the GHB open-label trial: 1.5 grams, 3.0 grams, and 4.5 grams. The initial dose for all patients in the GHB open-label trial was 6 grams of GHB nightly in divided doses. Dosage adjustments were permitted in the first two weeks of the trial as indicated for intolerance or lack of efficacy. The investigator was permitted to decrease the dose of GHB to 3 grams or 4.5 grams, or increase the dose to 7.5 grams or 9 grams nightly. After two weeks, further dosage adjustments were made if clinically indicated.

Thirty-five patients had their dose increased, and 16 patients had their dose decreased. Patients in the lowest dose group were disproportionately female and weighed 15 kg less than patients in the other two groups. Current dosing levels are noted below:

TABLE 3

Dosing Levels in the GHB Open-Label Trial

	Total	1.5 gram	3.0 gram	4.5 gram	6.0 gram	7.5 gram	9.0 gram
Number of Patients	95	0	4	10	39	12	30
Percent of Patients	100%	0%	4%	10%	41%	13%	32%

To achieve these individualized doses, it has been necessary to provide a combination of different dose strengths. This complexity would be very difficult to achieve with a marketed product. In addition, a month's supply of twin-pouches is quite bulky. A liquid formulation allows for ease in dosing adjustment with one dosage form. In addition "child-resistant" packaging has been developed with the liquid formulation.

A number of patients have also complained about the flavor with the twin-pouches. As follow-up the inventors sent questionnaires to participants in the inventors' clinical trial, and performed taste testing in normal volunteers. The questionnaire responses, taste testing results, and the clinical experience in narcolepsy patients of the study administrator have all confirmed that unflavored solutions were acceptable.

The concentration and volume of the GHB solution that the patient administers will be the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. This is illustrated in Chart 1 and Table 4:

Chart 1
Comparison of Liquid Solution to Twin-Pouch

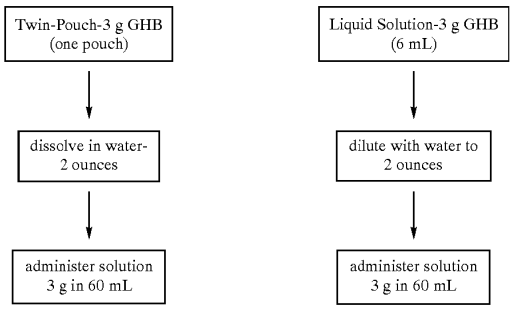


TABLE 4

Comparison of Liquid Solution to Twin-Pouch

Amount of GHB	Twin-Pouch 3 grams (1 pouch)	Liquid Solution 3 grams (6 mL)
Inactive Components	malic acid xylitol lemon/lime flavor orange flavor	malic acid
Final Concentration	50 mg/mL	50 mg/mL*
Final Volume	60 mL	60 mL

*Final concentration outside the range of the most stable formulation. This formulation strength may be only stable at short periods of time such as 48 hours. The twin pouch version could be solubilized at a a concentration within the preferred range of pH and GHB concentration for longer term storage.

Apart from the elimination of the sweetener (xylitol) and flavoring, the two formulations result in identical solutions.

CONCLUSIONS

The concentration and volume of the GHB solution that the patient administers is the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. Either method may be used to produce acceptably stable solutions of GHB.

EXAMPLE 2

Preferred Embodiments

Self Preserving Formulations of Gamma-Hydroxybutyrate Summary of Formulations Studies—Liquid Xyrem™

I. Maximum Solubility Range

As seen in FIG. **1** and Table 1, the solubility of GHB varies with pH levels at room temerature (25° C.). Additional amounts of GHB can be solubilized in a gel if heat is applied, in which case a 1000 mg/ml concentration can be achieved. The inventors contemplate that though the concentrations or contents of GHB shown in FIG. I and Table 1 are preferred for use, due to the ease of preparing and consuming unheated preparations, higher concentrations of GHB in aqueous medium may also be made, up to 1000 mg/ml.

II. Microbial Testing

The inventors used a three factor analysis involving pH, concentrations of GHB and the pH adjuster used. As seen in FIG. **1**, and Table 2, unacceptably low resistance to microbial challenge was seen at 150 mg/ml GHB at pH 3, 5, 7, and 9.0, using HCl as the pH adjusting agent. 150 mg/ml GHB at pH 10.3 without a pH adjusting agent also proved unacceptably resistant to microbial challenge. Borderline acceptable microbial preservativeness was seen in a solution pH adjusted with HCl at 500 mg/ml GHB at pH 9. At a concentration of 500 mg/ml at pH 6.0 or 7.5, adjusted with either malic acid or HCl, and 500 mg/ml at pH 9.0 adjusted with HCl, the formulation is very effective in a microbial challenge test. The inventors contemplate that a concentration of greater than about 150 mg/ml of GHB, up to the maximal solubility in aqueous solution of GHB, will be suitably resistant to microbial challenge from about pH 3 to pH 10.3. Preferably, the aqueous medium will contain a pH-adjusting or buffering agent.

III. Gamma-Butyrolactone Degradation Range

GBL begins to form if the pH is about 6 or less with the formulation tested thus far.

A. Liquid Formulation Development

The objective of these experiments was to develop a commercial formulation for sodium gamma hydroxybutyric acid. The initial formulation for sodium gamma hydroxybutyric acid (GHB) was intended to be an aqueous liquid formulation containing 150 mg/mL GHB, preservatives and flavoring agents. To develop this formulation, studies were conducted to establish the: solubility of the drug in water and as a function of pH, type and concentrations of suitable preservatives, type and concentrations of flavor ingredients, and stability of the formulations.

1. Solubility

The feasibility of preparing formulations containing 150 mg/mL of GHB at pH 3, 5 and 7 was established. Solutions containing 150 mg/mL GHB were prepared. The initial pH was greater than pH 7.5 and the final pH was adjusted to 3, 5 or 7 with hydrochloric acid. The solutions were observed for precipitation and assayed by HPLC for GHB content. The results showed that no precipitation was observed and the drug concentration was found to be 150 mg/mL by HPLC. This information was used as the basis for additional formulation development studies.

2. Preservatives

Preservative effectiveness studies were conducted to identify a suitable preservative for the GHB liquid formulation. The following formulations shown in Table 5 were prepared and tested using *Staphylococcus attreus* (ATCC #6538), *Pseudomonas aeruginosa* (ATCC #9027) and *Aspergillus niger* (ATCC #16404).

TABLE 5

Liquid Formulations Used in Preservative Effectiveness Testing

Formulation	pH	Sodium Benzoate	Methylparaben Propylparaben	Potassium Sorbate	Control
1	3	X			
2	5	X			
3	7	X			
4	3		X		
5	5		X		
6	7		X		
7	3			X	
8	5			X	
9	7			X	
10	3				X
11	5				X
12	7				X
13	no pH adjustment				X

The preservative used in each formulation is marked with an X. The results showed that formulations #3, 4, 6 and 9 reduced all three challenge microorganisms by >99.99% in 48 h of contact time. Formulations #1, 5 and 7 reduced all three challenge microorganism by >99.99% in 7 days of contact time. Formulations #2, 8, 10, 11, 12 and 13 did not reduce *Aspergillus niger* mold to >99.99%, although some reduction occurred in 7 days of contact time. Controls #10, 11, 12 and 13 demonstrated activity against *Pseudomonas aeruginosa.*

3. Stability

Based on the results of the preservative effectiveness testing, five formulations were selected for stability testing. Table 6 shows the composition of the formulations.

TABLE 6

Liquid Formulations Used in Informal Stability Program

Chemical	1	2	3	4	5
Potassium Sorbate	0.4 gm	0.4 gm			
Sodium Benzoate			1.0 gm		
Methyl-paraben				0.36 gm	0.36 gm
Propyl-paraben				0.04 gm	0.04 gm
GHB	30 gm	30 gm	30 gm	30 gm	30 gm
Xylitol	40 gm	40 gm	40 gm	40 gm	40 gm
Water q.s.	200 mL	200 mL	200 mL	200 mL	200 mL
Initial pH	8.68	8.68	9.30	7.75	7.75
Formulation Adjusted pH	3.01	5.00	3.00	2.98	4.98

The formulations were packaged in 125 mL, amber PET bottles with safety lined child-resistant caps and stored upright and inverted at 60° C., 40° C./75% relative humidity (RH) and 25° C./60% relative humidity. Samples were removed from the stability chambers after 1, 2 and 3 months and assayed by high performance liquid chromatography (HPLC) for GHB content. Appearance and pH were also monitored.

Table 7 shows the results for the 3 month time point. Samples stored at 60° C. changed color but samples at all other conditions remained unchanged in color.

The pH of all formulations migrated upward over the three month stability period 60C. The percent increase in pH from initial to 3 months, was greater for the formulations which were initially adjusted to lower values.

For example, the migration of pH in formulations 1,3 and 4 (adjusted down to pH 3) were 21–30 percent across all conditions in three months. The migration of pH in formulations 2 and 5 (adjusted down to pH5) were 4.2–12 percent across all conditions in 3 months. Maintenance of pH becomes important for long term storage since preservatives are known to degrade in formulations having pH levels above approximately pH 6.

Additionally, development of flavor systems to mask the negative taste of perservatives is difficult.

TABLE 7

Results of Liquid Formulation Informal Stability Study at Three Months

Formulation # (See Table 6)	Attribute	25° C./60% RH Upright	25° C./60% RH Inverted	40° C./75% RH Upright	40° C./75% RH Inverted	60° C. Upright
1	% t = 0	100.7	101.6	101.2	NA	NA
Potassium Sorbate (pH3) at 3 months storage	pH	3.63	3.64	3.84	3.82	3.91
	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light yellow
2	% t = 0*	102.1	105.0	104.0	102.0	99.6
Potassium Sorbate (pH5)	pH	5.21	5.28	5.55	5.56	5.61
	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light brown
3	% t = 0	102.4	104.1	99.1	102.6	97.0
Sodium Benzoate (pH3)	pH	3.60	3.74	3.78	3.75	3.79
	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, colorless
4	% t = 0	101.5	102.7	100.6	101.2	93.7
4 Methyl & Propyl Parabense (pH3)	pH	3.63	3.71	3.81	3.80	3.83
	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, colorless
5	% t = 0	103.1	105.8	101.9	103.1	95.6
4 methyl & Propyl Prabens (pH5)	pH	5.22	5.55	5.55	5.56	5.60
	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light yellow

*% GHB at t = 0 percent of label claim
** initial time (t = 0)

4. Liquid Formulation Organoleptic Testing

Based on the above stability data and preservative effectiveness testing, a pH 5 formulation containing potassium sorbate was selected as the primary base formulation for flavor system development and organoleptic testing. A pH 3 formulation containing potassium sorbate was selected as the back-up formulation.

B. Dry Powder Formulation Development

Developing a flavor system for the primary and back-up liquid formulations proved to be difficult and a decision was made to develop a dry powder formulation for reconstitution with water before consumption. This approach removed the need for a preservative system, the requirement to adjust pH to levels below pH6, and allowed the development of a suitable flavor system.

1. Dry Powder Formulation Organoleptic Testing

To develop a flavor system for the powder formulation, several parameters were evaluated. The flavor attributes of a GHB solution was characterized by a professional sensory panel. A mimic base containing similar sensory properties as a GHB solution for flavor system was developed. Generally Recognized As Safe (GRAS) excipients for flavor system

development were selected. Different excipients (flavorings, sweeteners, acidulants and flow agents) in the mimic base were screened. Three flavor systems for the focus group test were selected. A preferred flavor system was optimized based on comments obtained from the focus group testing. This final formulation with GHB was optimized.

Based on the above activities, the following formulations in Table 8 were selected for stability studies:

TABLE 8

Composition of Prototype Dry Powder Formulation

Ingredient	Composition (grams)	Purpose
GHB	3	Active
Xylitol	5.5	non-cariogenic sweetener
Malic acid	0.2	Acidulant
Flavor 1	0.2	Flavor ingredient
Flavor 2	0.04	Flavor ingredient
Silicon Dioxide (Cab-O-Sil ®)	0.03	Flow enhancer

2. Dry Powder Formulation Stability

A study was initiated to evaluate the stability of the above prototype formulation in two types of foil packages (high and moderate moisture resistant) as well as the stability of GHB alone in one type of foil package (high moisture resistant). Table 9 shows the Lots that were placed on stability. The foil packages were a high moisture resistant pouch and a moderate moisture resistant pouch. The study protocol, Table 10, required the samples to be stored at 40±2° C./75±5% relative humidity for six months, and 25±2° C./60±5% relative humidity for 12 months. Table 11 shows the tests, methods, number of packets/test and specifications for the study.

TABLE 9

Dry Powder Informal Stability Study Package Composition

Lot Number	Manufacture Date	Package Configuration	Special Comments
SPO #8018 A	Oct. 6, 1995	Foil Packet	Moderate moisture resistant pouch.
SPO #8018 B	Oct. 6, 1995	Foil Packet	Highest moisture protection pouch.
SPO #8018 C	Oct. 6, 1995	Foil Packet	Drug substance only. Highest moisture protection pouch.

TABLE 10

Dry Powder Informal Stability Study Protocol

	Stability Time in Months						
Storage Conditions	0	1	2	3	6	9	12
40 ± 2° C./75% ± 5% RH		X	X	X	X		
25 ± 2° C./60% ± 5% RH	X	X	C	C	R	R	R

X = Samples to be tested
C = Contingency Samples
R = Reduced testing; assay and H_2O only
RH = Relative Humidity

TABLE 11

Dry Powder Informal Stability Tests and Specifications

Test	Method	Packets/Test	Specification Limits
Appearance Dry Material	Visual	Use HPLC	White to off-white free flowing powder
Appearance Reconstituted Material	Visual	Use HPLC	Cloudy, off-white solution with visible particulates
Rate of Dissolution	Visual	Use HPLC	Material should dissolve completely in five min with mixing
Odor	Olfactory	Use HPLC	Characteristic Lemon/ Lime odor
Assay: GHB	HPLC	3	90.0%–110.0%
Assay: Malic Acid	HPLC	Use HPLC	90.0%–110.0%
Impurities/Degradants	HPLC	Use HPLC	Not more than 1% for for any individual impurity/degradant and Not more than 3% total impurity/ degradants
Vacuum Leak test	Visual	3	No Appearance of Leaking
pH	USP <791>	Use HPLC	For Information
Moisture	Karl Fisher	3	ReportValue - to be determined

After two months at 40±2° C./75±5% relative humidity, the potency (% label claim) of Lots SPO 8018A and SPO 8018B was less than 94.0%, the lower limit of the specification, whereas Lot SPO 8018C showed no loss in potency. Lots 8018A and 8018B showed approximately 96% potencies after 2 months at 25° C.±2° C./65%±5% relative humidity. Lot SPO 8018C again showed no loss in potency at this lower storage condition.

3. Appearance

After 2 months at 40° C.±2° C./75%±5% relative humidity, Lots SPO 8018A and SPO 8018B showed significant melting, whereas Lot 8018C showed no melting. Lots SPO 8018A and SPO 8018B also showed partial melting after 2 months at 25° C.±2° C./65%±5% relative humidity. Lot SPO 8018C again showed no evidence of melting at this lower storage condition.

Based on the physical changes in state observed during the stability studies, it was apparent that a solid state interaction between GHB and the excipient blend had occurred. Since xylitol made up the majority of the excipient blend, it was assumed that xylitol was the primary source of the drug-excipient interaction. An alternative hypothesis was also proposed, based on the possibility that the package was mediating the interaction between GHB and xylitol. Three studies were initiated to test these hypotheses.

4. Stability of GHB Solids in a Set Container-System

In the first study, the samples that were stored at 25±2° C./60±5% relative humidity were transferred to glass vials and then stored at 40±2° C./7±5% relative humidity. In the second study, mixtures of GHB and xylitol were gently rubbed between sheets of different types of foil packaging. The mixtures were observed for changes in physical appearance. In the third study, different mixtures of GHB and xylitol were prepared. Differential Scanning Calorimetry (DSC) thermograms were then done to look for changes in the thermograms. The results of these studies are summarized below.

Transfer to Glass: Samples of Lot 8018A and Lot 8018C that were previously stored at 25±2° C./60±5% relative

humidity were transferred to amber screw cap vials and stored at 40±2° C./75±5% relative humidity. Analyses similar to those shown in Table 6 were done. After 1 month, the potency of Lot 8018A was 94.6% whereas the potency of Lot 8018C (GHB only) was 100%. In addition, Lot 8018A also showed evidence of melting. The results supported the hypothesis that GHB and xylitol were interacting in the solid state and the interaction appeared to be independent of packaging.

Foil Study: Mixtures of GHB and xylitol were placed between folded sheets of several different foil packaging materials. Slight adhesion of the mixed granules with the foil lining was observed for all of the foils examined. No direct evidence of melting was observed, however, even when excessive force was applied to the outer foil surfaces. This data suggests that the packaging material was not responsible for the solid state interaction observed during the stability studies.

DSC thermographs were obtained for samples of GHB/xylitol containing GHB:xylitol mixtures of 33:66, 45:55 and 55 percent 45 respectively. The scans were conducted at a scan rate of 10° C./min. The thermograms showed that the sample containing GHB:xylitol 33:66 showed a broad endothermic transition starting at 35° C.-40° C. Samples with higher ratios of GHB:xylitol also showed broad endothermic transitions that started at temperatures of 45° C.–50° C. The changes seen in the thermograms supported the hypothesis that a solid state interaction may be occurring between GHB and xylitol that resulted in low potencies for formulations containing mixtures of these two agents.

As a result of the changes seen in the DSC thermograms for different mixtures of GHB:xylitol, a study was initiated to investigate the stability of a formulation containing GHB:xylitol excipient blend 55:45. A formulation containing GHB:xylitol excipient blend 33:66 was used as a control sample. The formulations were packaged in glass vials and stored at 50° C., 40±2° C./75±5% relative humidity and 25±2° C./60±5% relative humidity. The appearance and potency of the formulations were monitored through analyses of stability samples. The stability study also showed potency losses after 1 month at 40° C.±2° C./75%±5% relative humidity with both the 50/50 GHB:xylitol ratio as well as the original 33/66 ratio formulation. Partial evidence of melting was also observed in both formulations.

Studies with mixtures of GHB:xylitol excipient blend indicated that the mixture was incompatible in the solid state. However, when prepared as an aqueous solution, these mixtures were chemically compatible. Using this information, a decision was made to package the GHB formulation in dual pouches; one pouch containing GHB alone and the other containing a mixture of xylitol and the other flavor ingredients. The formulation will contain equal amounts of GHB and the excipient blend. This product will be prepared, packaged, and may be checked for stability.

EXAMPLE 3

The Pharmacokinetics of Gamma-Hydroxybutyrate

Study Objectives

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; patients generally ingested the first dose of this medication prior to bedtime and the second dose from 2.5 to 4.0 h later) to narcoleptic patients who are maintained on a chronic regimen of GHB.

II. Study Design

This pharmacokinetic study was conducted as an open-label, single-center investigation in 6 narcoleptic patients. The study design is summarized as follows:

TABLE 12

Screening/ Washout⇒	Treatment/Blood Sampling⇒	Follow-up
(1 or more days to dosing; washout, at least 8 h	(Two 3 g GHB oral doses, 4 h apart; 21 blood samples)	(Within 48 h after last blood sample)

Narcoleptic patients, 18 years of age or older, who volunteered for this study were screened at least one day prior to the treatment phase. Each patient was determined to be in stable health and evaluated for the presence of narcolepsy, defined for the purposes of this example as one or more years of medical history of narcolepsy as evidenced by a recent nocturnal polysomnogram (PSG) and a valid score from a Multiple Sleep Latency Test (MSLT).

Patients maintained on GHB were allowed to participate. These patients had been weaned from antidepressants, hypnotics, sedatives, antihistamines, clonidine, and anticonvulsants though a stable regimen of methylphenidate (immediate release or sustained release) was allowed. Each patient passed a pre-study physical examination (which included hematology, blood chemistry, urinalysis, and vital signs measurements) prior to the commencement of the treatment phase.

Before oral administration of the first GHB dose, an indwelling catheter was placed in an arm vein and a baseline blood sample was collected. Each patient then ingested a 3 g dose of GHB before bedtime. Another 3 g GHB dose was administered 4 h after the first dose. Twenty-one sequential blood samples were collected over 12 h (starting at 10 min after the first dose and ending at 8 h after the second dose). Upon completion of the treatment phase, a follow-up physical examination which included the measurement of vital signs was performed on each patient within 48 h after the last blood sample. A detailed description of the trial methodology is presented in Section IV.

III. Inclusion Criteria

Patients were included in the study if they: had signed an informed consent prior to beginning protocol required procedures; had not participated in such a study at an earlier date; were willing and able to complete the entire study as described in the protocol; were 18 years of age or older at study entry; had not taken any investigational therapy other than GHB within the 30-day period prior to screening for this study; had an established diagnosis of narcolepsy for at least one year with documentation from a qualified laboratory by a nocturnal polysomnogram (PSG) and a Multiple Sleep Latency Test (MSLT) which demonstrated mean sleep latency to be less than 5 min and REM onset in at least 2 of 5 naps; had not been diagnosed with uncontrolled sleep apnea syndrome, defined as a sleep Apnea Index of 5 or an Apnea Hypopnea Index (AHI) greater than 10 per hour or any other cause of daytime sleepiness; and were free of any medication for their narcolepsy (including hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants) other than GHB and methylphenidate (IR or SR). Patients admitted to this study if they were not experiencing unstable cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, metabolic, neurological, pulmonary, and/or renal disease

which would place them at risk during the study or compromise the protocol objective; did not have neurological or psychiatric disorders (including transient ischemic attacks, epilepsy, or multiple sclerosis) which, in the investigator's opinion, would preclude the patients' participation and completion of this study; did not have a current or recent (within one year) history of alcohol or drug abuse; did not have a serum creatinine greater than 2.0 mg/dL, abnormal liver function tests (SGOT or SGPT more than twice the upper limit of normal, or serum bilirubin more than 1.5 times normal). Female patients were entered into the study if they were either post-menopausal (i.e. no menstrual period for a minimum of 6 months), surgically sterilized or provided evidence of effective birth control. Females of childbearing potential must agree to continue to use an IUD, diaphragm, or take their oral contraceptives for the duration of the study. Female patients of childbearing potential must have a negative pregnancy test upon entry into the study.

IV. Trial Methodology

A time and events schedule is presented in Table 12.

A. Screening Period/Washout

Six narcoleptic patients who were chronically being treated with GHB were recruited to participate in this pharmacokinetic study. The screening period was at least one day prior to the treatment phase. During the screening period each patient completed the following procedures for the assessment of their physical condition: medical history evaluation; physical examination evaluation; clinical laboratory evaluation; inclusion criteria review. Each patient's GHB and methylphenidate regimen also were recorded on an appropriate case report form (CRF). The investigator also ensured that there was at least an 8-hour washout period for GHB prior to the treatment.

B. Treatment Period/Blood Samples Collection

All patients were hospitalized from approximately four hours prior to first GHB dosing (around 6 p.m.) until the end of the treatment period (around 10 a.m. the next morning). Patients ate their dinner at the clinical research unit soon after arrival and fasted until breakfast next morning. At least three hours elapsed between the completion of dinner and the administration of the first GHB dose. An indwelling catheter was placed in an arm vein of each patient for blood sampling at approximately 30 min and 1 h before the first GHB dose and a baseline blood sample (5 mL) was collected.

The first GHB dose (3 g) was administered at around 10 p.m. Dosing of individual patients were staggered. The second GHB dose was administered at 4 h after the first GHB dose (i.e. immediately after the 4 h blood sample). The exact dosing times in each patient were recorded on appropriate CRF pages. Blood samples (5 mL each) were collected through the indwelling catheter into heparinized tubes at 0.2, 0.4, 0.6, 0.8, 1, 1.5, 2, 3, 4, 4.2, 4.4, 4.6, 4.8, 5, 5.5, 5, 7, 8, 10, and 12 h after the first GHB dose. Blood samples were processed according to the procedures described herein. Patients were monitored for adverse experiences throughout the study according to the specific procedures.

C. Follow-up

Follow-up occurred within 48 h after the last blood sample had been collected. An abbreviated physical examination which included vital signs measurement was performed. Adverse experiences and concomitant medication use, if any, were assessed. Any ongoing adverse experiences and clinically important findings in a patient were followed to the investigator's and/or sponsor's satisfaction before the patient was discharged from the study.

D. Methods of Assessment

1. Medical History

The medical history was recorded during the screening period. The history included gender, age, race, height, prior reaction to drugs, use of alcohol and tobacco, history and treatment, if any, of cardiovascular pulmonary, gastrointestinal, hepatic, renal, immunologic, neurological, or psychiatric diseases and confirmation of inclusion criteria.

2. Physical Examination

Physical Examination included body system review as well as measurement of body weight and vital signs and a neurological examination.

3. Vital Signs

Vital signs measurements included recording of blood pressure, heart rate, respiration, and body temperature.

4. Clinical Laboratory

All clinical laboratory tests were performed at a local laboratory. The laboratory tests and analysis were required of each patient included: hematology, including hemoglobin, hematocrit, red blood cell count, white blood cell count and differential; fasting blood chemistries included blood urea nitrogen (BUN), uric acid, glucose, creatinine, calcium, phosphorus, total protein, albumin, sodium, potassium, SCOT (AST), SGPT (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), and total bilirubin; midstream catch urinalysis included specific gravity, pH, protein, occult blood, ketones and glucose by dipstick determination as well as a microscopic examination of urine sediment for RBC, WBC, epithelial cells or casts or crystals; and a urine pregnancy test, if applicable. Any laboratory parameter that was out of range and considered clinically significant excluded the patient from participation in this study. The investigator would provide an explanation of all observations that were significantly outside the reference range.

5. Concomitant Medication

The continued use of a fixed dose of methylphenidate immediate release or sustained release (IR or SR) is acceptable. The methylphenidate regimen was recorded on the appropriate case report form.

6. Adverse Experiences

An adverse experience are any undesirable event experienced by a patient or volunteer whether or not considered drug-related by the investigator. An undesirable event can be, but is not limited to, subjective symptoms experienced by a patient or, objective findings such as significant clinical laboratory abnormalities. Adverse experience is considered synonymous with the term "adverse event".

The investigators report in detail all adverse experiences and symptoms that occurred during or following the course of trial drug administration for up to 2 days. Included in the description was the nature of the sign or symptom; the date of onset; date or resolution (duration); the severity; the relationship to trial treatment or other therapy; the action taken, if any; and the outcome.

A serious adverse experience is defined as one that is fatal, life threatening, permanently disabling, or which results in or prolongs hospitalization. In addition, overdose, congenital anomaly and occurrences of malignancy are always considered to be serious adverse experiences. An unexpected adverse experience is one not previously reported.

Any serious or unexpected adverse experience (including death) due to any cause which occurs during the course of

this investigation, whether or not it is related to the investigational drug, was reported within 24 h by telephone or facsimile. Appropriate authorities were to be informed if the serious or unexpected adverse experience, in the opinion of inventors, was likely to affect the safety of other patients or volunteers or the conduct of the trial.

7. Clinical Supplies-Study Medication

Formulation: Unit 3 g GHB doses (Lot PKI) were obtained from Orphan Medical. Each unit dose comprised twin foil pouches: one pouch containing GHB and the other containing a flavor excipient blend. (Table 8 formulation)

Labeling: The clinical supplies for individual patients were packaged in separate containers. Each container included two unit doses, i.e. two twin-pouches. Clinical supplies for eight patients (including those for two replacement patients) were delivered to the investigator. Foil twin-pouches were identified with a two-part label.

Dose Administration: The investigator or designee prepared the oral solution for dosing within 30 min prior to the first oral administration to individual patients. The contents of one twin-pouch was emptied into a dosing cup to which two ounces of water were added. After replacing the lid of the dosing cup, it 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 ingesting in its entirety at 4 h after the first GHB dose.

Investigational Drug Accountability: At the conclusion of the study, all clinical supplies were accounted for on the drug accountability form and unused drug supplies were returned for proper disposition.

8. Determination of Plasma GHB Concentrations

Plasma samples were analyzed for GHB by the Department of Bioanalytical Chemistry (Covance (previously known as Hazelton Corning), Madison, Wis.) A gas chromatographic method with mass selective detection (GC-MSD) was used in the analysis.

9. Data Management and Analysis

Data Base: An EXCEL data base (spreadsheet) was constructed from data recorded on Case Report Forms (CFR) and plasma GHB concentration data sets received from Covance (Corning Hazleton). Each entry in the EXCEL spreadsheet was checked against the CRFs and any data entry error found was corrected.

Pharmacokinetic Analysis: Pharmacokinetic parameters were determined for individual sets of plasma GHB concentration vs. time data using the non-compartmental routine in WinNonlin Version 1.1. The peak GHB concentrations (C_{max}) and the times of their respectively occurrences (t_{max}) were observed values. Terminal half-life ($T_{1/2}$) was obtained by log-linear regression analysis of the terminal phase of concentration vs. time curves. The area under the curve (AUC_{inf}) and the area under the first moment curve ($AUMC_{inf}$) were calculated by the linear trapezoidal rule up to the last determined concentration and included extrapolated areas to time infinity. Apparent oral clearance (CL/F) was calculated as Dose/AUC_{inf}. Volume of distribution (Vz/F) was determined by taking the ratio between CL/F and λ_z (elimination rate constant). Mean residence time (MRT) was estimated from the ratio between $AUMC_{inf}$ and AUC_{inf}.

Safety Analyses: Results of physical examinations, vital signs, clinical laboratory data were summarized in tabular form and presented by patient number. Adverse events also were tabulated in a similar fashion.

10. Results

Patient and Study Accountability: Six narcoleptic patients were enrolled and all six completed the study in its entirety.

Protocol Compliance: There were no inclusion criteria violations. All patients admitted into the study met the study entrance requirements and completed the screening phase at least one day before the treatment phase.

All six patients took non-study medications in addition to methylphenidate and GHB doses because none of their concomitant medications (Synthyroid, Premarin, Lovastatin, Flovastatin, furosemide, potassium, hydrochlorothiazide, lansoprazole, and verapamil) were on the exclusion list (which included hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants). Adverse experience probes, vital sign measurements, and essentially all pharmacokinetic blood samples were performed at protocol specified times; the few deviations in blood sampling times should not have any impact on the outcome of the study since actual blood sampling times were used in the pharmacokinetic analysis.

The diagnosis of narcolepsy for at least one year in each patient was verified by a nocturnal polysomnogram (NSG) and a Multiple Sleep Latency Test (MSLT) conducted at a qualified laboratory. Five patients have been maintained on GHB nightly for over 10 years and one patient has been receiving GHB nightly for two years. One patient (Subject 101) also had multiple sclerosis; however, the attending physician, judged that it would not interfere with the objective of this study. A few of the screening clinical laboratory results marginally fell outside the reference range but none was considered by the attending physician to be clinically significant.

Exposure to Study Drug: All patients ingested the two GHB doses as scheduled (immediately prior to bedtime). The GHB doses per kg body weight ranged from 26.4 to 52.4 mg/kg.

Plasma GHB Concentration Profiles: It was noted that, in certain cases, (Patients #103, and #106), plasma GHB concentrations did not decline from the first C_{max} to zero concentration at h 4. Upon achievement of the second C_{max}, the semi-logarithmic plots of concentration versus time data in Patients #102, #103, and #105 exhibited a convex decline profile. Such a decline pattern suggested non-linear pharmacokinetics. The highest plasma GHB concentration observed in the study was 125.0 μg/mL which occurred in Subject 101 after the second 3 g GHB dose.

Pharmacokinetic Parameter Estimates: The mean (±SD) showed that maximum GHB concentrations (C_{max}) were 62.8±27.4 μg/mL and 91.2±25.6 μg/mL for the first and second GHB doses, respectively. The corresponding mean observed times to maximum concentrations were 40±6 and 36±7 min after the first and second GHB doses, respectively. The mean AUC_{inf} was 17732±4603 μg/mL.h. The mean CL/F was 4.2±1 mL/min/kg and the mean V_2/F was 307±96 mL/kg. The mean MRT_{inf} was 249±56 min. The mean GHB $T_{1/2}$, estimated by linear regression of log[C] vs. time data of the terminal phase of the second GHB dose was 53±19 min.

Adverse Experiences: No adverse experiences were reported in the study.

Follow-up Safety Assessments: Inspection of screen and follow-up physical examination results per individual patient did not identify any changes attributable to GHB.

11. Discussion

To the inventors' knowledge, the level of GHB in human systemic circulation has not been reported in the literature.

Hence, baseline (0 h) plasma samples were analyzed for GHB concentrations. The GC-MSD method used in the present study had a limit of quantification (LOQ) of 7.02 μg/mL and analysis of the baseline plasma samples showed the endogenous levels of GHB are below this sensitivity limit. This finding was confirmed by adding known amounts of GHB (5, 10, and 25 μg per mL of plasma) to blank human plasma samples and subjected these samples to GC-MSD analysis. This method of standard addition allowed an estimation of the endogenous GHB level in human plasma which was found to average about 2.02 μg/mL, (i.e. approximately ⅔ of the Limit Of Quantitation (LOQ) for a validated assay. Hence, the endogenous GHB level was not subtracted from exogenous GHB concentrations prior to pharmacokinetic analysis.

Values of mean t_{max} (~40 min after dosing) and $t_{1/2}$ (~35 min) suggest that the GHB solution administered to narcoleptic patients in this study was readily absorbed and rapidly eliminated. In 3 out of 6 patients the drug was essentially gone from the systemic circulation by h 4 after the first GHB dose whereas in the remaining three patients residual GHB levels of ~15 μg/mL was still detected at h 4.

The convex nature of the decline of plasma GHB concentrations in three patients after achievement of the second C_{max} indicated that elimination of GHB from the systemic circulation in these three patients is capacity limited. Nevertheless, it should be noted that plasma GHB concentrations were no longer detectable by h 6 after the second GHB dose (10 h after the first GHB dose). The mean apparent oral clearance found in this study was 4.2±1.0 mL/min/kg and appeared to be comparable to the apparent oral clearance of 5.3±2.2 mL/min/kg reported in the literature for a group of alcohol dependent patients who were administered a dose of 50 mg/kg (Ferrara, 1992). While it appeared that the GHB dose (ranging from 26.4 to 52.4 mg/kg with a mean of 36.5 mg/kg) in the present study was lower than the comparison GHB dose (50 mg/kg) administered to the alcohol dependent patients (Ferrara, 1992), it should be noted that each patient in the present study was administered two consecutive GHB doses at four-hour interval and residual GHB levels were detected in three out of six patients immediately prior to the second GHB dose. The GHB pharmacokinetic non-linearity in alcohol dependent patients easily can be observed from the apparent oral clearance which increased to 8.1±4.8 mL/min/kg when the GHB dose is reduced to 25 mg/kg dose (Ferrara, 1992). In the present study, the non-linearity was less obvious because each narcoleptic patient received two consecutive fixed 3 g doses regardless of body weight.

The mean elimination half-life of GHB in the six narcoleptic patients was determined to be 53±19 min, longer than that in alcohol dependent patients after a 50 mg/kg GHB dose (Ferrara, 1992). The lengthening of GHB elimination half-life observed in this study partially was caused by the wider spacing in sampling time points. However, capacity limited elimination of this drug in some of the narcoleptic patients also could have contributed to this prolongation.

GHB appears to have a shortcoming in that its elimination from the body is capacity limited in some patients when the drug is administered at a fixed regimen of 3 g twice nightly at four-hour interval. However, from a therapeutic perspective, GHB offers an advantage in the treatment of narcolepsy because by the time a patient wakes up in the morning (i.e. 8 to 10 h after the first GHB dose), all GHB, including that from the second dose, will have been eliminated from the systemic circulation. GHB was also well tolerated by narcoleptic patients in this study. No adverse experience was reported.

12. Conclusions

The capacity limited elimination kinetics was observed in three out of six patients who had been administered two consecutive 3 g oral doses of GHB, 4 h apart. From a pharmacokinetic perspective, dividing the nightly GHB dose into two portions and administering the two portions to narcoleptic patients at a 2.5- to 4-h interval was rational because the elimination half-life of GHB was short (<1 h). The pharmacokinetic profiles of GHB in narcoleptic patients who had been receiving this agent nightly for years appeared to be comparable to those in alcohol dependent patients (Ferrara, 1992).

EXAMPLE 4

Sodium Oxybate Formulation Study

I. Study Objectives

This example described ways that sodium oxybate may be prepared and tested for stability to determine preferred formulations. Various formulations of sodium oxybate ill water were prepared under different conditions of mixing and with addition of selected acidulents at multiple pH levels (Neo-Pharm Laboratories, Blainville, Quebec). Selected formulations were placed on real time and accelerated stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Therefore several acidulents across a range of 6.0–9.0 were evaluated.

II. Study Design-Part I

The following experimental work is designed to be performed in two stages. Initial studies were conducted to evaluate the impact of conditions of formulation, pH and acidulent on the resultant levels of impurities, specified and unspecified, and potency of sodium oxybate. Sodium oxybate was prepared (MDS Neo-Pharm Laboratories, Quebec Canada), under different conditions of mixing and with addition of selected acidulents at multiple pH levels. These formulations of sodium oxybate acidulent were then tested.

A. Preliminary studies

1. Formulations Description

All formulations were prepared at a concentration of 500 mg/cc of sodium oxybate in water. Three acidulents (HCl, malic acid, and phosphoric acid), were selected and tested at pH 6.0, 7.5 and 9.0.

2. Method of Formulation

Solutions, were prepared using the described methods:

a. Rapid mix method

Sodium oxybate was dissolved in water and concentrated acidulent was added immediately without temperature control. Temperature of solution was monitored and recorded prior to and during addition of acidulent. The time of equiliberation to room temperature was also recorded. After the solution reached ambient room temperature, it was filtered through a 10 μm filter.

b. Cool mix method:

Sodium oxybate was dissolved in water. Acidulent was diluted to 10% and slowly added. The solution was cooled by water with jacket or ice bath. Monitor and record the temperature of the solution was monitored and recorded during addition of acidulent. The time of equilibrium from room temperature was also recorded. The preferred maximum temperature should be maintained at less than 40° C. The solution was filtered through a 10 μm filter.

c. Reverse order of addition:

Acidulent was added to water and cooled to room temperature. The sodium oxybate was dissolved in the diluted

acidulent solution. The temperature of solution was monitored and recorded during addition of sodium oxybate. The solution was filtered through a 10 μm filter.

d. Sodium oxybate control

Sodium oxybate was dissolved in water to a concentration of 500 mg/cc with no added acidulent. The final pH was recorded and the solution was filtered through a 10 μm (micron or micrometer) filter.

3. Solution Data:

Data was recorded for each solution which included: I) date of preparation 2) date of analysis, 3) amount of acidulent required to achieve target pH, 4) length of time for dissolution of sodium oxybate, 5) temperature profile of solution over time of solution preparation to be recorded at 15 minute intervals, 6) final pH of solution.

4. Testing Requirements:

The following methods were used to test the prepared solutions: pH, HPLC (High Pressure Liquid Chromotography) for potency (sodium oxybate), and for impurities. Time 0 analysis was performed immediately (within 24 h). RRT=(relative retention time).

B. Summary of Part i:

1. Preliminary Evaluation of Sodium Oxybate Formulations

Tables 13, 14 and 15 provide test results for the three methods of preparation of sodium oxybate formulations.

Formulation Study/PR98068

Results of Formulation Study—Time Zero determination of Sodium Oxybate, GBL and Unspecified Impurities

TABLE 13

Preparation Method A

Addition of Concentrated Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/cc % [95–105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (Apr. 23, 1998) (10 drops over 2 minutes)	pH 9.0	9.0	509 mg/cc 101%	0.009%	RRT 4.88 = 0.01%
(2.5 ml/4 minutes)	pH 7.5	7.5	507 mg/cc 101%	0.01%	RRT 4.89 = 0.02%
(45 ml/34 minutes)	pH 6.0	6.0	504 mg/cc 101%	0.033%	RRT 4.89 = 0.33%
Malic Acid (Apr. 24, 1998) (0.12 gm)	pH 9.0	9.1	498 mg/cc 99.6%	0.009%	RRT 4.89 = 0.01%
(1.6 gm)	pH 7.5	7.6	506 mg/cc 101%	0.009%	RRT 4.89 = 0.01%
(25 gm)	pH 6.0	6.2	493 mg/cc 98.6%	0.011%	RRT 4.89 = 0.01%
H_3PO_4 (Apr. 24, 1998) (2 drops)	pH 9.0	9.0	493 mg/cc 98.6%	0.009%	RRT 4.89 = 0.01%
(1.0 ml)	pH 7.5	7.5	493 mg/cc 98.6%	0.009%	RRT 4.89 = 0.02%
(17.3 ml)	pH 6.0	6.1	497 mg/cc 99.4%	0.063%	RRT 4.89 = 0.02%
Sodium Oxybate Control No Acidulent	n.a.	9.8	500 mg/cc 100%	0.009%	RRT 4.89 = 0.04%

*Method A = Mix Method with Concentrated Acidulent and Temperature Monitoring

TABLE 14

Preparation Method B

Addition of Diluted Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95–105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (25%) (Apr. 28, 1998) (20 drops)	pH 9.0	9.1	500 mg/cc 100%	0.009%	RRT 4.88 = 0.01%
(8.0 ml)	pH 7.5	7.6	499 mg/cc 99.8%	0.009%	RRT 4.88 = 0.01%
(175 ml)	pH 6.0	6.0	502 mg/cc 101%	0.016%	RRT 4.88 = 0.02%
H_3PO_4 (25%) (Apr. 29, 1998) (0.3 ml)	pH 9.0	8.9	499 mg/cc 99.8%	0.007%	RRT 4.92 = 0.02%
(4.0 ml)	pH 7.5	7.5	497 mg/cc 99.4%	0.008%	RRT 4.89 = 0.02%
(120 ml)	pH 6.0	6.0	499 mg/cc 99.8%	0.019%	RRT 4.89 = 0.01%

TABLE 14-continued

Preparation Method B

Addition of Diluted Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95–105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
Malic Acid (500 mg/cc) (Apr. 30, 1998) (0.115 gm/0.23 ml)	pH 9.0	9.0	495 mg/cc 99%	0.008%	RRT 4.92 = 0.02%
(1.75 gm/3.5 ml)	pH 7.5	7.4	488 mg/cc 97.5%	0.009%	RRT 4.92 = 0.01%
(35 gm/70 ml)	pH 6.0	6.0	487 mg/cc 97.0%	0.013%	RRT 4.92 = 0.01%

*Acidulent added slowly at the rate of 2–3 drops/second

TABLE 15

Preparation Method C

Reverse Order of Addition* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95–105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (May 1, 1998) (20 drops)	pH 9.0	9.0	497 mg/cc 99.4%	0.006%	RRT 4.92 = 0.03%
(2.4 ml)	pH 7.5	7.6	504 mg/cc 101%	0.004%	RRT 4.92 = 0.04%
(45 ml)	pH 6.0	6.0	493 mg/cc 98.6%	0.044%	RRT 4.92 = 0.04%
H_3PO_4 (May 4, 1998) (0.08 ml)	pH 9.0	8.9	496 mg/cc 99.2%	0.005%	RRT 4.91 = 0.03%
(1.0 ml)	pH 7.5	7.6	496 mg/cc 99.2%	0.004%	RRT 4.91 = 0.04%
(30 ml)	pH 6.0	6.1	489 mg/cc 97.8%	0.023%	RRT 4.91 = 0.04%
Malic Acid (May 5, 1998) (0.12 gm)	pH 9.0	9.0	495 mg/cc 99%	0.006%	RRT 4.93 = 0.02%
(1.6 gm)	pH 7.5	7.6	497 mg/cc 99.4%	0.004%	RRT 4.93 = 0.04%
(35 gm)	pH 6.0	6.2	495 mg/cc 99%	0.044%	RRT 4.93 = 0.04%

*Acidulent added to water first, GHB added second

Review of the data indicated that the optimum method for preparation of sodium oxybate with minimal impurity levels is Method B: Controlled mixing with diluted acidulent. Method 2b resulted in formulations with lowest levels of GBL.

2. Conclusions.

Additional evaluations were carried out on selected formulations: 1) sodium oxybate with HCl as acidulent, at pH 7.5, and 2) sodium oxybate with malic acid as acidulent, pH 6.0, 7.5, and 9.0.

III. Study Design-Part II

Microbial Challenge and Stability Tested to determine the most preferred embodiments, the number of formulations was limited to three based on the data prepared from the above experiments.

A. Kinetic Stability Study with Selected Formulations

Samples of formulations are stored in tightly closed containers. Storage Conditions were 25° C., 40° C., and 60° C. Time points in brackets were tested at the inventor's discretion. The samples were tested according to the following schedule: at 25° C. storage temperature, the assay points will be 0, 14, 28, 45, 60 days and 120 days; at 40° C. storage temperature, the assay points will be 0, 7, 14, 28, 45, 60 days; at 60° C storage temperature, the assay points will be at 0, 3, 7, 14, 28, 45 days, and, 60 days.

The testing requirements included pH, HPLC for sodium oxybate (duplicate injections of single sample preparation), and impurities, specified and unspecified.

B. Preservative Effectiveness Testing of Selected Formulations

Microbial challenge testing of formulations was preformed according to USP XXIII, <51>, Eighth Supplement. Solutions are determined to "Pass or Fail" based upon the USP criteria for perservative effectivness which states: For Bacteria, "Not less than I log reduction from the initial microbial count at 14 days and no increase from the 14 days count at 28 days;" and for yeast and molds, "No increase from the initial calculated count at 14 and 28 days." Solutions which met these criteria were designated as "Pass" and those that did not meet these criteria were designated as "Fail".

C. Summary Stability Results:

1. Formulations prepared with Malic Acid as acidulents:

a. Malic Acid, pH 6.0 formulation (25°), GBL and impurity A levels were very low on Day 0, however, by Day 45 GBL levels had reached 2.8%. Impurity A increased from 0.01 to 1.0%, and pH increased from 6.0 to 6.3 by day 45. This formulation stored at 40° C. and 60° C. showed GBL levels up to 5.4%, impurity A levels increased to 2.3%, and pH increased to 6.3 by Day 14.

b. Malic Acid, pH 7.5 formulation (25° C.), GBL levels were 0.009% on Day 0, and increased to 0.17% by day 45. Impurity A increased from 0.01% to 0.1% and pH increased from 7.5 to 7.9. Malic acid, pH 7.5 GBL levels are reached (40° C.) and 60° C. a maximum of 0.22%. Impurity A levels reached 0.1% and pH increased to 8.0. Under accelerated conditions, all parameters reached an apparent maximum by Day 7 and did not increase significantly thereafter.

c. Malic Acid, pH 9.0 formulation (25° C.,) GBL levels measure 0.008% on Day 0, and increased slightly to 0.013% on Day 45. Impurity A did not increase nor did pH increase. Under accelerated conditions, GBL increased from 0.008% to a maximum of 0.018% by Day 14. Impurity A increased slightly from 0.10 to 0.014% by Day 14.

2. Formulations prepared with HCl as acidulents.

HCl, pH 6.0 formulation (25°) GBL levels measured 2.8% by Day 30, and impurity A 0.004%, and pH 6.0. Accelerated storage conditions (40° C.) GBL levels were measured at 6.6%, and impurity A measured 3.1% by Day 30.

HCl, pH 7.5 formulation (25%) GBL levels measured 0 041% on Day 0, Impurity A measured 0.02%, and by Day 18 GBL measured to 0.12% and impurity A to 0.07%. Under accelerated conditions (40° C. and 60° C.), GBL increased to a maximum of 0.21%, impurity A increased from 0.02% to 0.1%, and pH increased from 7.5 to 8.0. As with Malic Acid at pH 7.5, the measured parameters reached maximum by Day 7 and did not increase significantly thereafter.

HCl, pH 9.0 formulation (25° C.) GBL levels reached 0.022% by Day 18. Impurity A stayed constant at 0.01% for 18 days. Under accelerated conditions (40° C.) GBL levels were equivalent to 25° C. storage (0.21%). Impurity A showed no increase over 25° C. conditions.

3. Conclusions.

Formulations selected for microbial challenge testing were the following: HCl, pH 7.5, and malic acid, pH 7.5. The rationale for this decision was twofold. First, the formulations were selected based on minimal formation of GBL and impurity A. Second, the formulations were selected to maintain a pH in the neutral range.

EXAMPLE 5

Further Evaluation of Sodium Oxybate Formulations

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of gamma-hydroxybutyrate.

Scope: Various formulations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple pH levels. Solutions were prepared and tested at Neo-Pharm Laboratories, Blainville, Quebec. All formulations successfully prepared were placed on limited stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Conditions of varying pH and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Procedures: Solutions were prepared as summarized and microbial challenge testing carried out as follows:

I. Evaluation of Sodium Oxybate Formulations

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of gamma-hydroxybutyrate.

Scope: Various formulations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple pH levels. Selected formulations were studied for limited stability. Earlier studies demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Conditions of varying pH and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Responsibility: It was the responsibility of Neo-Pharm Laboratories to prepare selected formulations and perform testing per this protocol. Orphan Medical, New Medicine Development and Quality Assurance were responsible for reviewing raw data at the defined decision point, defining which formulations will be included in stability testing. Orphan Medical was also responsible for reviewing final results (raw data) and the final report.

Procedure: The following formulations were prepared by scientists at Neo-Pharm following the steps listed below and dispensed into containers (amber PET 240 ml bottle, OMI CS-460) and closures (Clic-Loc III, 24–400, OMI CS-470) to a volume of 200 ml each bottle. The bottles were tested by 28-day microbial challenge and by limited stability testing at 25° C. including, appearance, pH, potency, and impurity profile on day 1 (day of preparation) and day 28.

A. Formulations Prepared and Evaluated Using Sodium Oxybate:

TABLE 16

Formulations Prepared and Evaluated Using Sodium Oxybate

Formulation ID No.	Sodium Oxybate Concentration	Acidulent	Final pH
1	500 mg/cc	Malic Acid	7.5
2	250 mg/cc	Malic Acid	7.5
3	350 mg/cc	Malic Acid	7.5
4	450 mg/cc	Malic Acid	7.5
5	550 mg/cc	Malic Acid	7.5
6	650 mg/cc	Malic Acid	7.5
7	500 mg/cc	Citric Acid	7.5
8	500 mg/cc	Malic Acid	5.0

1. Preparation: Method for preparation of various formulations: As previously determined in PR98068, the method of choice for preparation of liquid formulations of sodium oxybate was the following:

a. For a one liter quantity of product, add the sodium oxybate in 500 ml of purified and stir until dissolved. Prepare a 10% solution of the acid (Malic or Citric) and add slowly to the solution of sodium oxybate. The solution should be monitored for pH and temperature and both variables recorded at reasonable intervals (every 10 or 15 minutes). When the target pH is attained, the solution will be Q. S. to 1 liter, and pH rechecked and recorded.

b. The final solutions will be filtered through 10 μm filters and 200 mL dispensed into 5 amber PET bottles with closures (provied by Orphan Medical, Inc.). Two bottles will be used for microbial chal-

lenge studies and the remaining three bottles will be placed on limited stability.

2. Testing: Formulations were tested by two methods of evaluation:

a. Limited stability evaluation:

(1) Storage Conditions: 25° C.

(2) Pull Points: Day 0 (day of preparation), and day 28

(3) Testing Requirements:

Test	Method
Appearance	Visual
Potency	HPLC Neopharm 764
Impurities	HPLC Neopharm 793DT
pH	USP <791>

b. Microbial challenge:

(1) Storage Conditions: Microbial challenge studies of above formulations were set up with 5 microorganisms and stored for 28 days at 20–25° C., per USP <51> Eighth Supplement.

(2) Microorganisms: After a sufficient quantity of each formulation is prepared, aliquots were inoculated with 5 microorganisms at a concentration of at least 10^5 microorganisms/cc:

(a) *Escherichia coli*, ATCC 8739

(b) *Pseudomonas aeruginosa*, ATCC 9027

(c) *Staphylococcus aureus*, ATCC 6538

(d) *Aspergillus niger*, ATCC 18404

(e) *Candida albicans*, ATCC 10231

(3) Time Points: A determination of the viable cell concentration in each inoculated container was performed after 0, 1, 3, 7, 14, 21 and 28 days.

B. Formulations To Be Prepared From Alternative Salts of Gamma-Hydroxybutyrate: This work may be staged to take place at a later time than the work described above.

TABLE 17

Formulation Detail				
Formulation ID No.	Salt of GHB	Concentration of Salt of GHB	Acidultent	Final pH
9	Calcium salt	500 mg/cc (Or maximum possible*)	Malic Acid (If compatible)	7.5

1. Solubility determination: Little information is available about the solubility of this alternative salt of gamma-hydroxybutyrate and a determination of solubility was done in advance of efforts to prepare formulations for evaluation by stability and microbial challenge. Maximum solubility is evaluated for pH unadjusted soluations and within the pH range desired for this formulation (pH 6.0–8.0). If solubility is limited, the formulation will be changed to accommodate the solubility limitations. The preferred acidulent for this work is Malic acid. If acid is not compatible with the salt, then an alternative acid can be selected.

2. Preparation: Method for preparation of alternative salt formulations:

a. The previously described method (Part A) is used for preparation of formulations of calcium gamma-hydroxybutyrate at the concentrations and specified pH determined by solubility experiments.

b. The final solutions were filtered through 10 μm filters and dispensed into 5 amber PET bottles with closures (provided by Orphan Medical, Inc.). Two bottles are used for microbial challenge studies and two bottles are placed on limited stability. The remaining bottles are retained for any additional studies at a future time.

3. Testing: Formulations are tested as described above.

C. Reporting of Results: The results will be reported for the Stability and Microbial Challenge results in standard format as defined by the described Orphan Medical Development. Copies of HPLC chromatograms and any raw data from these studies will be provided with results.

D. Acceptance Criteria: Specific acceptance criteria for this study can be described analogous to those for sodium oxybate.

Results: Summarized as follows in Tables 18, 19 and 20 for various studies.

TABLE 18

Result Summary
Results of Protocol 98126 Microbial Challenge Study

	0	Day 1	Day 7	Day 14	Day 21	Day 28
Lot Number MCH1064-33						
GHB, pH 7.50, 500 mg/cc Malic Acid						
E. coli	490,000	5,500	<100	<10	<10	<10
P. aeruginosa	141,000	21,600	<100	<10	<10	<10
S. aureus	1,035,000	405,000	79,500	8,300	1,645	375
C. albicans	835,000	147,000	<100	<10	<10	<10
A. niger	370,000	285,000	120,500	246,500	148,500	183,000

TABLE 18-continued

Result Summary
Results of Protocol 98126 Microbial Challenge Study

	0	Day 1	Day 7	Day 14	Day 21	Day 28
	Lot Number MCH1064-35					
GHB, pH 7.50, 250 mg/cc Malic Acid						
E. coli	705,000	229,500	<100	<10	<10	<10
P. aeruginosa	224,500	5,200	<100	<10	<10	<10
S. aureus	1,135,000	390,000	262,500	31,500	4,250	155
C. albicans	705,000	435,000	52,000	850	<10	<10
A. niger	510,000	515,000	155,500	176,000	147,500	184,000
	Lot Number MCH1064-37					
GHB, pH 7.50, 350 mg/cc Malic Acid						
E. coli	365,000	310,000	13,400	<10	<10	<10
P. aeruginosa	205,000	15,600	50	<10	<10	<10
S. aureus	1,170,500	605,000	67,500	<60	60	<10
C. albicans	870,000	355,000	8,300	<10	<10	<10
A. niger	540,000	525,000	172,000	155,500	155,500	163,500
	Lot Number MCH1064-43					
GHB, pH 7.50, 550 mg/cc Malic Acid						
E. coli	425,000	63,500	700	<10	<10	<10
P. aeruginosa	171,500	211,550	250	<10	<10	<10
S. aureus	1,020,000	520,000	41,500	1,050	180	10
C. albicans	880,000	157,500	800	<10	<10	<10
A. niger	545,000	505,000	131,000	156,500	205,000	187,500
	Lot Number MCH1064-45					
GHB, pH 7.50, 550 mg/cc Malic Acid						
E. coli	660,000	58,500	450	<10	<10	<10
P. aeruginosa	896,000	14,450	900	<10	<10	<10
S. aureus	860,000	132,000	19,750	935	110	45
C. albicans	1,125,000	166,000	<100	<10	<10	<10
A. niger	530,000	530,000	105,500	153,000	157,500	177,000
	Lot Number MCH1046-47					
GHB, pH 7.50, 650 mg/cc Malic Acid						
E. coli	630,000	119,000	1,350	<10	<10	<10
P. aeruginosa	183,500	5,900	50	<10	<10	<10
S. aureus	890,000	650,000	76,000	14,550	510	1,150
C. albicans	675,000	145,500	<100	<10	<10	<10
A. niger	535,000	385,000	103,000	162,000	187,000	173,000
	Lot Number MCH1064-85					
Ca-Oxybate, pH 7.50, 500 mg/cc Malic Acid						
E. coli	425,000	121,000	1,650	<10	<10	<10
P. aeruginosa	420,000	22,000	300	<10	<10	<10
S. aureus	265,000	2,000	<100	<10	<10	<10
C. albicans	565,000	440,000	29,500	<1000	<10	<10
A. niger	1,310,000	965,000	370,000	640,000	690,000	675,000
	Lot Number MCH1064-49					
GHB, pH 7.50, 500 mg/cc Citric Acid						
E. coli	615,000	6,500	<100	<10	<10	<10
P. aeruginosa	69,500	14,600	<100	<10	<10	<10
S. aereus	650,000	305,000	1,700	<10	<10	<10
C. albicans	720,000	107,000	<100	<10	<10	<10
A. niger	375,000	380,000	99,500	178,500	212,500	165,500

TABLE 19

Result Summary
Data from Dec. 30, 1997

	(n= 3) Inoculu	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Results
GHB (pH 7.5)									
750 mg/cc									
E. coli	470,000	160,000	64,500	4,300	420	<10	<10	<10	
P. aeruginos	437,500	152,000	3,500	10	<10	<10	<10	<10	
S. aureus	447,500	330,000	24,500	42,000	8,050	1,935	15	10	
C. albicans	375,000	234,500	28,000	1,950	<10	<10	10	<10	
A. niger	475,500	395,000	395,000	229,000	101,500	161,500	101,000	202,000	
750 mg/cc + 0.2% MP/PP, pH 7.50									
E. coli	470,000	127,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginos	437,500	61,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	350,000	3,000	4,050	<10	<10	<10	<10	
C. albicans	375,000	103,500	<1,000	<10	<10	<10	<10	<10	
A. niger	457,500	315,000	415,000	35,500	79,500	38,500	87,500	6,400	
750 mg/cc + 0.1% MP/PP, pH 7.5									
E. coli	470,000	157,000	7,000	<10	<10	<10	<10	<10	
P. aeruginos	437,500	90,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	239,000	5,500	16,950	600	<10	<10	<10	
C. albicans	375,000	169,000	<1,000	<100	<10	<10	<10	<10	
A. niger	457,500	335,000	425,000	34,500	168,500	90,500	95,500	99,000	
750 mg/cc + 0.2% Potassium sorbate, pH 7.5									
E. coli	470,000	180,000	735,000	6,200	475	<10	<10	<10	
P. aeruginos	437,500	152,000	1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	264,000	27,500	49,800	14,550	2,370	<10	<10	
C. albicans	375,000	300,000	41,500	3,800	<10	<10	<10	<100	
A. niger	457,500	325,000	360,000	25,000	202,000	500,000	345,000	425,000	
GHB (pH 6.0)									
500 mg/cc									
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10	
P. aeruginos	437,500	172,000	3,000	<10	<10	<10	<10	<10	
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10	
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10	
A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600	
									PASS
500 mg/cc + 0.2% MP/PP, pH 6.0									
E. coli	470,000	163,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginos	437,500	60,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	243,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	150,500	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	400,000	38,000	<10	<10	<10	<10	<10	
									PASS
500 mg/cc + 0.1% MP/PP, pH 6.0									
E. coli	470,000	206,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginos	437,500	118,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	330,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	221,000	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	355,000	93,500	59,000	8,700	315	35	<10	
									PASS
500 mg/cc + 0.2% Potassium sorbate, pH 6.0									
E. coli	470,000	222,000	46,500	150	<10	<10	<10	<10	
P. aeruginos	437,500	136,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	410,000	<1,000	130	<10	<10	<10	<10	
C. albicans	375,000	395,000	28,500	<100	<10	<10	<10	<10	
A. niger	475,500	405,000	270,000	63,000	51,000	49,500	39,000	11,150	
									PASS

TABLE 20

		Result Summary						
500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
		Data from Study Dated Dec. 30, 1997						
GHB (pH 6.0)								
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10
P. aeruginosa	437,500	172,000	3,000	<10	<10	<10	<10	<10
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10
A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600
		Data From Study Begun Mar. 12, 1998						
GHB (pH 6.0)								
E. coli	500,000	370,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	198,500	nd	nd	<100	<10	<10	<10
S. aureus	280,000	480,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	340,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	445,000	nd	nd	9,050	20,500	9,450	1,120
GHB (pH 6.0)								
E. coli	500,000	199,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	192,500	nd	nd	<100	<10	<10	<10
S. aureus	280,000	300,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	370,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	445,000	nd	nd	10,100	22,750	3,800	4,050
		Data From Study Begun Mar. 12, 1998						
GHB (pH 9.0)								
E. coli	500,000	320,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	12,000	nd	nd	<100	<10	<10	<10
S. aureus	280,000	530,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	510,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	345,000	nd	nd	13,800	158,500	315,000	110,500
GHB (pH 9.0)								
E. coli	500,000	305,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	20,000	nd	nd	<100	<10	<10	<10
S. aureus	280,000	495,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	380,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	355,000	nd	nd	12,550	157,500	365,000	365,000
GHB (pH 6.0 + Excipients)								
E. coli	500,000	96,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	26,000	nd	nd	<100	<10	<10	<10
S. aureus	280,000	155,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	205,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	131,500	nd	nd	6,250	1,825	870	370
GHB (pH 6.0 + Excipients)								
E. coli	500,000	93,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	30,500	nd	nd	<100	<10	<10	<10
S. aureus	280,000	185,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	135,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	121,500	nd	nd	5,400	1,785	795	505

TABLE 21

		Result Summary						
GHB (pH 7.50)	HCl	Jul. 2, 1998 Start Date						
500 mg/cc	Initial Conc	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	97000	82000	19200	nd	1000	<10	<10	<10
P. aeruginosa	48500	29500	520	nd	<10	<10	<10	<10
S. aureus	54500	58000	42350	nd	4950	245	<10	<10
C. albicans	58500	38500	1060	nd	<100	<10	<10	<10
A. niger	77500	48000	21450	nd	46000	46000	38000	54000

TABLE 21-continued

GHB (pH 7.50) 500 mg/cc	Malic Acid Initial Conc	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	97000	83000	44450	nd	3050	70	<10	<10
P. aeruginosa	48500	15650	545	nd	<10	<10	<10	<10
S. aureus	54500	59500	48400	nd	17400	6500	820	505
C. albicans	58500	44000	6200	nd	500	<10	<10	<10
A. niger	77500	35500	24100	nd	28000	49000	44500	44000

For Category 1C Products:
Bacteria: Not less that 1 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days.
Yeast and Molds: No increase from the initial calculated count at 14 and 28 days.

GHB (pH 7.50)	HCl	Jul. 2, 1998 Start Date						
500 mg/cc	Initial Co	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	9.70E+04	8.20E+04	1.92E+04	nd	1.00E+03	<10	<10	<10
P. aeruginosa	4.85E+04	2.95E+04	5.20E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.80E+04	4.24E+04	nd	4.95E+03	2.45E+02	<10	<10
C. albicans	5.85E+04	3.85E+04	1.06E+03	nd	<100	<10	<10	<10
A. niger	7.75E+04	4.80E+04	2.15E+04	nd	4.60E+04	4.60E+04	3.80E+04	5.40E+04

GHB (pH 7.50) 500 mg/cc	Malic Acid Initial Co	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	9.70E+04	8.30E+04	4.45E+04	nd	3.05E+03	7.00E+01	<10	<10
P. aeruginosa	4.85E+04	1.57E+04	5.45E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.95E+04	4.84E+04	nd	1.74E+04	6.50E+03	8.20E+02	5.05E+02
C. albicans	5.85E+04	4.40E+04	6.20E+03	nd	5.00E+02	<10	<10	<10
A. niger	7.75E+04	3.55E+04	2.41E+04	nd	2.80E+04	4.90E+04	4.45E+04	4.40E+04

TABLE 22

pH Variable Result Summary

GHB, pH 7.5 750 mg/cc Dec. 30, 1997	Inoculum	0	Day 14	Day 28	GHB, pH 6.0 500 mg/cc Dec. 30, 1997	Inoculum	0	Day 14	Day 28
E. coli	470,000	160,000	<10	<10	*E. coli*	470,000	221,000	<10	<10
P. aeruginosa	437,500	152,000	<10	<10	*P. aeruginosa*	437,500	172,000	<10	<10
S. aureus	447,500	330,000	1,935	10	*S. aureus*	447,500	320,000	<10	<10
C. albicans	375,000	234,500	<10	<10	*C. albicans*	375,000	310,000	<10	<10
A. niger	475,500	395,000	161,500	202,000	*A. niger*	475,500	270,000	48,500	8,600
GHB, pH 7.5 750 mg/cc + 0.2% MP/PP Dec. 30, 1997					GHB, pH 6.0 500 mg/cc + 0.2% MP/PP Dec. 30, 1997				
E. coli	470,000	127,000	<10	<10	*E. coli*	470,000	163,000	<10	<10
P. aeruginosa	437,500	61,000	<10	<10	*P. aeruginosa*	437,500	60,000	<10	<10
S. aureus	447,500	350,000	<10	<10	*S. aureus*	447,500	243,000	<10	<10
C. albicans	375,000	103,500	<10	<10	*C. albicans*	375,000	150,500	<10	<10
A. niger	457,500	315,000	38,500	6,400	*A. niger*	475,500	400,000	<10	<10
GHB, pH 7.5 750 mg/cc + 0.1% MP/PP					GHB, pH 6.0 500 mg/cc + 0.1% MP/PP Dec. 30, 1997				
E. coli	470,000	157,000	<10	<10	*E. coli*	470,000	206,000	<10	<10
P. aeruginosa	437,500	90,000	<10	<10	*P. aeruginosa*	437,500	118,000	<10	<10
S. aureus	447,500	239,000	<10	<10	*S. aureus*	447,500	330,000	<10	<10
C. albicans	375,000	169,000	<10	<10	*C. albicans*	375,000	221,000	<10	<10
A. niger	457,500	335,000	90,500	99,000	*A. niger*	475,500	355,000	315	<10
GHB, pH 7.5 750 mg/cc + 0.2% Potassium sorbate	xxxxx x				GHB, pH 6.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coli					*E. coli*				

TABLE 22-continued

pH Variable Result Summary

P. aeruginosa *S. aureus* *C. albicans* *A. niger*					*P. aeruginosa* *S. aureus* *C. albicans* *A. niger*				
GHB, pH 6.0 500 mg/cc + 0.2% Potassium sorbate Dec. 30, 1997					GHB, pH 6.0 500 mg/cc + Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coli	470,000	222,000	<10	<10	*E. coli*	500,000	199,000	<10	<10
P. aeruginosa	437,500	136,000	<10	<10	*P. aeruginosa*	350,000	192,500	<10	<10
S. aureus	447,500	410,000	<10	<10	*S. aureus*	280,000	300,000	<10	<10
C. albicans	375,000	395,000	<10	<10	*C. albicans*	450,000	370,000	<10	<10
A. niger	475,500	405,000	49,500	11,150	*A. niger*	450,000	445,000	22,750	4,050
GHB, pH 6.0 500 mg/cc + Excipients Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 6.0 500 mg/cc + Excipients Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	93,000	<10	<10	*E. coli*	500,000	96,000	<10	<10
P. aeruginosa	350,000	30,500	<10	<10	*P. aeruginosa*	350,000	26,000	<10	<10
S. aureus	280,000	185,000	<10	<10	*S. aureus*	280,000	155,000	<10	<10
C. albicans	450,000	135,000	<10	<10	*C. albicans*	450,000	205,000	<10	<10
A. niger	450,000	121,500	1,785	505	*A. niger*	450,000	131,500	1,825	370
GHB, pH 9.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 7.50 500 mg/cc, HCl July 2, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	320,000	<10	<10	*E. coli*	97000	82000	<10	<10
P. aeruginosa	350,000	12,000	<10	<10	*P. aeruginosa*	48500	29500	<10	<10
S. aureus	280,000	530,000	<10	<10	*S. aureus*	54500	58000	245	<10
C. albicans	450,000	510,000	<10	<10	*C. albicans*	58500	38500	<10	<10
A. niger	450,000	345,000	158,500	110,500	*A. niger*	77500	48000	46000	54,000
GHB, pH 9.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 7.5 500 mg/cc, Malic Acid July 2, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	305,000	<10	<10	E. coli	97000	83000	70	<10
P. aeruginosa	350,000	20,000	<10	<10	*P. aeruginosa*	48500	15650	<10	<10
S. aureus	280,000	495,000	<10	<10	*S. aureus*	54500	59500	6500	505
C. albicans	450,000	380,000	<10	<10	*C. albicans*	58500	44000	<10	<10
A. niger	450,000	355,000	157,500	365,000	*A. niger*	77500	35500	49000	44,000

Short term stability testing was carried out as described in Appendix A and results are summarized in—Results of Limited Stability Testing—Xyrem oral solution—are show as follows:

TABLE 23-A

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999

NO.: 333198

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	512 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.068%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.021% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.02% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge Test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 1: 500 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328841

TABLE 23-B

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO.: 331347

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	510 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.36%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.23% RRT 4.31: 0.1%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 days (25° C., 60% RH)
Formulation 1: 500 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.02%
RRT 3.93: 0.008%

TABLE 23-C

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO.: 333197

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	258 mg/ml (103%)	NPLC-793-D
Impurities total	≦2.0%	0.045%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.016% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.79: 0.009%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 2: 250 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328845

TABLE 23-D

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO.: 331346

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	256 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.18%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.13% RRT 4.31: 0.03%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 2: 250 mg/cc; Malic acid; pH 7.5
*A: RRT 1.29: 0.007%
RRT 3.93: 0.008%

TABLE 23-E

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO.: 333196

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	360 mg/ml (103%)	NPLC-793
Impurities total	≦2.0%	0.050%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.017% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.006% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.7	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 3: 350 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328847

TABLE 23-F

ORPHAN MEDICAL INC. DATE: 21 Jan. 1999
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA NO.: 331345

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION LOT: MCH1064-3 CODE:
PROTOCOL 98126 REQUISITION: 1741
ORPHAN MEDICAL

TEST	SPECIFICATION	RESULTAT/ RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	363 mg/ml (104%)	NPLC-793-D
Impurities total	≦2.0%	0.21%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.14% RRT 4.31: 0.05%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	8.0	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 3: 350 mg/cc; Malic acid; pH 7.5
*A: RRT 1.29: 0.009%
RRT 3.93: 0.008%

TABLE 23-G

ORPHAN MEDICAL INC. DATE: 26 Jan. 1999
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA NO.: 333195

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST) LOT: MCH1064-4 CODE: 1741
PROTOCOL 98126 REQUISITION: 1741
ORPHAN MEDICAL

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	461 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.065%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.018% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.02% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 4: 450 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328875

TABLE 23-H

ORPHAN MEDICAL INC. DATE: 21 Jan. 1999
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA NO.: 331343

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION LOT: MCH1064-4 CODE:
PROTOCOL 98126 REQUISITION: 1741
ORPHAN MEDICAL

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	454 mg/ml (101%)	NPLC-793-D
Impurities total	≦2.0%	0.40%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.26% RRT 4.31: 0.1%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 4: 450 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.03%
RRT 3.93: 0.008%

TABLE 23-I

ORPHAN MEDICAL INC. DATE: 26 Jan. 1999
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA NO.: 333194

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST) LOT: MCH1064-4 CODE:
PROTOCOL 98126 REQUISITION: 1741
ORPHAN MEDICAL

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	563 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.077%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.020% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.29: 0.03% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 5: 550 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328883

TABLE 23-J

ORPHAN MEDICAL INC. DATE: 21 Jan. 1999
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA NO.: 331341

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION LOT: MCH1064-4
PROTOCOL 98126 CODE:
ORPHAN MEDICAL REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	561 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.56%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.31% RRT 4.31: 0.2%	NPLC-793 D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 5: 550 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.04%
RRT 3.93: 0.007%

TABLE 23-K

ORPHAN MEDICAL INC. DATE: 26 Jan. 1999
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA NO.: 333193

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST) LOT: MCH1064-4
PROTOCOL 98126 CODE:
ORPHAN MEDICAL REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	666 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.10%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.025% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.05% RRT 3.78: 0.007%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 6: 650 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328885

TABLE 23-L

ORPHAN MEDICAL INC. DATE: 21 Jan. 1999
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA NO.: 331336

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION LOT: MCH1064-4
PROTOCOL 98126 CODE:
ORPHAN MEDICAL REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	660 mg/ml (102%)	NPLC-764
Impurities total	≦2.0%	0.81%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.43% RRT 4.31: 0.3%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 6: 650 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.07%
RRT 3.93: 0.007%

TABLE 23-M

ORPHAN MEDICAL INC. DATE: 26 Jan. 1999
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA NO.: 333192

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM. (28 DAYS CHALLENGE TEST) LOT: MCH1064-4
PROTOCOL 98126 CODE:
ORPHAN MEDICAL REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	518 mg/ml (104%)	NPLC-793
Impurities total	≦2.0%	0.065%	NPLC-793D
Impurities specified GBL-RRT 1.6	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.45: 0.018% RRT 4.17: 0.02%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.79: 0.007% RRT 5.99: 0.02%	NPLC-793D
PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 7: 500 mg/cc; Citric acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 329033

TABLE 23-N

ORPHAN MEDICAL INC. DATE: 21 Jan. 1999
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA NO.: 331335

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION LOT: MCH1064-4 CODE:
PROTOCOL 98126 REQUISITION: 1741
ORPHAN MEDICAL

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	515 mg/ml (103%)	NPLC-793-D
Impurities total	≦2.0%	0.38%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦ 0.5% Impurity A (RRT 4.3): ≦0.5%	RRT 1.46: 0.27% RRT 4.31: 0.1%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.93: 0.007%	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 7: 500 mg/cc; Citric acid; pH 7.5

TABLE 23-O

ORPHAN MEDICAL INC. DATE: 9 Feb. 1999
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA NO.: 330721

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM LIQUID FORM. (28 DAYS CHALLENGE TEST) LOT: MCH1064-85 CODE:
PROTOCOL 98126 REQUISITION: 1741
ORPHAN MEDICAL

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Challenge Test	Conforms to USP (0, 1, 7, 14, 21 and 28 days)	Conforms	USP 23 <51> S.8
Potency	Report	501 mg/ml (100%)	NPLC-793
Impurities total	≦2.0%	1.2%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
Impurities specified	Gamma-Butyrolactone Report:	RRT 1.46: 0.013%	NPLC-793D
PH	Report	7.3	USP <791>
Solubility study	Report	*B	PR 98126 HA

COMMENTS:
Initial test
500 mg/ml cc; Malic acid; pH 7.5
*A: RRT 1.31: 0.02% RRT 1.67: 0.008%
RRT 1.91: Interference with peak of dilution solvent cannot calculate.
RRT 3.47: 0.1% RRT 3.79: 0.009% RRT 3.84: 0.01%
RRT 4.18: 0.06% RRT 5.10: 0.008% RRT 5.35: 0.02%
RRT 6.74: 0.9% RRT 6.90: 0.08% RRT 7.41: 0.006%
*B: Maximum solubility: 700 mg/ml no pH adjustment.

TABLE 23-P

ORPHAN MEDICAL INC. DATE: 26 Feb. 1999
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA NO.: 331307

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM LIQUID FORM. LOT: MCH1064-85
PROTOCOL 98126 CODE:
ORPHAN MEDICAL REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANO-LEPTIC
Potency	Report	508 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.70%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
Impurities specified	Gamma-Butyrolactone Report:	RRT 1.37: 0.054%	NPLC-793 D
PH	Report	7.6	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
500 mg/cc; Malic acid; pH 7.5
*A: RRT 1.17: 0.03% RRT 3.47: 0.2%
RRT 5.46: 0.01% RRT 6.87: 0.3%
RRT 7.04: 0.007%
RRT 1.78: Can not calculate because it interfere with a dilution solvant peak.

This report summarizes the results of the above described study and provides a summary of previous development work which evaluated conditions other than those evaluated in this study. The purposes of this information is to define the scope and limitations of the self-preserving properties of Xyrem® oral solution for completion of patent application.

II. Summary of Results

A. Preparation of various formulations of Sodium Oxybate and formulations using an alternative salt of GHB.

1. Various formulations of sodium oxybate were prepared as directed in the above Protocol. Sodium oxybate, 500 mg/cc with Malic Acid was not soluble at pH 5.0, and further evaluation of this solution was discontinued. All other solutions were successfully prepared as described.

2. The preparation of an alternative salt of gamma-hydroxybutyrate was described as the calcium salt, prepared at 500 mg/cc (or maximum possible) with Malic Acid at pH 7.5.

a. The calcium salt of gamma-hydroxybutyrate was prepared by Toronto Research and shipped to NeoPharm for determination of solubility and evaluation according to the Protocol. The absolute limit of solubility, without pH adjustment, was determined to be 700 mg/cc. The pH of this solution was 8.4. Solutions of lower pH were more difficult to prepare at 500 mg/cc using Malic acid as acidulant. When pH was adjusted to 6.0 with Malic acid, the solubility of the calcium oxybate was limited (longer stirring required to solubilize). The desired solution of 500 mg/cc, pH 7.5 was prepared with Malic acid as acidulant without difficulty. Appearance of the final solution was slightly yellow in color.

Copies of the laboratory record for preparation of these solutions is available.

B. Microbial Challenge Testing of the various formulations parepared by MDS NeoPharm.

The microbial challenge testing was carried as specified in the Protocol and the following table summarizes the results

of microbial challenge testing of various formulations of sodium oxybate and the single calcium oxybate formulation prepared.

TABLE 24

Testing of Sodium and Calcium GHB Salts

Concentration	pH of Solution	Microbial Challenge Result
Sodium Oxybate		
1. 500 mg/cc	7.5 (Malic acid)	Pass
2. 250 mg/cc	7.5 (Malic acid)	Pass
3. 350 mg/cc	7.5 (Malic acid)	Pass
4. 450 mg/cc	7.5 (Malic acid)	Pass
5. 550 mg/cc	7.5 (Malic acid)	Pass
6. 650 mg/cc	7.5 (Malic acid)	Pass
7. 500 mg/cc	7.5 (Citric acid)	Pass
Calcium Oxybate		
500 mg/cc	7.5	Pass

C. Short term stability evaluation of various formulations of sodium oxybate and a formulation of calcium oxybate.

Solutions were tested on day zero (preparation day) and day 28 according to the described Protocol. The results of the stability evaluation are summarized in Table 25 below:

TABLE 25

Sodium and Calcium GHB Evaluation

Sodium oxybate solution	Potency mg/cc (%)	Impurities (Total)	Impurities (Unspecified)	Impurities (Specified - GLB)	pH
500 mg/cc pH 7.5 Malic Acid Day 0	512 mg/cc (102%)	0.68%	0.041%	0.027%	7.6
Day 28	510 mg/cc (103%)	0.36%	0.33%	0.028%	7.9
250 mg/cc pH 7.5 Malic Acid Day 0	258 mg/cc (103%)	0.045%	0.009%	0.026%	7.6
Day 28	256 mg/cc (102%)	0.18%	0.015%	0.16%	7.9
350 mg/cc pH 7.5 Malic Acid Day 0	360 mg/cc (103%)	0.050%	0.013%	0.037%	7.7
Day 28	363 mg/cc (104%)	0.21%	0.017%	0.19%	8.0
450 mg/cc pH 7.5 Malic Acid Day 0	461 mg/cc (102%)	0.065%	0.027%	0.038%	7.5
Day 28	454 mg/cc (101%)	0.40%	0.038%	0.36%	7.8
550 mg/cc pH 7.5 Malic Acid Day 0	563 mg/cc (102%)	0.077%	0.037%	0.040%	7.6
Day 28	561 mg/cc (102%)	0.56%	0.047%	0.51%	7.9
650 mg/cc pH 7.5 Malic Acid Day 0	666 mg/cc (102%)	0.10%	0.057%	0.045%	7.6
Day 28	660 mg/cc (102%)	0.81%	0.077%	0.73%	7.8
500 mg/cc pH 7.5 Citric Acid Day 0	518 mg/cc (104%)	0.065%	0.027%	0.038%	7.5
Day 28	515 mg/cc (103%)	0.38%	0.007%	0.37%	7.9

TABLE 25-continued

Sodium and Calcium GHB Evaluation

Calcium oxybate solution	Potency	Impurities (Total)	Impurities (Specified)	Impurities (Un-specified)	pH
500 mg/cc pH 7.5 Malic Acid Day 0	501 mg/cc (100%)	1.2%	>0.1% (See C of A Attached)	0.013%	7.3
Day 28	508 mg/cc (102%)	0.70%	>0.1% (See C of A)	0.054%	7.6

D. Summary of Pertinent Solubility and Microbial Challenge Data are shown in Tables 26 and 27.

TABLE 26

Limits of Solubility

Maximum Solubility	pH of Solution	Comments
Sodium oxybate		
450 mg/cc	pH 4 (HCl)	25°
500 mg/cc	pH 5 (HCl)	25°
600 mg/cc	pH 6 (HCl)	25°
750 mg/cc	pII 6.8 (IICl)	25°
750 mg/cc +	pH 10.3	25°
1000 mg/cc	pH (unadjusted)	65° Soluble, 25° Gel
Calcium oxybate		
700 mg/cc	pH 8.4 (unadjusted)	25°
500 mg/cc	pH 6.0	25°

TABLE 27

Microbial Challenge Results

Concentration (Date)	pH of Solution	Microbial Challenge Results
Sodium oxybate		
750 mg/cc (December 1997)	7.5 (HCl)	pass
500 mg/cc (December 1997)	6.0 (HCl)	pass
500 mg/cc + Excipients (Xylitol) (March 1998)	6.0 (Malic Acid)	pass
500 mg/cc (March 1998)	9.0 (HCl)	pass (Borderline aspergillus)
150 mg/cc (BDL 1995)	5.0 (HCl)	fail (aspergillus only)
150 mg/cc (BDL 1995)	7.0 (HCl)	fail (aspergillus and staph)
150 mg/cc (BDL 1995)	3.0 (HCl)	fail (aspergillus only)
150 mg/cc (BDL 1995)	10.3 (unadjusted)	fail (aspergillus and staph)
500 mg/cc (May 1998)	6.0 (Malic Acid)	discontinued
500 mg/cc (May 1998)	7.5 (Malic Acid)	pass
500 mg/cc (May 1998)	9.0 (Malic Acid)	discontinued
500 mg/cc (May 1998)	7.5 (HCl)	pass
500 mg/cc	7.5 (Malic Acid)	pass
250 mg/cc	7.5 (Malic Acid)	pass
350 mg/cc	7.5 (Malic Acid)	pass
450 mg/cc	7.5 (Malic Acid)	pass
550 mg/cc	7.5 (Malic Acid)	pass
650 mg/cc	7.5 (Malic Acid)	pass
500 mg/cc	7.5 (Citric Acid)	pass
Calcium oxybate		
500 mg/cc	7.5 (Malic Acid)	pass

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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What is claimed is:

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.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,780,889 B2
DATED : August 24, 2004
INVENTOR(S) : Cook et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [56], **References Cited**, FOREIGN PATENT DOCUMENTS,
After " 3/1963" insert -- A61K/81(1) --.

Drawings,
Below "Fig 1", delete "rresistant" and insert -- resistant --, therefor.

Column 1,
Line 60, delete "el al," and insert -- et al., --, therefor.
Line 66, delete "et a.," and insert -- et al., --, therefor.

Column 2,
Line 8, delete "et al," and insert -- et al., --, therefor.

Column 3,
Line 45, delete "tip" and insert -- up --, therefor.
Line 52, delete "GLIB" and insert -- GHB --, therefor.

Column 4,
Line 19, delete "290 mg/mi" and insert -- 290 mg/ml --, therefor.

Column 5,
Line 51, insert -- , -- before "about 21° C".

Column 24,
Line 18, delete "for" before "any".

Column 32,
Line 20, delete "ill" and insert -- in --, therefor.

Column 33,
Line 11, delete "I)" and insert -- 1) --, therefor.

Column 34,
Line 7, delete "Part i" and insert -- Part I --, therefor.
Line 15, delete "determination" and insert -- determinations --, Therefor.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,780,889 B2
DATED : August 24, 2004
INVENTOR(S) : Cook et al.

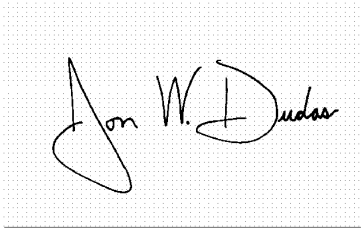
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 36,
Line 61, delete "I log" and insert -- 1 log --, therefor.

Column 62,
Line 5, delete "(loses" and insert -- doses --, therefor.

Signed and Sealed this

Tenth Day of May, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT C

US007262219B2

(12) **United States Patent**
Cook et al.

(10) **Patent No.: US 7,262,219 B2**
(45) **Date of Patent: Aug. 28, 2007**

(54) **MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY**

(75) Inventors: **Harry Cook**, Eden Prairie, MN (US); **Martha Hamilton**, St. Paul, MN (US); **Douglas Danielson**, Otsego, MN (US); **Colette Goderstad**, St. Paul, MN (US); **Dayton Reardan**, Excelsior, MN (US)

(73) Assignee: **Orphan Medical, Inc.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 470 days.

(21) Appl. No.: **10/841,709**

(22) Filed: **May 7, 2004**

(65) **Prior Publication Data**

US 2004/0209955 A1 Oct. 21, 2004

Related U.S. Application Data

(62) Division of application No. 10/194,021, filed on Jul. 11, 2002, now Pat. No. 6,780,889, which is a division of application No. 09/470,570, filed on Dec. 22, 1999, now Pat. No. 6,472,431.

(60) Provisional application No. 60/113,745, filed on Dec. 23, 1998.

(51) **Int. Cl.**
A61K 31/19 (2006.01)
A61K 31/365 (2006.01)
A61K 31/12 (2006.01)

(52) **U.S. Cl.** **514/557**; 514/553; 514/473; 514/529

(58) **Field of Classification Search** 514/557, 514/473, 553, 529
See application file for complete search history.

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(Continued)

Primary Examiner—Brian Kwon
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg, Woessner & Kluth P.A.

(57) **ABSTRACT**

Disclosed are formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial growth. Also disclosed are formulations of gamma-hydroxybutyrate that are also resistant to the conversion into GBL. Disclosed are methods to treat sleep disorders, including narcolepsy, with these stable formulations of GHB. The present invention also provides methods to treat alcohol and opiate withdrawal, reduced levels of growth hormone, increased intracranial pressure, and physical pain in a patient.

4 Claims, 1 Drawing Sheet

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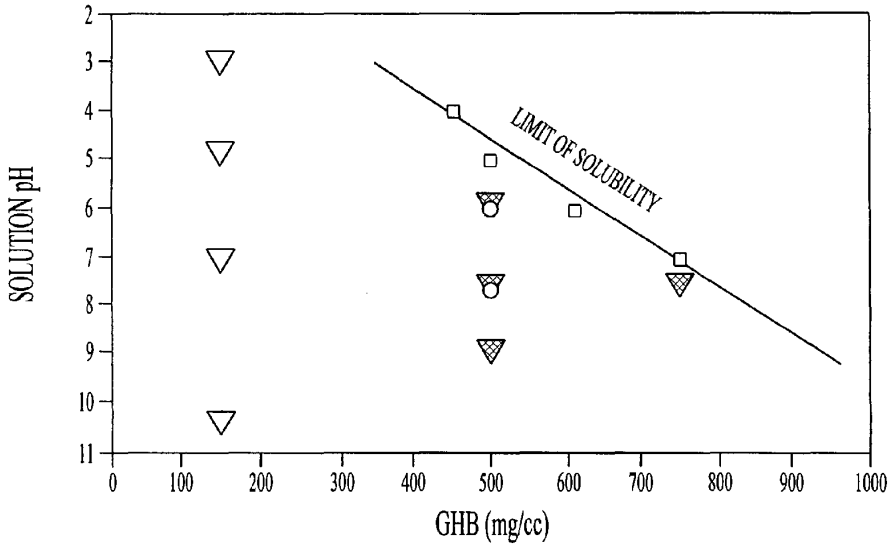

□ DATA POINTS INDICATING LIMIT OF SOLUBILITY OF GHB AS A FUNCTION OF CONCENTRATION AND pH, SEE TABLE 1.

▽ SOLUTIONS SUSCEPTIBLE TO MICROBIAL GROWTH, DESIGNATED "FAIL". (ALL SOLUTIONS DEMONSTRATED ACTIVITY AGAINST PSEUDOMONAS AERUGINOSA. SOME REDUCTION OF ASPERGILLUS NIGER MOLD OCCURRED IN 7 DAYS OF CONTACT TIME.)

▽ SOLUTIONS RESISTANT TO MICROBIAL GROWTH, DESIGNATED "PASS". RATE OF REDUTION OF MICROORGANISM COUNTS WAS SLIGHTLY HIGHER AT pH 7.5 AND 6.0 THAN pH 9.0. THE RATE OF REDUCTION OF FORMULATIONS AT 750mg/cc GHB WERE SLIGHTLY LOWER THAN FORMULATIONS AT 500 mg/cc GHB.)

○ SOLUTIONS RESISTANT TO MICROBIAL GROWTH, DESIGNATED "PASS". RESULTS WERE SIMILAR FOR MALIC ACID AND HCl. TASTE VARIATIONS HAS IMPLICATIONS FOR DEVELOPMENT OF FLAVOR SYSTEMS.

▽ ▽ INDICATES pH ADJUSTMENT WITH HCl.

○ INDICATES pH ADJUSTMENT WITH MALIC ACID.

NOTE: SOLUTIONS WITH pH AT 9.0 ARE NOT PALATABLE OR SAFE FOR ORAL CONSUMPTION.

FIG. 1

MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY

RELATED APPLICATIONS

This application is a divisional of U.S. patent application Ser. No. 10/194,021, filed Jul. 11, 2002, patented U.S. Pat. No. 6,780,889, which is a divisional of U.S. patent application Ser. No. 09/470,570, filed Dec. 22, 1999, patented U.S. Pat. No. 6,472,431, which claims priority from U.S. Provisional Patent Application Ser. No. 60/113,745, filed Dec. 23, 1998, both of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention relates generally to the fields of pharmaceutical compositions to be used in treatments, such as, sleeping disorders, such as, e.g., narcolepsy (particularly cataplexy), drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or for an increased level of intracranial pressure or the like. The present 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, e.g.

II. Description of Related Art

GHB is an endogenous compound with hypnotic properties that is found in many human body tissues. GHB is present, for example, in the mammalian brain and other tissues. In brain the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter (Snead and Morley, 1981). The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB is converted to succinate and then metabolized via the Krebs cycle. Clinical trials have shown that GHB increases delta sleep and improves the continuity of sleep (Ladinsky et al., 1983; Anden and Stock, 1973; Stock et al., 1973; Laborit, 1973; Lapierre et al., 1988; Lapierre et al., 1990; Yamda et al., 1967; Grove-White and Kelman, 1971; Scharf, 1985).

GHB has typically been administered in clinical trials as an oral solution (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993). GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e. daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency (Mamelak et al, 1973; Yamada et al., 1967; Bedard et al., 1989), reduces sleep apnea (Series et al, 1992; Scrima et al., 1987), and improves general anesthesia (Hasenbos and Gielen, 1985).

GHB has several clinical applications other than narcolepsy and sleep disorders. GHB has been reported to reduce alcohol craving, the number of daily drinks consumed, and the symptoms of alcohol withdrawal in patients (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992). GHB has been used to decrease the symptoms of opiate withdrawal, including both heroin and methadone withdrawal (Gallimberti et al, 1994; Gallimberti et al., 1993). It has analgesic effects that make it suitable as a pain reliever (U.S. Pat. No. 4,393,236). Intravenous administration of GHB has been reported to reduce intracranial pressure in patients (Strong, A. 1984). Also, administration of GHB was reported to increase growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970).

A good safety profile for GHB consumption, when used long term for treatment of narcolepsy, has been reported. Patients have been safely treated for many years with GHB without development of tolerance (Scharf, 1985). Clinical laboratory tests carried out periodically on many patients have not indicated organ or other toxicities (Lammers, 1993; Scrima, 1990; Scharf, 1985; Mamelack, 1977; Mamelak, 1979; Gallimberti, 1989; Gallimberti, 1992; Gessa, 1992). The side effects of GHB treatment have been minimal in incidence and degree of severity, though they include sleepwalking, enuresis, headache, nausea and dizziness (Broughton and Mamelak, 1979; Mamelak et al., 1981; Mamelak et al., 1977; Scrima et al., 1989; Scrima et al., 1990; Scharf et al., 1985).

The pharmacokinetics of GHB have been investigated in alcohol dependent patients (Ferrara et al., 1992) and in normal healthy males (Palatini et al., 1993) after oral administration. GHB possesses a rapid onset and short pharmacological effect (Ferrara et al., 1992; Palatine et al., 1993; Lee, C., 1977; van der Bogert; Gallimberti, 1989; Gallimberti, 1992; Lettieri and Fung, 1978; Arena and Fung, 1980; Roth and Giarman, 1966; Vickers, 1969; Lee,: 1977). In alcohol dependent patients, GHB absorption into and elimination from the systemic circulation were fast processes. Virtually no unchanged drug could be recovered in the urine. There were preliminary indications that the pharmacokinetics of GHB might be non-linear or dose-dependent (Ferrara et al., 1992). In the healthy volunteers study, the pharmacokinetics of three rising GHB doses (12.5, 25, and 50 mg/kg) were investigated. These findings indicate that both the oral absorption and elimination processes of GHB were capacity-limited though the degree of dose dependency was moderate (Palatini et al., 1993).

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). 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.

SUMMARY OF THE INVENTION

The present invention overcomes deficiencies in the prior art by providing compositions of GHB in an aqueous medium that are resistant to microbial growth. These compositions are also resistant to the uncontrolled degradation of GHB into GBL or other substances. The compositions of the present invention are stable compositions of GHB that improve shelf-life; and provide a titratable formulation of GHB for easy dose measurement. In addition, the concentrated solutions embodied in this invention reduce shipping and storage requirements and allow patients to carry more drugs for their convenience. The present invention provides methods to treat a number of conditions treatable by GHB, referred to herein as "therapeutic categories." Therapeutic categories for the present invention include, but are not limited to, sleeping disorders, drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders, such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or an increased level of intracranial pressure or other conditions treatable with GHB.

The invention first provides a pharmaceutical composition of GHB rendered chemically stable and/or resistant to microbial growth in an aqueous medium. Preferred GHB salts of the present invention include sodium, ammonium and calcium. As used herein in certain embodiments, "stable" may mean resistant to degradation of GHB into its known or unknown decomposition elements. The level of GBL that is acceptable can be up to 0.1% of the formulation as per the ICH guidelines for shelf-life determination, As used herein in certain embodiments, "resistant to microbial growth" or "resistant to microbial challenge" means that the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days. As used herein in certain embodiments, an "aqueous medium" may mean a liquid comprising more than about 50% water. In certain preferred embodiments, an "aqueous medium" may be a solution, suspension, gel or emulsion of GHB, with a solution of GHB being most preferred. Preferred gels are thixotropic gels. Compositions that are resistant to microbial growth are created by dissolving or mixing GHB in an aqueous medium to a concentration or content of greater than of about 150 mg/ml GHB to the maximal solubility of GHB. The solubility of GHB is up to about 750 mg/ml at room temperature (20° C. to about 25° C.), however, heating the aqueous medium during preparation up to 100° C. will increase GHB solubility to at least about 1000 mg/ml. A preferred concentration or content of GHB is about 500 mg/ml.

The amount of GHB that may be mixed or dissolved into an aqueous medium and still be resistant to microbial growth depends upon the pH of the aqueous medium. In certain embodiments the presence of a preservative may allow the amount of GHB contained in the compositions of the present invention to be increased and still maintain resistance to chemical degradation and/or microbial growth. In one embodiment of the present invention, the pH of the aqueous medium of the pharmaceutical composition is about 3 to about 10.

In a preferred embodiment, the pH of said aqueous medium is about 6 to about 7.5. The pH may be from about 3.0 to about 10.3, namely of about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0, about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, about 10.0, about 10.1, about 10.2, or about 10.3, and all pH values between each of the listed pH values, of the aqueous media. This will produce a GHB composition that is resistant to microbial growth as defined by the test described herein. As used herein, the term "about" generally means within about 10-20%.

These pH values will produce compositions resistant to microbial growth in an aqueous medium if the amount of GHB added, admixed, or dissolved is from above about 150 mg/ml to about 450 mg/ml, namely, above about 150 mg/ml, about 160 mg/ml, about 170 mg/ml, about 180 mg/ml, about 190 mg/ml, about 200 mg/ml, about 210 mg/ml, about 220 mg/ml, about 230 mg/ml, about 240 mg/ml, about 250 mg/ml, about 260 mg/ml, about 270 mg/ml, about 280 mg/ml, about 290 mg/ml, about 300 mg/ml, about 310 mg/ml, about 320 mg/ml, about 330 mg/ml, about 340 mg/ml, about 350 mg/ml, about 360 mg/ml, about 370 mg/ml, about 380 mg/ml, about 390 mg/ml, about 400 mg/ml, about 410 mg/ml, about 420 mg/ml, about 430 mg/ml, about 440 mg/ml, to about 450 mg/ml, and all amounts of GHB between the values listed.

At the medium to high end of the concentration or content of GHB that may be dissolved or mixed in the aqueous medium, the maximal pH that may be used is reduced at room temperature. This is shown in FIG. **1**, a graphical presentation of acceptable formulation ranges. At a concentration or content of about 450 mg/ml GHB, the pH may be of about 3.9 to about 10.3. At a concentration or content of about 500 mg/ml GHB, the pH may be of about 4.75 to about 10.3. At a concentration or content of about 600 mg/ml GHB, the pH may be of about 6.1 to about 10.3. At a concentration or content of about 750 mg/ml GHB, the pH may be of about 7.0 to about 10.3. Of course, all pH and concentration or content values in between each of the listed pH and concentration or content values are encompassed by the invention.

Certain embodiments may be selected as sub-ranges from these values of GHB content and aqueous medium pH. For example, a specific embodiment may be selected as a content of about 170 mg/ml to about 440 mg/ml GHB in an aqueous medium, at a pH range of about pH 5.5 to about pH 8.7. Another example of how a range may be selected in an embodiment would be the selection of a content of about 155 mg/ml of GHB, which is a value between the above listed values, to a content of about 350 mg/ml of GHB, and the selection of a pH range of the aqueous medium, such as a pH range of about 8.87, which is a value between the listed pH values, to a pH of about 8.93, which is another value between the listed values of pH. A third example of ranges that may be selected for a specific embodiment would be selection of a single content or concentration of GHB, such as about 200 mg/ml of GHB, and the selection of a pH range, such as a pH of about 3.5 to about 8.2. A fourth example of ranges that may be selected for a specific embodiment would be selection of a content or concentration of GHB over a range, such as about 300 mg/ml to about 400 mg/ml, and the selection of a single pH value for the aqueous medium, such as a pH of about 3. Another example of a range selected for an embodiment may be the selection of a single content or concentration of GHB, such as 400 mg/ml GHB, and a single pH value of the aqueous medium, such as pH 7.7.

Other examples of how a range of an embodiment of GHB content or concentration may be selected include a range of GHB content or concentration from about 200 mg/ml to about 460 mg/ml GHB, encompassing the ranges for GHB described herein, and a range of pH for the aqueous medium may be from about pH 4.3 to about pH 7, encompassing ranges for GHB in an aqueous medium at room temperature described herein. Another example would be the selection of a range of GHB content or concentration from about 153 mg/ml to about 750 mg/ml, and a pH range of about 7 to about 9, encompassing ranges between the listed values of GHB content and pH described herein. An example may be the selection as a GHB concentration or content of about 170 mg/ml to about 640 mg/ml in an aqueous medium, at a pH range of about pH 6.5 to about pH 7.7. Another example of how a range may be selected in an embodiment would be a content or concentration of about 185 mg/ml of GHB, which is a value between the listed values, to a content or concentration of about 750 mg/ml of GHB, at a pH range of about 7.87, which is a value between the listed pH values, to a pH of about 8.91, which is another value between the listed values of pH. An additional example of ranges that may be selected for a specific embodiment would be a content or concentration of about 200 mg/ml of GHB at a pH of about 7 to about 8.2. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 750 mg/ml to about 400 mg/ml at a pH of about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 300 mg/ml to about 750 mg/ml at a pH of about 8.5 to about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 400 mg/ml to about 600 mg/ml at a pH of about 9 to about 5.8. And so forth. Thus, all ranges of pH and GHB concentration or content that can be selected from the values herein and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

The chemical stability of GHB is affected by pH, with compositions of GHB in an aqueous medium with a pH below about 6 being less effective in maintaining the chemical stability of GHB. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, all concentrations or content of GHB in an aqueous medium, as described herein, and as would be understood by those of ordinary skill in the art, may be selected to produce compositions of the present invention.

Additionally, the ranges described above are for a composition at room temperature, which is defined herein as from about about 20° C. to about 25° C., namely, about 20° C. about 21° C., about 22° C., about 23° C., about 24° C., to about 25° C. Within the values and ranges of pH described above, the ranges of concentration or content of GHB may increase at temperatures greater than room temperature. Thus, the maximal content or concentration of GHB in an aqueous medium at a temperature of from about 26° C. to about 100° C., namely about 26° C., about 27° C., about 28° C., about 29° C., about 30° C., about 31° C., about 32° C., about 33° C., about 34° C., about 35° C., about 36° C., about 37° C., about 38° C., about 39° C., about 40° C., about 41° C., about 42° C., about 43° C., about 44° C., about 45° C., about 46° C., about 47° C., about 48° C., about 49° C., about 50° C., about 51° C., about 52° C., about 53° C., about 54° C., about 55° C., about 56° C., about 57° C., about 58° C., about 59° C., about 60° C., about 61° C., about 62° C., about 63° C., about 64° C., about 65° C., about 66° C., about 67° C., about 68° C., about 69° C., about 70° C., about 71° C., about 72° C., about 73° C., about 74° C., about 75° C., about 76° C., about 77° C., about 78° C., about 79° C., about 80° C., about 81° C., about 82° C., about 83° C., about 84° C., about 85° C., about 86° C., about 87° C., about 88° C., about 89° C., about 90° C., about 91° C., about 92° C., about 93° C., about 94° C., about 95° C., about 96° C., about 97° C., about 98° C., about 99° C., to about 100° C. may be from about 750 to about 1 g/ml, namely to about 751 mg/ml, about 760 mg/ml, about 770 mg/ml, about 780 mg/ml, about 790 mg/ml, about 800 mg/ml, about 810 mg/ml, about 820 mg/ml, about 830 mg/ml, about 840 mg/ml, about 850 mg/ml, about 860 mg/ml, about 870 mg/ml, about 880 mg/ml, about 890 mg/ml, about 900 mg/ml, about 910 mg/ml, about 920 mg/ml, about 930 mg/ml, about 940 mg/ml, about 950 mg/ml, about 960 mg/ml, about 970 mg/ml, about 980 mg/ml, about 990 mg/ml, to about 1000 mg/ml. At temperatures below room temperature, the solubility of GHB may decrease, and compositions at lower temperature and solubility of GHB at the pH values and ranges described herein are also encompassed by the invention. Additionally, differences of atmospheric pressure may also increase or decrease the solubility of GHB within the ranges described, and embodiments of the invention with an increased or decreased content of GHB due to changes in pressure are also encompassed by the invention. Of course, it is understood that the present invention encompasses embodiments of GHB concentration or content in an aque-

ous medium at higher or lower temperature within the values described herein, such as about 980 mg/ml to about 200 mg/ml at 95° C. GHB at a pH of about 9 to about 7.5. Or about 150 mg/ml GHB at about 17° C. at about pH 6 to about pH 7. And so forth. Thus, all ranges of pH and GHB content that can be selected at various temperatures and pressures from the values above, and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

In certain other embodiments of the present invention, the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids, bases, or combinations thereof. In certain embodiments, the acid may be an organic acid, preferably a carboxylic acid or alphahydroxy carboxylic acid. In certain other embodiments, the acid is selected from the group including, but not limited to, acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like. In a preferred embodiment, the acid is malic or hydrochloric acid. In certain other embodiments, the pH adjusting agent may be a base selected from the group including, but not limited to, acetanilide, ammonia, apomorphine, atropine, benzocaine, caffeine, calcium hydroxide, cocaine, codeine, ephedrine, morphine, papaverine, physostigmine, pilocarpine, potassium bicarbonate, potassium hydroxide, procaine, quinine, reserpine, sodium bicarbonate, sodium dihydrogen phosphate, sodium citrate, sodium taitrate, sodium carbonate, sodium hydroxide, theobromine, thiourea or urea. 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.

In certain embodiments, the composition may contain one or more salts. A "salt" is understood herein to mean certain embodiments to mean a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base. Various salts, including salts of GHB, are also encompassed by the invention, particularly as pH adjusting or buffering agents. Pharmaceutically acceptable salts, include inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as malic, acetic, oxalic, tartaric, mandelic, and the like. Salts formed can also be derived from inorganic bases such as, for example, sodium, potassium, silicates, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Alkali metal salts, such as lithium, potassium, sodium, and the like may be used, preferably with an acid to form a pH adjusting agent. Other salts may comprise ammonium, calcium, magnesium and the like. In one embodiment, a salt of GHB comprising an alkali metal may be combined with an acid to create a composition that achieves the desired pH when admixed with an aqueous medium. In another embodiment, a weak base may be combined with GHB to create a composition that achieves the desired pH when admixed with an aqueous solution. Of course, other salts can be formed from compounds disclosed herein, or as would be known to one of ordinary skill in the art, and all such salts are encompassed by the invention.

In certain embodiments, excipients may be added to the invention. An "excipient" as used herein shall mean certain embodiments which are more or less inert substances added as diluents or vehicles or to give form or consistency when the remedy is in a solid form, though they may be contained in liquid form preparations, e.g. syrups, aromatic powders, honey, and various elixirs. Excipients may also enhance resistance to microbial growth, and thus act as a preservative. Such excipients include, but are not limited to, xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, cellulose derivatives, magnesium carbonate and the like.

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, propyl gallate BP, sorbic acid, chlorobutanol, dihydroacetic acid, monothioglycerol, potassium benzoate, propylparaben, benzoic acid, benzalkonium chloride, alcohol, benzoic acid, benzalkonium chloride, benzethonium chloride, benzyl alcohol, butylparaben, cetylpyridinium chloride, ethylenediamine, ethylpareben, ethyl vanillin, glycerin, hypophophorus acid, methylparaben, phenol, phenylethyl alcohol, phenymercuric nitrate, propylparaben, sassafras oil, sodium benzoate, sodium propionate, thimerosal and potassium sorbate. Preferred preservatives may be selected from the group comprising, but not limited to, xylitol, sodium benzoate, methylparaben, propylparaben and potassium sorbate. Xylitol is particularly preferred in certain compositions of the invention, because it acts as an preservative and a sweetener, is a caries preventative, is less laxative than other sweeteners, and is recommended for diabetics.

In certain embodiments, the pharmaceutical composition may also contain an antioxidant. An "antioxidant" is understood herein to mean certain embodiments which are substances that inhibits oxidation. Such antioxidants include, but are not limited to, asocrbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, potassium metabisulfite, sodium metabisulfite, anoxomer and maleic acid BP.

In certain embodiments, the pharmaceutical composition may also contain a flavoring agent. A "flavoring agent" is understood herein to mean certain embodiments which are substances that alters the flavor of the composition during oral consumption. A type of "flavoring agent" would be a sweetener. Preferred sweeteners or flavoring agents would be microbially non-metabolizable. Especially preferred sweeteners or flavoring agents would be carbohydrates such as xylitol and sorbitol. Such flavoring agents include, but are not limited to, acacia syrup, anethole, anise oil, aromatic elixir, benzaldehyde, benzaldehyde elixir-compound, caraway, caraway oil, cardamom oil, cardamom seed, cardamom spirit, cardamom tincture-compound, cherry juice, cherry

syrup, cinnamon, cinnamon oil, cinnamon water, citric acid, citric acid syrup, clove oil, coca, coca syrup, coriander oil, dextrose, eriodictyon, eriodictyon fluidextract, eriodictyon syrup-aromatic, ethyl acetate, ethyl, vanillin, fennel oil, ginger, ginger fluidextract, ginger oleoresin, glucose, glycerin, glycyrrhiza, glycyrrhiza elixir, glycyrrhiza extract, glycyrrhiza extract-pure, glycyrrhiza fluidextract, glycyrrhiza syrup, honey, non-alcoholic elixir, lavender oil, citrus extract or oil, lemon oil, lemon tincture, mannitol, methyl salicylate, nutmeg oil, orange-bitter-elixir, orange-bitter-oil, orange flower oil, orange flower water, orange oil, orange peel-bitter, orange-peel-sweet-tincture, orange spirit-compound, compound, orange syrup, peppermint, peppermint oil, peppermint spirit, peppermint water, phenylethyl alcohol, raspberry juice, raspberry syrup, rosemary oil, rose oil, rose water, saccharin, saccharin calcium, saccharin sodium, sarsaparilla syrup, sorbitol solution, spearmint, spearmint oil, sucrose, syrup, thyme oil, tolu balsam, tolu balsam syrup, vanilla, vanilla tincture, vanillin or wild cherry syrup.

Salts, excipients, pH adjusting agents such as acids, bases and buffering agents, flavoring agents, and other agents that may be combined with the compositions of the present invention, or may be used to prepare the compositions of the present invention, are well known in the art, (see for example, "Remington's Pharmaceutical Sciences" 8th and 15th Editions, and Nema et al., 1997, incorporated herein in their entirety), and are encompassed by the invention.

In certain other embodiments, the pharmaceutical composition comprises GHB, a pH adjusting or buffering agent, and an aqueous medium, wherein the components are admixed (sequentially or simultaneously) to prepare said pharmaceutical composition. The pH adjusting or buffering agent and aqueous medium may be any described herein.

The invention also provides a method of preparing a chemically stable and microbial growth-resistant pharmaceutical composition for the treatment of a condition responsive to GHB, comprising admixing GHB and a pH-adjusting or buffering agent in an aqueous medium. In certain embodiments, the method of preparing the pharmaceutical composition further comprises admixing a preservative with the pharmaceutical composition. Other components, such as flavoring agents, salts, and the like, may be added to the composition. The pH adjusting or buffering agent, aqueous medium, preservative, flavoring agents, salts, or other ingredient may be any described herein.

In certain other embodiments, the method of preparing the pharmaceutical composition comprises admixing GHB, a pH adjusting or buffering agent, and an aqueous medium soon before administration to a patient suspected of having a condition responsive to GHB.

The invention also provides a method of treating any therapeutic category of disorder responsive to GHB, comprising administering to a patient suspected of having such a condition a therapeutic amount of a pharmaceutical composition comprising chemically stable GHB (e.g. 1-10 gms.) in an aqueous medium resistant to microbial growth. In certain embodiments, the method of treating a condition responsive to GHB comprises a patient taking a first dosage of from about 0.1 g to about 10 g, namely about 0.1, about 0.2 about 0.3 about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0, about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, to about 10 grams of GHB, or as needed by the patient as would be recognized by one of skill in the art. Of course, it will be understood that all values in between those listed, such as 9.45 grams, 6.32 grams, etc. may be administered, and those values are encompassed well. In preferred embodiments, the first dose is administered within an hour of sleep. In preferred embodiments, a second dose of GHB within the values described above may be administered. This second dose is administered preferably within about 2.0 to about 5.0 hrs, namely about 2.0, about 2.1, about 2.2, about 2.3, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3,.about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, to about 5.0 hours after the first dose, though it may be administered at a time outside of the preferred range.

In certain embodiments, a second pharmaceutical may be administered with the composition of GHB. Such a second pharmaceutical may be e.g., a stimulant administered within the same 24 hour period as the first dose of GHB. The stimulant may be, e.g., but not limited to, methylphenidate or pemoline to counter the residual effects of GHB treatment during periods of wakefulness. In certain embodiments, the method of treating a sleep disorder may include the discontinuation of other second pharmaceuticals used to control a sleep disorder. Such second pharmaceuticals may include, but are not limited to, a tricyclic antidepressant.

In certain embodiments, the invention provides a method of treating any appropriate therapeutic category of disorder, by administration of GHB compositions of the present invention as described above for the treatment of sleep disorders. When GHB is used in methods of treating any therapeutic category of disorder, the GHB composition of the present invention may be mixed with the aqueous medium, and optionally pH adjusting or buffering agent or other additives, by the patient or administrator soon before consumption. The patient may prepare the composition within a few minutes to hours before administration. Alternatively, one or more of the components may be premixed for ready use. The components of the GHB composition of the present invention, GHB, an aqueous medium, pH adjusting or buffering agent, excipients, preservatives, flavoring agents, and/or other components or additives may be stored in a container means suitable to aid preservation. Preferably,

the container means is in the form of a set. A "set" as used herein certain embodiments is one or more components of the composition packaged in a container or other suitable storage means.

The present invention also provides a set for the treatment of a condition responsive to GHB comprising, in suitable storage means, GHB and a pH adjusting or buffering agent. In certain embodiments, the GHB and the pH adjusting or buffering agent are separately packaged. In certain other embodiments the GHB and the pH-adjusting or buffering agent may be mixed. The set may contain an aqueous medium. In certain other embodiments, at least one component selected from the group including, but not limited to, GHB, the pH-adjusting or buffering agent and/or an aqueous medium is separately packaged. In certain other embodiments, at least two of the components selected from the group comprising GHB, a pH adjusting or buffering agent and an aqueous medium are mixed together. In some embodiments, the set further contains a preservative. Such a set may have one, two, or more components from the group comprising GHB, a pH-adjusting or buffering agent, an aqueous medium or a preservative packaged separately. Such a set may have two or more components mixed together. Thus, both liquid and dry formulations of GHB and other components may be packaged in a set for mixing before administration, or one or more components may be premixed and packaged together with other components, or all the components may be premixed and packaged in a set.

It is understood that the compositions of the present invention, including those in a set, may be dispersed in a pharmaceutically acceptable carrier solution as described below. Such a solution would be sterile or aseptic and may include water, co-solvent vehicle buffers, isotonic agents, pharmaceutical aids or other ingredients known to those of skill in the art that would cause no allergic or other harmful reaction when administered to an animal or human subject. Therefore, the present invention may also be described as a pharmaceutical composition of GHB with increased stability in a pharmaceutically acceptable carrier solution.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also as used herein, the term "a" "an" or "the" is understood to include the meaning "one or more". Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. **1**. The Range of Gamma-Hydroxybutyrate's Resistance to Microbial Growth and Chemical Stability in Aqueous Solution. The ordinate is the pH of solutions of GHB. The axis is the concentration (mg/ml) of GHB in aqueous solution. The region below the diagonal line [/] is the range of GHB solubility at room temperature. Greater solubility can be achieved, up to 1 g/ml, by heating the solution up to 100° C. Three solutions were adjusted with HCl and were susceptible to microbial growth (Δ). Two solutions were pH adjusted with malic acid and were resistant to microbial growth (●). Of these two solutions, the one at pH 6 contained xylitol as an excipient. Three solutions were pH adjusted with hydrochloric acid and were resistant to microbial growth (▲). One solution was not pH adjusted and was susceptible to microbial growth (*).

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

I. Formulations of Gamma-Hydroxybutyrate

A. Microbial Growth and Gamma-Butyrolactone Formation

The present invention arises from the discovery of chemically stable and microorganism resistant formulations of GHB in an aqueous medium, preferably a solution, and the efficacy of these formulations in the treatment of therapeutic categories of disorders, such as narcolepsy and other sleep disorders. Specifically, GHB is prepared at a concentration greater than about 150 mg/ml in an aqueous medium, up to the limits of GHB's solubility or retention in an aqueous medium, to produce the compositions of the present invention.

The maximum solubility of GHB is affected by the pH of the aqueous medium. At about pH 4, the maximum amount of sodium-GHB that can be dissolved is about 450 mg/ml. The value of pH that is conducive to GHB solubility increases, as is shown at FIG. **1**, so that the minimal pH that will dissolve 750 mg/ml GHB was found to be about pH 6.8. This is shown in Table 1.

TABLE 1

	Limits of Sodium Oxybate Solubility		
ID	Sodium Oxybate Maximum Solubility	pH of Solution	Temperature
A			
B	450 mg/cc	pH 4 (HCl)	25°
C	500 mg/cc	pH 5 (HCl)	25°
D	600 mg/cc	pH 6 (HCl)	25°
E	750 mg/cc	pH 6.8 (HCl)	25°
F	750 mg/cc+	pH 10.3	25°
G	1000 mg/cc	pH unadjusted	65° Soluble, 25° Gel

The pH of the aqueous medium also affects the resistance of the composition to microbial growth at about 500 mg/ml GHB. GHB at this concentration in an aqueous medium that is between about pH 5 and pH 9 is resistant to microbial growth, with compositions at about pH 6 to about pH 7.5 being particularly resistant to microbial growth. However, at concentrations of GHB greater than about 750 mg/ml above about pH 7.5, the resistance to microbial growth is reduced.

This is shown at Table 2.

TABLE 2

ID H	Microbial Challenge Data Summary: Sodium Oxybate Concentration	pH of Solution	Microbial Challenge Result
I	750 mg/cc	7.5 (HCl)	pass
J	500 mg/cc	6.0 (HCl)	pass
K	500 mg/cc + Excipients (Xylitol)	6.0 (Malic Acid)	pass
L	500 mg/cc	9.0 (HCl)	pass (borderline *aspergillus*)
M	150 mg/cc (BDL 1995)	5.0 (HCl)	fail (*aspergillus* only)
N	150 mg/cc (BDL 1995)	7.0 (HCl)	fail (*aspergillus* & *staph*)
O	150 mg/cc (BDL 1995)	3.0 (HCl)	fail (*aspergillus* only)
P	150 mg/cc (BDL 1995)	10.3 (unadjusted)	fail (*aspergillus* and *staph*)
Q	500 mg/cc	6.0 (Malic Acid)	discontinued
R	500 mg/cc	7.5 (Malic Acid)	pass
S	500 mg/cc (May 1998)	9.0 (Malic Acid)	discontinued
T	500 mg/cc (May 1998)	7.5 (HCl)	pass*
U	Others: 200 mg/cc–800 mg/cc	5.0–9.0	pending

*pass is generally defined as:

For Category 1C Products	
Bacteria:	Not less than 1.0 log reduction from the initial cout at 14 days, and no increase from the 14 days' count at 28 days.
Yeast and Molds:	No increase from the initial calculated count at 14 and 28 days.

The data from Table 1 and Table 2 are graphically shown in FIG. **1**. The concentration of GHB in the composition, when evaluated in relationship to the pH, affects the resistance of the GHB composition to microbial challenge. Compositions of GHB at or below 150 mg/ml are poorly resistant to microbial challenge from a pH range of about pH 3 to about pH 9. However, concentrations of GHB of greater than about 150 mg/ml, up to about 1000 mg/ml of GHB, are believed to be suitably resistant to microbial contamination at these pH ranges.

The chemical stability of GHB is affected by pH. Accordingly, the method for preparing GHB, as described herein, particularly as disclosed in the specific examples, varies with pH. GBL begins to form if the pH is about 6 or less. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, any pH or range of pH values where a clinically acceptable amount of GBL is produced is also contemplated as being preferred, and is encompassed by the present invention. The range of GBL could be regulatorily broadened with availability of sufficient toxicological data.

In certain embodiments of the invention, a pH-adjusting agent may be added to the composition. The choice of a pH adjusting agent may affect the resistance to microbial challenge and/or the stability of GHB, as measured by the reduction in assayable GHB. Compositions of GHB, pH adjusted with malic acid are resistant to both microbial growth and chemical degradation of GHB, and are preferred. Other pH adjusting or buffering agents may be selected. Agents that adjust pH that are selected on this basis will undergo a taste testing study. However, any pH adjusting agent disclosed herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the invention. Of course, any salt, flavoring agent, excipient, or other pharmaceutically acceptable addition described herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the invention.

Any of the above formulations may be prepared and/or packaged as a powdered or dry form for mixing with an aqueous medium before oral administration, or they may be prepared in an aqueous medium and packaged. After mixing with an aqueous medium, preferrably to prepare a solution, these formulations are resistant to both microbial growth and chemical conversion of GHB to GBL, thereby increasing the shelf-life of therapeutic formulations of GHB in an aqueous medium. These formulations then provide an easily titratable liquid medium for measuring the dosage of GHB to be administered to a patient. Additional embodiments of the composition and methods of preparation are described below and in the examples.

B. Pharmaceutical Compositions

1. Pharmaceutically Acceptable Carriers

Aqueous compositions of the present invention comprise an effective amount of GHB dissolved or dispersed in a pharmaceutically acceptable carrier and/or an aqueous medium. The phrases "pharmaceutically or pharmacologically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is not appropriate. Supplementary com-

patible active ingredients can be incorporated into the compositions. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by the Food and Drug Administration (FDA).

The GHB may be lyophilized for more ready formulation into a desired vehicle where appropriate. The active compounds may be formulated for parenteral administration, e.g., formulated for injection via intravenous, intraarterial, intramuscular, sub-cutaneous, intralesional, intraperitoneal or other parenteral routes. The preparation of an aqueous composition that contains a GHB agent as an active component or ingredient will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for using to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including, e.g., aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

Solutions of the active compounds as free acid or pharmacologically acceptable salts can be prepared in water suitably mixed with hydroxypropylcellulose and/or a pharmacueutically acceptable surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof as well as in oils. Under ordinary conditions of storage and use, these preparation may best contain a preservative to further prevent the growth of microorganisms.

A GHB composition of the present invention can be formulated into a composition in a neutral or salt form. Such salts can be formed from any of the acids and bases described herein particularly depending on the particular GHB or GHB salt used, or as would be known to one of ordinary skill in the art.

The carrier can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, or the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a substance, such as lecithin (e.g. a coating), by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by any of the preservatives desribed herein, or as would be known to one of ordinary skill in the art, including various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with, various of the other ingredients enumerated above, as required. followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The preparation of more, or highly, concentrated solutions for direct injection is also contemplated, where the use of DMSO as solvent (although DMSO may not now be a permitted human drug) is envisioned to result in extremely rapid penetration, delivering high concentrations of the active agents to a small area.

Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above, but drug release capsules and the like can also be employed.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The active GHB may be formulated within a therapeutic mixture to comprise about 100 to about 10,000 milligrams per dose. Multiple doses can also be administered.

In addition to the compounds formulated for parenteral administration, such as intravenous or intramuscular injection, other pharmaceutically acceptable forms include, e.g., tablets or other solids; liposomal formulations; time release capsules; and any other form currently used, including cremes, which then may be admixed with an aqueous medium for oral administration.

One may also use nasal solutions or sprays, aerosols or inhalants in the present invention. Nasal solutions are usually aqueous solutions designed to be administered to the nasal passages in drops or sprays. Nasal solutions are prepared so that they are similar in many respects to nasal secretions, so that normal ciliary action is maintained. Thus, the aqueous nasal solutions usually are isotonic and slightly

buffered to maintain a pH of 5.5 to 6.5, though other pH ranges disclosed herein the specific examples, such as pH 3 to about pH 9, or pH 6 to about 7.5, are contemplated. In addition, preservatives, similar to those used in ophthalmic preparations, and appropriate drug stabilizers, if required, may be included in the formulation. Various commercial nasal preparations are known and include, for example, antibiotics and antihistamines and are used for asthma prophylaxis.

The perferred oral formulations may include such normally employed excipients, as, for example, pharmaceutical grades of xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate and the like. These compositions can take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders to be admixed with an aqueous medium. In certain defined embodiments, oral pharmaceutical compositions will comprise an inert diluent or assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsule, or they may be compressed into tablets, or the GHB may be packaged separately from or in combination with the excipients, salts, flavorings or any other components described herein, to be admixed with an aqueous medium for oral or injectable formulations, or they may be incorporated directly with the food (i.e. a beverage) of the diet.

For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of tablets, buccal tablets or tabs, troches, capsules, elixirs, suspensions, syrups, wafers, and the like, to be admixed with an aqueous medium. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations.may, of course, be varied and may conveniently be between about 2 to about 75% of the weight of the unit, or preferably between 25-60%. The amount of active compounds in such therapeutically useful compositions is such that a suitable dosage will be obtained.

The tablets, troches, pills, capsules and the like may also contain the following: a binder, nutural as gum tragacanth, acacia, cornstarch, or gelatin or synthetic as polyvinyl acetate; excipients, such as dicalcium phosphate;sa disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a natural or synthetic flavoring agent. When the dosage unit form is a capsule for admixing with a specific volume of an aqueous medium, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with sugar, natural or synthetic polymers, or both. A syrup or elixir may contain the active compounds, sucrose as a sweetening agent, a preservative, a dye and/or a flavoring.

Additionally, any excipient, salt, acid, pH-mediating, adjusting or buffering compound or agent, flavoring, solution, solvent, dispersion, glycerol, glycol, oil, antibacterial and antifungal agents, antibiotics and antihistamines, binders, disintegrating agents, lubricants, sweetening agents, or any other additive or ingredient from those enumerated above or in the examples, or in any pharmaceutically acceptable composition or carrier described herein, or as would be known by one of skill in the art, is contemplated for use in aqueous mediums or solid forms of the GHB compositions of the invention. One or more of these compositions may be packaged with GHB or packaged separately from GHB prior to consumption. If packaged separately, useful compositions of GHB may be obtained by mixing GHB with the other components with an aqueous medium prior to consumption. Such components may be packaged in a set, described below.

2. Sets

Therapeutic sets of the present invention are sets comprising GHB. Such sets will generally contain, in suitable container, a pharmaceutically acceptable formulation of GHB. The set may have a single container, or it may have distinct container for each component, or distinct container for various combinations of components.

When the components of the set are provided in one or more liquid formulations, the liquid formulation is an aqueous medium, with a sterile aqueous solution being particularly preferred. The GHB compositions may also be formulated into a syringeable composition. In which case, the container means may itself be a syringe, pipette, vial, ampule or other such like apparatus, from which the formulation may be applied to an infected area of the body, injected into an animal, or even applied to and mixed with the other components of the set.

However, the components of the set may be provided as dried powder(s). When reagents or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent. It is envisioned that the solvent may also be provided in another container means.

The container means will generally include at least one vial, test tube, flask, bottle, pouch syringe or other container means, into which the GHB formulation or components thereof are placed, preferably, suitably allocated. The sets may also comprise a second container means for containing a sterile, pharmaceutically acceptable buffer or other diluent.

The sets of the present invention will also typically include a means for containing the vials in close confinement for commercial sale, such as, e.g., injection or blow-molded plastic containers into which the desired vials are retained.

Irrespective of the number or type of containers, the sets of the invention may also comprise, or be packaged with, an instrument for assisting with the injection/administration or placement of the GHB composition within the body of an animal. Such an instrument may be a drinking cup, syringe, pipette, or any such medically approved delivery vehicle.

II. Methods of Treatment with the GHB Compositions

Because GHB has been shown to be effective in treating narcolepsy and sleep disorders (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993), reducing alcohol craving and alcohol withdrawal symptoms, (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992), reducing opiate withdrawal symptoms (Gallimberti et al, 1994; Gallimberti et al., 1993), reducing pain (U.S. Pat. No. 4,393,236), reducing intracranial pressure in patients (Strong, A. 1984),

and increasing growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970), the formulations of the present invention are also contemplated to be useful in the treatment of any of these disorders or conditions in patients. GHB has also been used alone as a narcotic in patients with a terminal carcinomatous state. GHB has been used with other analgesics, neuroleptics, or with a subliminal barbiturate dose for use as an anesthesia. GHB has been used in closed cranio-cerebral trauma and as a soporific (U.S. Pat. No. 5,380,937). The inventors contemplate the use of the GHB compositions of the present invention as a narcotic, hypnotic, or as a soporific. The inventors also contemplate the use of the GHB compositions of the present invention in combination with analgesics, neuroleptics or barbiturates for use as an anesthesia. The GHB compositions of the present invention may be prepared and administered by any of the means described herein, particularly those described in the section "Pharmaceutical Compositions" and the examples, or by any means as would be known to those of skill in the art.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

Preferred Embodiments

XYREM™ Clinical Trials

The inventors developed a liquid formulation composed of GHB, xylitol, and preservative in water (XYREM™). Subsequent instability of the preservative in this formulation and a desire to initiate clinical trials in a timely manner led to a change in the formulation to a foil pouch. One clinical trial utilized a twin-pouch dosage form, with one side (pouch 1) of the foil packet containing GHB and the other side (pouch 2) containing the flavoring agents (Xylitol, [NF]; Malic Acid, NF;

Patients were instructed to open the twin-pouch with a scissors, empty the contents into a dosing cup, add 2 ounces of water, snap the lid on the dosing cup, shake to dissolve, and drink the entire contents of the cup. Clinical trials conducted by the inventors have been performed using the twin-pouch dosage form.

However, the inventors have continued development of a liquid solution and have now overcome inherent problems with particular formulations and/or preservatives. The inventors have converted patients currently enrolled in a GHB open-label trial to a liquid solution composed of GHB, malic acid, and water—that is diluted with water immediately prior to oral administration.

The need for a liquid solution dosage form is further evidenced by the range of doses being used in a subsequent GHB open-label trial. Three sizes of pouches were prepared for the GHB open-label trial: 1.5 grams, 3.0 grams, and 4.5 grams. The initial dose for all patients in the GHB open-label trial was 6 grams of GHB nightly in divided doses. Dosage adjustments were permitted in the first two weeks of the trial as indicated for intolerance or lack of efficacy. The investigator was permitted to decrease the dose of GHB to 3 grams or 4.5 grams, or increase the dose to 7.5 grams or 9 grams nightly. After two weeks, further dosage adjustments were made if clinically indicated.

Thirty-five patients had their dose increased, and 16 patients had their dose decreased. Patients in the lowest dose group were disproportionately female and weighed 15 kg less than patients in the other two groups. Current dosing levels are noted below:

TABLE 3

Dosing Levels in the GHB Open-Label Trial

	Total	1.5 gram	3.0 gram	4.5 gram	6.0 gram	7.5 gram	9.0 gram
Number of Patients	95	0	4	10	39	12	30
Per Cent of Patients	100%	0%	4%	10%	41%	13%	32%

To achieve these individualized doses, it has been necessary to provide a combination of different dose strengths. This complexity would be very difficult to achieve with a marketed product. In addition, a month's supply of twin-pouches is quite bulky. A liquid formulation allows for ease in dosing adjustment with one dosage form. In addition "child-resistant" packaging has been developed with the liquid formulation.

A number of patients have also complained about the flavor with the twin-pouches. As follow-up the inventors sent questionnaires to participants in the inventors' clinical trial, and performed taste testing in normal volunteers. The questionnaire responses, taste testing results, and the clinical experience in narcolepsy patients of the study administrator have all confirmed that unflavored solutions were acceptable.

The concentration and volume of the GHB solution that the patient administers will be the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. This is illustrated in Chart 1 and Table 4:

CHART 1
Comparison of Liquid Solution to Twin-Pouch

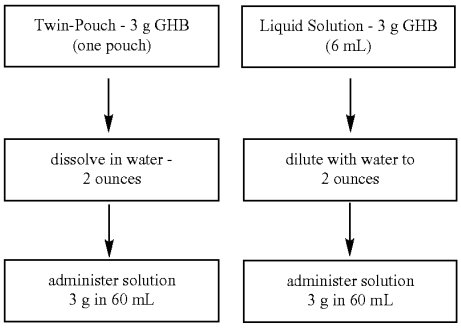

TABLE 4

Comparison of Liquid Solution to Twin-Pouch

	Twin-Pouch	Liquid Solution
Amount of GHB	3 grams (1 pouch)	3 grams (6 mL)
Inactive Components	malic acid xylitol lemon/lime flavor orange flavor	malic acid
Final Concentration	50 mg/mL	50 mg/mL*
Final Volume	60 mL	60 mL

*Final concentration outside the range of the most stable formulation. This formulation strength may be only stable at short periods of time such as 48 hours. The twin pouch version could be solubilized at a a concentration within the preferred range of pH and GHB concentration for longer term storage.

Apart from the elimination of the sweetener (xylitol) and flavoring, the two formulations result in identical solutions.

Conclusions

The concentration and volume of the GHB solution that the patient administers is the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. Either method may be used to produce acceptably stable solutions of GHB.

EXAMPLE 2

Preferred Embodiments

Self Preserving Formulations of Gamma-Hydroxybutyrate Summary of Formulation Studies—Liquid XYREM™

I. Maximum Solubility Range

As seen in FIG. **1** and Table 1, the solubility of GHB varies with pH levels at room temerature (25° C.). Additional amounts of GHB can be solubilized in a gel if heat is applied, in which case a 1000 mg/ml concentration can be achieved. The inventors contemplate that though the concentrations or contents of GHB shown in FIG. **1** and Table 1 are preferred for use, due to the ease of preparing and consuming unheated preparations, higher concentrations of GHB in aqueous medium may also be made, up to 1000 mg/ml.

II. Microbial Testing

The inventors used a three factor analysis involving pH, concentrations of GHB and the pH adjuster used. As seen in FIG. **1**, and Table 2, unacceptably low resistance to microbial challenge was seen at 150 mg/ml GHB at pH 3, 5, 7, and 9.0, using HCl as the pH adjusting agent. 150 mg/ml GHB at pH 10.3 without a pH adjusting agent also proved unacceptably resistant to microbial challenge. Borderline acceptable microbial preservativeness was seen in a solution pH adjusted with HCl at 500 mg/ml GHB at pH 9. At a concentration of 500 mg/ml at pH 6.0 or 7.5, adjusted with either malic acid or HCl, and 500 mg/ml at pH 9.0 adjusted with HCl, the formulation is very effective in a microbial challenge test. The inventors contemplate that a concentration of greater than about 150 mg/ml of GHB, up to the maximal solubility in aqueous solution of GHB, will be suitably resistant to microbial challenge from about pH 3 to pH 10.3. Preferably, the aqueous medium will contain a pH-adjusting or buffering agent.

III. Gamma-Butyrolactone Degradation Range

GBL begins to form if the pH is about 6 or less with the formulation tested thus far.

A. Liquid Formulation Development

The objective of these experiments was to develop a commercial formulation for sodium gamma hydroxybutyric acid. The initial formulation for sodium gamma hydroxybutyric acid (GHB) was intended to be an aqueous liquid formulation containing 150 mg/mL GHB, preservatives and flavoring agents. To develop this formulation, studies were conducted to establish the: solubility of the drug in water and as a function of pH, type and concentrations of suitable preservatives, type and concentrations of flavor ingredients, and stability of the formulations.

1. Solubility

The feasibility of preparing formulations containing 150 mg/mL of GHB at pH 3, 5 and 7 was established. Solutions containing 150 mg/mL GHB were prepared. The initial pH was greater than pH 7.5 and the final pH was adjusted to 3, 5 or 7 with hydrochloric acid. The solutions were observed for precipitation and assayed by HPLC for GHB content. The results showed that no precipitation was observed and the drug concentration was found to be 150 mg/mL by HPLC. This information was used as the basis for additional formulation development studies.

2. Preservatives

Preservative effectiveness studies were conducted to identify a suitable preservative for the GHB liquid formulation. The following formulations shown in Table 5 were prepared and tested using *Staphylococcus attreus* (ATCC #6538), *Pseudomonas aeruginosa* (ATCC #9027) and *Aspergillus niger* (ATCC #16404).

TABLE 5

Liquid Formulations Used in Preservative Effectiveness Testing

Formulation	pH	Sodium Benzoate	Methylparaben Propylparaben	Potassium Sorbate	Control
1	3	X			
2	5	X			
3	7	X			
4	3		X		
5	5		X		
6	7		X		
7	3			X	
8	5			X	
9	7			X	
10	3				X
11	5				X
12	7				X
13	no pH adjustment				X

The preservative used in each formulation is marked with an X. The results showed that formulations #3, 4, 6 and 9 reduced all three challenge microorganisms by >99.99% in 48 h of contact time. Formulations #1, 5 and 7 reduced all three challenge microorganism by >99.99% in 7 days of contact time. Formulations #2, 8, 10, 11, 12 and 13 did not reduce *Aspergillus niger* mold to >99.99%, although some reduction occurred in 7 days of contact time. Controls #10, 11, 12 and 13 demonstrated activity against *Pseudomonas aeruginosa*.

3. Stability

Based on the results of the preservative effectiveness testing, five formulations were selected for stability testing. Table 6 shows the composition of the formulations.

TABLE 6

Liquid Formulations Used in Informal Stability Program

Chemical	1	2	3	4	5
Potassium Sorbate	0.4 gm	0.4 gm			
Sodium Benzoate			1.0 gm		
Methylparaben				0.36 gm	0.36 gm
Propylparaben				0.04 gm	0.04 gm
GHB	30 gm	30 gm	30 gm	30 gm	30 gm
Xylitol	40 gm	40 gm	40 gm	40 gm	40 gm
Water q.s.	200 mL	200 mL	200 mL	200 mL	200 mL
Initial pH	8.68	8.68	9.30	7.75	7.75
Formulation Adjusted pH	3.01	5.00	3.00	2.98	4.98

The formulations were packaged in 125 mL, amber PET bottles with safety lined child-resistant caps and stored upright and inverted at 60° C., 40° C./75% relative humidity (RH) and 25° C./60% relative humidity. Samples were removed from the stability chambers after 1, 2 and 3 months and assayed by high performance liquid chromatography (HPLC) for GHB content. Appearance and pH were also monitored.

Table 7 shows the results for the 3 month time point. Samples stored at 60° C. changed color but samples at all other conditions remained unchanged in color.

The pH of all formulations migrated upward over the three month stability period 60C. The percent increase in pH from initial to 3 months, was greater for the formulations which were initially adjusted to lower values.

For example, the migration of pH in formulations 1,3 and 4 (adjusted down to pH 3) were 21-30 percent across all conditions in three months. The migration of pH in formulations 2 and 5 (adjusted down to pH5) were 4.2-12 percent across all conditions in 3 months. Maintenance of pH becomes important for long term storage since preservatives are known to degrade in formulations having pH levels above approximately pH 6.

Additionally, development of flavor systems to mask the negative taste of perservatives is difficult.

TABLE 7

Results of Liquid Formulation Informal Stability Study at Three Months

Formulation # (See Table 6)	Attribute	25° C./ 60% RH Upright	25° C./ 60% RH Inverted	40° C./ 75% RH Upright	40° C./ 75% RH Inverted	60° C. Upright
1 Potassium Sorbate (pH3) at 3 months storage	% t = 0	100.7	101.6	101.2	NA	NA
	pH	3.63	3.64	3.84	3.82	3.91
	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light yellow
2 Potassium Sorbate (pH5)	% t = 0*	102.1	105.0	104.0	102.0	99.6
	pH	5.21	5.28	5.55	5.56	5.61
	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light brown
3 Sodium Benzoate (pH3)	% t = 0	102.4	104.1	99.1	102.6	97.0
	pH	3.60	3.74	3.78	3.75	3.79
	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, colorless

TABLE 7-continued

Results of Liquid Formulation Informal Stability Study at Three Months

Formulation # (See Table 6)	Attribute	25° C./ 60% RH Upright	25° C./ 60% RH Inverted	40° C./ 75% RH Upright	40° C./ 75% RH Inverted	60° C. Upright
4	% t = 0	101.5	102.7	100.6	101.2	93.7
4 Methyl &	pH	3.63	3.71	3.81	3.80	3.83
Propyl Parabense	Appearance	clear,	clear,	clear,	clear,	clear,
(pH3)		colorless	colorless	colorless	colorless	colorless
5	% t = 0	103.1	105.8	101.9	103.1	95.6
4 methyl &	pH	5.22	5.55	5.55	5.56	5.60
Propyl Prabens	Appearance	clear,	clear,	clear,	clear,	clear, light
(pH5)		colorless	colorless	colorless	colorless	yellow

*% GHB at t = 0 percent of label claim
**initial time (t = 0)

4. Liquid Formulation Organoleptic Testing

Based on the above stability data and preservative effectiveness testing, a pH 5 formulation containing potassium sorbate was selected as the primary base formulation for flavor system development and organoleptic testing. A pH 3 formulation containing potassium sorbate was selected as the back-up formulation.

B. Dry Powder Formulation Development

Developing a flavor system for the primary and back-up liquid formulations proved to be difficult and a decision was made to develop a dry powder formulation for reconstitution with water before consumption. This approach removed the need for a preservative system, the requirement to adjust pH to levels below pH6, and allowed the development of a suitable flavor system.

1. Dry Powder Formulation Organoleptic Testing

To develop a flavor system for the powder formulation, several parameters were evaluated. The flavor attributes of a GHB solution was characterized by a professional sensory panel. A mimic base containing similar sensory properties as a GHB solution for flavor system was developed. Generally Recognized As Safe (GRAS) excipients for flavor system development were selected. Different excipients (flavorings, sweeteners, acidulants and flow agents) in the mimic base were screened. Three flavor systems for the focus group test were selected. A preferred flavor system was optimized based on comments obtained from the focus group testing. This final formulation with GHB was optimized.

Based on the above activities, the following formulations in Table 8 were selected for stability studies:

TABLE 8

Composition of Prototype Dry Powder Formulation

Ingredient	Composition (grams)	Purpose
GHB	3	Active
Xylitol	5.5	non-cariogenic sweetener
Malic acid	0.2	Acidulant
Flavor 1	0.2	Flavor ingredient
Flavor 2	0.04	Flavor ingredient
Silicon Dioxide (Cab-O-Sil ®)	0.03	Flow enhancer

2. Dry Powder Formulation Stability

A study was initiated to evaluate the stability of the above prototype formulation in two types of foil packages (high and moderate moisture resistant) as well as the stability of GHB alone in one type of foil package (high moisture resistant). Table 9 shows the Lots that were placed on stability. The foil packages were a high moisture resistant pouch and a moderate moisture resistant pouch. The study protocol, Table 10, required the samples to be stored at 40±2° C./75±5% relative humidity for six months, and 25±2° C./60±5% relative humidity for 12 months. Table 11 shows the tests, methods, number of packets/test and specifications for the study.

TABLE 9

Dry Powder Informal Stability Study Package Composition

Lot Number	Manufacture Date	Package Configuration	Special Comments
SPO #8018 A	Oct. 6, 1995	Foil Packet	Moderate moisture resistant pouch.
SPO #8018 B	Oct. 6, 1995	Foil Packet	Highest moisture protection pouch.
SPO #8018 C	Oct. 6, 1995	Foil Packet	Drug substance only. Highest moisture protection pouch.

TABLE 10

Dry Powder Informal Stability Study Protocol

	Stability Time in Months						
Storage Conditions	0	1	2	3	6	9	12
40 ± 2° C./75% ± 5% RH		X	X	X	X		
25 ± 2° C./60% ± 5% RH	X	X	C	C	R	R	R

X = Samples to be tested
C = Contingency Samples
R = Reduced testing; assay and H_2O only
RH = Relative Humidity

TABLE 11

Dry Powder Informal Stability Tests and Specifications

Test	Method	Packets/ Test	Specification Limits
Appearance Dry Material	Visual	Use HPLC	White to off-white free flowing powder
Appearance Reconstituted Material	Visual	Use HPLC	Cloudy, off-white solution with visible particulates
Rate of Dissolution	Visual	Use HPLC	Material should dissolve completely in five min with mixing
Odor	Olfactory	Use HPLC	Characteristic Lemon/Lime odor
Assay: GHB	HPLC	3	90.0%–110.0%
Assay: Malic Acid	HPLC	Use HPLC	90.0%–110.0%
Impurities/ Degradants	HPLC	Use HPLC	Not more than 1% for any individual impurity/degradant and Not more than 3% total impurity/degradants
Vacuum Leak test	Visual	3	No Appearance of Leaking
pH	USP <791>	Use HPLC	For Information
Moisture	Karl Fisher	3	Report Value - to be determined

After two months at 40±2° C./75±5% relative humidity, the potency (% label claim) of Lots SPO 8018A and SPO 8018B was less than 94.0%, the lower limit of the specification, whereas Lot SPO 8018C showed no loss in potency. Lots 8018A and 8018B showed approximately 96% potencies after 2 months at 25° C.±2° C./65%±5% relative humidity. Lot SPO 8018C again showed no loss in potency at this lower storage condition.

3. Appearance

After 2 months at 40° C.±2° C./75%±5% relative humidity, Lots SPO 8018A and SPO 8018B showed significant melting, whereas Lot 8018C showed no melting. Lots SPO 8018A and SPO 8018B also showed partial melting after 2 months at 25° C.±2° C.,/65%±5% relative humidity. Lot SPO 8018C again showed no evidence of melting at this lower storage condition.

Based on the physical changes in state observed during the stability studies, it was apparent that a solid state interaction between GHB and the excipient blend had occurred. Since xylitol made up the majority of the excipient blend, it was assumed that xylitol was the primary source of the drug-excipient interaction. An alternative hypothesis was also proposed, based on the possibility that the package was mediating the interaction between GHB and xylitol. Three studies were initiated to test these hypotheses.

4. Stability of GHB Solids in a Set Container-System

In the first study, the samples that were stored at 25±2° C./60±5% relative humidity were transferred to glass vials and then stored at 40±2° C./7±5% relative humidity. In the second study, mixtures of GHB and xylitol were gently rubbed between sheets of different types of foil packaging. The mixtures were observed for changes in physical appearance. In the third study, different mixtures of GHB and xylitol were prepared. Differential Scanning Calorimetry (DSC) thermograms were then done to look for changes in the thermograms. The results of these studies are summarized below.

Transfer to Glass: Samples of Lot 8018A and Lot 8018C that were previously stored at 25±2° C./60±5% relative humidity were transferred to amber screw cap vials and stored at 40±2° C./75±5% relative humidity. Analyses similar to those shown in Table 6 were done. After I month, the potency of Lot 8018A was 94.6% whereas the potency of Lot 8018C (GHB only) was 100%. In addition, Lot 8018A also showed evidence of melting. The results supported the hypothesis that GHB and xylitol were interacting in the solid state and the interaction appeared to be independent of packaging.

Foil Study: Mixtures of GHB and xylitol were placed between folded sheets of several different foil packaging materials. Slight adhesion of the mixed granules with the foil lining was observed for all of the foils examined. No direct evidence of melting was observed, however, even when excessive force was applied to the outer foil surfaces. This data suggests that the packaging material was not responsible for the solid state interaction observed during the stability studies.

DSC thermographs were obtained for samples of GHB/xylitol containing GHB:xylitol mixtures of 33:66, 45:55 and 55 percent 45 respectively. The scans were conducted at a scan rate of 10° C./min. The thermograms showed that the sample containing GHB:xylitol 33:66 showed a broad endothermic transition starting at 35° C. -40° C. Samples with higher ratios of GHB:xylitol also showed broad endothermic transitions that started at temperatures of 45° C.-50° C. The changes seen in the thermograms supported the hypothesis that a solid state interaction may be occurring between GHB and xylitol that resulted in low potencies for formulations containing mixtures of these two agents.

As a result of the changes seen in the DSC thermograms for different mixtures of GHB:xylitol, a study was initiated to investigate the stability of a formulation containing GHB:xylitol excipient blend 55:45. A formulation containing GHB:xylitol excipient blend 33:66 was used as a control sample. The formulations were packaged in glass vials and stored at 50° C., 40±2° C./75±5% relative humidity and 25±2° C./60±5% relative humidity. The appearance and potency of the formulations were monitored through analyses of stability samples. The stability study also showed potency losses after 1 month at 40° C.±2° C./75% ±5% relative humidity with both the 50/50 GHB:xylitol ratio as well as the original 33/66 ratio formulation. Partial evidence of melting was also observed in both formulations.

Studies with mixtures of GHB:xylitol excipient blend indicated that the mixture was incompatible in the solid state. However, when prepared as an aqueous solution, these mixtures were chemically compatible. Using this information, a decision was made to package the GHB formulation in dual pouches; one pouch containing GHB alone and the other containing a mixture of xylitol and the other flavor ingredients. The formulation will contain equal amounts of GHB and the excipient blend. This product will be prepared, packaged, and may be checked for stability.

EXAMPLE 3

The Pharmacokinetics of Gamma-Hydroxybutyrate

I. Study Objectives

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; patients generally ingested the first dose of this medication prior to bedtime and the second dose from 2.5 to 4.0 h later) to narcoleptic patients who are maintained on a chronic regimen of GHB.

II. Study Design

This pharmacokinetic study was conducted as an open-label, single-center investigation in 6 narcoleptic patients. The study design is summarized as follows:

TABLE 12

Screening/Washout ⇒	Treatment/Blood Sampling ⇒	Follow-up
(1 or more days to dosing; washout, at least 8 h	(Two 3 g GHB oral doses, 4 h apart; 21 blood samples)	(Within 48 h after last blood sample)

Narcoleptic patients, 18 years of age or older, who volunteered for this study were screened at least one day prior to the treatment phase. Each patient was determined to be in stable health and evaluated for the presence of narcolepsy, defined for the purposes of this example as one or more years of medical history of narcolepsy as evidenced by a recent nocturnal polysomnogram (PSG) and a valid score from a Multiple Sleep Latency Test (MSLT).

Patients maintained on GHB were allowed to participate. These patients had been weaned from antidepressants, hypnotics, sedatives, antihistamines, clonidine, and anticonvulsants though a stable regimen of methylphenidate (immediate release or sustained release) was allowed. Each patient passed a pre-study physical examination (which included hematology, blood chemistry, urinalysis, and vital signs measurements) prior to the commencement of the treatment phase.

Before oral administration of the first GHB dose, an indwelling catheter was placed in an arm vein and a baseline blood sample was collected. Each patient then ingested a 3 g dose of GHB before bedtime. Another 3 g GHB dose was administered 4 h after the first dose. Twenty-one sequential blood samples were collected over 12 h (starting at 10 min after the first dose and ending at 8 h after the second dose). Upon completion of the treatment phase, a follow-up physical examination which included the measurement of vital signs was performed on each patient within 48 h after the last blood sample. A detailed description of the trial methodology is presented in Section IV.

III. Inclusion Criteria

Patients were included in the study if they: had signed an informed consent prior to beginning protocol required procedures; had not participated in such a study at an earlier date; were willing and able to complete the entire study as described in the protocol; were 18 years of age or older at study entry; had not taken any investigational therapy other than GHB within the 30-day period prior to screening for this study; had an established diagnosis of narcolepsy for at least one year with documentation from a qualified laboratory by a nocturnal polysomnogram (PSG) and a Multiple Sleep Latency Test (MSLT) which demonstrated mean sleep latency to be less than 5 min and REM onset in at least 2 of 5 naps; had not been diagnosed with uncontrolled sleep apnea syndrome, defined as a sleep Apnea Index of 5 or an Apnea Hypopnea Index (AHI) greater than 10 per hour or any other cause of daytime sleepiness; and were free of any medication for their narcolepsy (including hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants) other than GHB and methylphenidate (IR or SR). Patients admitted to this study if they were not experiencing unstable cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, metabolic, neurological, pulmonary, and/or renal disease which would place them at risk during the study or compromise the protocol objective; did not have neurological or psychiatric disorders (including transient ischemic attacks, epilepsy, or multiple sclerosis) which, in the investigator's opinion, would preclude the patients' participation and completion of this study; did not have a current or recent (within one year) history of alcohol or drug abuse; did not have a serum creatinine greater than 2.0 mg/dL, abnormal liver function tests (SGOT or SGPT more than twice the upper limit of normal, or serum bilirubin more than 1.5 times normal). Female patients were entered into the study if they were either post-menopausal (i.e. no menstrual period for a minimum of 6 months), surgically sterilized or provided evidence of effective birth control. Females of childbearing potential must agree to continue to use an IUD, diaphragm, or take their oral contraceptives for the duration of the study. Female patients of childbearing potential must have a negative pregnancy test upon entry into the study.

IV. Trial Methodology

A time and events schedule is presented in Table 12.

A. Screening Period/Washout

Six narcoleptic patients who were chronically being treated with GHB were recruited to participate in this pharmacokinetic study. The screening period was at least one day prior to the treatment phase. During the screening period each patient completed the following procedures for the assessment of their physical condition: medical history evaluation; physical examination evaluation; clinical laboratory evaluation; inclusion criteria review. Each patient's GHB and methylphenidate regimen also were recorded on an appropriate case report form (CRF). The investigator also ensured that there was at least an 8-hour washout period for GHB prior to the treatment.

B. Treatment Period/Blood Samples Collection

All patients were hospitalized from approximately four hours prior to first GHB dosing (around 6 p.m.) until the end of the treatment period (around 10 a.m. the next morning). Patients ate their dinner at the clinical research unit soon after arrival and fasted until breakfast next morning. At least three hours elapsed between the completion of dinner and the administration of the first GHB dose. An indwelling catheter was placed in an arm vein of each patient for blood

sampling at approximately 30 min and 1 h before the first GHB dose and a baseline blood sample (5 mL) was collected.

The first GHB dose (3 g) was administered at around 10 p.m. Dosing of individual patients were staggered. The second GHB dose was administered at 4 h after the first GHB dose (i.e. immediately after the 4 h blood sample). The exact dosing times in each patient were recorded on appropriate CRF pages. Blood samples (5 mL each) were collected through the indwelling catheter into heparinized tubes at 0.2, 0.4, 0.6, 0.8, 1, 1.5, 2, 3, 4, 4.2, 4.4, 4.6, 4,8, 5, 5.5, 5, 7, 8, 10, and 12 h after the first GHB dose. Blood samples were processed according to the procedures described herein. Patients were monitored for adverse experiences throughout the study according to the specific procedures.

C. Follow-Up

Follow-up occurred within 48 h after the last blood sample had been collected. An abbreviated physical examination which included vital signs measurement was performed. Adverse experiences and concomitant medication use, if any, were assessed. Any ongoing adverse experiences and clinically important findings in a patient were followed to the investigator's and/or sponsor's satisfaction before the patient was discharged from the study.

D. Methods of Assessment

1. Medical History

The medical history was recorded during the screening period. The history included gender, age, race, height, prior reaction to drugs, use of alcohol and tobacco, history and treatment, if any, of cardiovascular pulmonary, gastrointestinal, hepatic, renal, immunologic, neurological, or psychiatric diseases and confirmation of inclusion criteria.

2. Physical Examination

Physical Examination included body system review as well as measurement of body weight and vital signs and a neurological examination.

3. Vital Signs

Vital signs measurements included recording of blood pressure, heart rate, respiration, and body temperature.

4. Clinical Laboratory

All clinical laboratory tests were performed at a local laboratory. The laboratory tests and analysis were required of each patient included: hematology, including hemoglobin, hematocrit, red blood cell count, white blood cell count and differential; fasting blood chemistries included blood urea nitrogen (BUN), uric acid, glucose, creatinine, calcium, phosphorus, total protein, albumin, sodium, potassium, SCOT (AST), SGPT (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), and total bilirubin; midstream catch urinalysis included specific gravity, pH, protein, occult blood, ketones and glucose by dipstick determination as well as a microscopic examination of urine sediment for RBC, WBC, epithelial cells or casts or crystals; and a urine pregnancy test, if applicable. Any laboratory parameter that was out of range and considered clinically significant excluded the patient from participation in this study. The investigator would provide an explanation of all observations that were significantly outside the reference range.

5. Concomitant Medication

The continued use of a fixed dose of methylphenidate immediate release or sustained release (IR or SR) is acceptable. The methylphenidate regimen was recorded on the appropriate case report form.

6. Adverse Experiences

An adverse experience are any undesirable event experienced by a patient or volunteer whether or not considered drug-related by the investigator. An undesirable event can be, but is not limited to, subjective symptoms experienced by a patient or, objective findings such as significant clinical laboratory abnormalities. Adverse experience is considered synonymous with the term "adverse event".

The investigators report in detail all adverse experiences and symptoms that occurred during or following the course of trial drug administration for up to 2 days. Included in the description was the nature of the sign or symptom; the date of onset; date or resolution (duration); the severity; the relationship to trial treatment or other therapy; the action taken, if any; and the outcome.

A serious adverse experience is defined as one that is fatal, life threatening, permanently disabling, or which results in or prolongs hospitalization. In addition, overdose, congenital anomaly and occurrences of malignancy are always considered to be serious adverse experiences. An unexpected adverse experience is one not previously reported.

Any serious or unexpected adverse experience (including death) due to any cause which occurs during the course of this investigation, whether or not it is related to the investigational drug, was reported within 24 h by telephone or facsimile. Appropriate authorities were to be informed if the serious or unexpected adverse experience, in the opinion of inventors, was likely to affect the safety of other patients or volunteers or the conduct of the trial.

7. Clinical Supplies-Study Medication

Formulation: Unit 3 g GHB doses (Lot PK1) were obtained from Orphan Medical. Each unit dose comprised twin foil pouches: one pouch containing GHB and the other containing a flavor excipient blend. (Table 8 formulation)

Labeling: The clinical supplies for individual patients were packaged in separate containers. Each container included two unit doses, i.e. two twin-pouches. Clinical supplies for eight patients (including those for two replacement patients) were delivered to the investigator. Foil twin-pouches were identified with a two-part label.

Dose Administration: The investigator or designee prepared the oral solution for dosing within 30 min prior to the first oral administration to individual patients. The contents of one twin-pouch was emptied into a dosing cup to which two ounces of water were added. After replacing the lid of the dosing cup, it 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 ingesting in its entirety at 4 h after the first GHB dose.

Investigational Drug Accountability: At the conclusion of the study, all clinical supplies were accounted for on the drug accountability form and unused drug supplies were returned for proper disposition.

8. Determination of Plasma GHB Concentrations

Plasma samples were analyzed for GHB by the Department of Bioanalytical Chemistry (Covance (previously known as Hazelton Corning), Madison, Wis.) A gas chromatographic method with mass selective detection (GC-MSD) was used in the analysis.

9. Data Management and Analysis

Data Base: An EXCEL data base (spreadsheet) was constricted from data recorded on Case Report Forms (CFR) and plasma GHB concentration data sets received from Covance (Corning Hazleton). Each entry in the EXCEL spreadsheet was checked against the CRFs and any data entry error found was corrected.

Pharmacokinetic Analysis: Pharmacokinetic parameters were determined for individual sets of plasma GHB concentration vs. time data using the non-compartmental routine in WinNonlin Version 1.1. The peak GHB concentrations (C_{max}) and the times of their respectively occurrences (t_{max}) were observed values. Terminal half-life ($T_{1/2}$) was obtained by log-linear regression analysis of the terminal phase of concentration vs. time curves. The area under the curve (AUC_{inf}) and the area under the first moment curve ($AUMC_{inf}$) were calculated by the linear trapezoidal rule up to the last determined concentration and included extrapolated areas to time infinity. Apparent oral clearance (CL/F) was calculated as Dose/AUC_{inf}. Volume of distribution (Vz/F) was determined by taking the ratio between CL/F and λ_z (elimination rate constant). Mean residence time (MRT) was estimated from the ratio between $AUMC_{inf}$ and AUC_{inf}.

Safety Analyses: Results of physical examinations, vital signs, clinical laboratory data were summarized in tabular form and presented by patient number. Adverse events also were tabulated in a similar fashion.

10. Results

Patient and Study Accountability: Six narcoleptic patients were enrolled and all six completed the study in its entirety.

Protocol Compliance: There were no inclusion criteria violations. All patients admitted into the study met the study entrance requirements and completed the screening phase at least one day before the treatment phase.

All six patients took non-study medications in addition to methylphenidate and GHB doses because none of their concomitant medications (Synthyroid, Premarin, Lovastatin, Flovastatin, furosemide, potassium, hydrochlorothiazide, lansoprazole, and verapamil) were on the exclusion list (which included hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants). Adverse experience probes, vital sign measurements, and essentially all pharmacokinetic blood samples were performed at protocol specified times; the few deviations in blood sampling times should not have any impact on the outcome of the study since actual blood sampling times were used in the pharmacokinetic analysis.

The diagnosis of narcolepsy for at least one year in each patient was verified by a nocturnal polysomnogram (NSG) and a Multiple Sleep Latency Test (MSLT) conducted at a qualified laboratory. Five patients have been maintained on GHB nightly for over 10 years and one patient has been receiving GHB nightly for two years. One patient (Subject 101) also had multiple sclerosis; however, the attending physician, judged that it would not interfere with the objective of this study. A few of the screening clinical laboratory results marginally fell outside the reference range but none was considered by the attending physician to be clinically significant.

Exposure to Study Drug: All patients ingested the two GHB doses as scheduled (immediately prior to bedtime). The GHB doses per kg body weight ranged from 26.4 to 52.4 mg/kg.

Plasma GHB Concentration Profiles: It was noted that, in certain cases, (Patients #103, and #106), plasma GHB concentrations did not decline from the first C_{max} to zero concentration at h 4. Upon achievement of the second C_{max}, the semi-logarithmic plots of concentration versus time data in Patients #102, #103, and #105 exhibited a convex decline profile. Such a decline pattern suggested non-linear pharmacokinetics. The highest plasma GHB concentration observed in the study was 125.0 μg/mL which occurred in Subject 101 after the second 3 g GHB dose.

Pharmacokinetic Parameter Estimates: The mean (±SD) showed that maximum GHB concentrations (C_{max}) were 62.8±27.4 μg/mL and 91.2±25.6 μg/mL for the first and second GHB doses, respectively. The corresponding mean observed times to maximum concentrations were 40±6 and 36±7 min after the first and second GHB doses, respectively. The mean AUC_{inf} was 17732±4603 μg/mL.h. The mean CL/F was 4.2±1 mL/min/kg and the mean V_z/F was 307±96 mL/kg. The mean MRT_{inf} was 249±56 min. The mean GHB $T_{1/2}$, estimated by linear regression of log[C] vs. time data of the terminal phase of the second GHB dose was 53±19 min.

Adverse Experiences: No adverse experiences were reported in the study.

Follow-up Safety Assessments: Inspection of screen and follow-up physical examination results per individual patient did not identify any changes attributable to GHB.

11. Discussion

To the inventors' knowledge, the level of GHB in human systemic circulation has not been reported in the literature. Hence, baseline (0 h) plasma samples were analyzed for GHB concentrations. The GC-MSD method used in the present study had a limit of quantification (LOQ) of 7.02 μg/mL and analysis of the baseline plasma samples showed the endogenous levels of GHB are below this sensitivity limit. This finding was confirmed by adding known amounts of GHB (5, 10, and 25 μg per mL of plasma) to blank human plasma samples and subjected these samples to GC-MSD analysis. This method of standard addition allowed an estimation of the endogenous GH1B level in human plasma which was found to average about 2.02 μg/mL, (i.e. approximately 2/7 of the Limit Of Quantitation (LOQ) for a validated assay. Hence, the endogenous GHB level was not subtracted from exogenous GHB concentrations prior to pharmacokinetic analysis.

Values of mean t_{max} (~40 min after dosing) and $t_{1/2}$ (~35 min) suggest that the GHB solution administered to narcoleptic patients in this study was readily absorbed and rapidly eliminated. In 3 out of 6 patients the drug was essentially gone from the systemic circulation by h 4 after the first GHB dose whereas in the remaining three patients residual GHB levels of ~15 μg/mL was still detected at h 4.

The convex nature of the decline of plasma GHB concentrations in three patients after achievement of the second C_{max} indicated that elimination of GHB from the systemic circulation in these three patients is capacity limited. Nevertheless, it should be noted that plasma GHB concentrations were no longer detectable by h 6 after the second GHB dose (10 h after the first GHB dose). The mean apparent oral clearance found in this study was 4.2±1.0 mL/min/kg and appeared to be comparable to the apparent oral clearance of 5.3±2.2 mL/min/kg reported in the literature for a group of alcohol dependent patients who were administered a dose of 50 mg/kg (Ferrara, 1992). While it appeared that the GHB dose (ranging from 26.4 to 52.4 mg/kg with a mean of 36.5 mg/kg) in the present study was lower than the comparison GHB dose (50 mg/kg) administered to the alcohol dependent patients (Ferrara, 1992), it should be noted that each patient in the present study was administered two consecutive GHB doses at four-hour interval and residual GHB levels were detected in three out of six patients immediately prior to the second GHB dose. The GHB pharmacokinetic non-linearity in alcohol dependent patients easily can be observed from the apparent oral clearance which increased to 8.1±4.8 mL/min/kg when the GHB dose is reduced to 25 mg/kg dose (Ferrara, 1992). In the present study, the non-linearity was less obvious because each narcoleptic patient received two consecutive fixed 3 g doses regardless of body weight.

The mean elimination half-life of GHB in the six narcoleptic patients was determined to be 53±19 min, longer than that in alcohol dependent patients after a 50 mg/kg GHB dose (Ferrara, 1992). The lengthening of GHB elimination half-life observed in this study partially was caused by the wider spacing in sampling time points. However, capacity limited elimination of this drug in some of the narcoleptic patients also could have contributed to this prolongation.

GHB appears to have a shortcoming in that its elimination from the body is capacity limited in some patients when the drug is administered at a fixed regimen of 3 g twice nightly at four-hour interval. However, from a therapeutic perspective, GHB offers an advantage in the treatment of narcolepsy because by the time a patient wakes up in the morning (i.e. 8 to 10 h after the first GHB dose), all GHB, including that from the second dose, will have been eliminated from the systemic circulation. GHB was also well tolerated by narcoleptic patients in this study. No adverse experience was reported.

12. Conclusions

The capacity limited elimination kinetics was observed in three out of six patients who had been administered two consecutive 3 g oral doses of GHB, 4 h apart. From a pharmacokinetic perspective, dividing the nightly GHB dose into two portions and administering the two portions to narcoleptic patients at a 2.5- to 4-h interval was rational because the elimination half-life of GHB was short (<1 h). The pharmacokinetic profiles of GHB in narcoleptic patients who had been receiving this agent nightly for years appeared to be comparable to those in alcohol dependent patients (Ferrara, 1992).

EXAMPLE 4

Sodium Oxybate Formulation Study

I. Study Objectives

This example described ways that sodium oxybate may be prepared and tested for stability to determine preferred formulations. Various formulations of sodium oxybate in water were prepared under different conditions of mixing and with addition of selected acidulents at multiple pH levels (Neo-Pharm Laboratories, Blainville, Quebec). Selected formulations were placed on real time and accelerated stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Therefore several acidulents across a range of 6.0-9.0 were evaluated.

II. Study Design-Part I

The following experimental work is designed to be performed in two stages. Initial studies were conducted to evaluate the impact of conditions of formulation, pH and acidulent on the resultant levels of impurities, specified and unspecified, and potency of sodium oxybate. Sodium oxybate was prepared (MDS Neo-Pharm Laboratories, Quebec Canada), under different conditions of mixing and with addition of selected acidulents at multiple pH levels. These formulations of sodium oxybate acidulent were then tested.

A. Preliminary Studies

1. Formulations Description

All formulations were prepared at a concentration of 500 mg/cc of sodium oxybate in water. Three acidulents (HCl, malic acid, and phosphoric acid), were selected and tested at pH 6.0, 7.5 and 9.0.

2. Method of Formulation

Solutions, were prepared using the described methods:

a. Rapid Mix Method

Sodium oxybate was dissolved in water and concentrated acidulent was added immediately without temperature control. Temperature of solution was monitored and recorded prior to and during addition of acidulent. The time of equiliberation to room temperature was also recorded. After the solution reached ambient room temperature, it was filtered through a 10 μm filter.

b. Cool Mix Method:

Sodium oxybate was dissolved in water. Acidulent was diluted to 10% and slowly added. The solution was cooled by water with jacket or ice bath. Monitor and record the temperature of the solution was monitored and recorded during addition of acidulent. The time of equilibrium from room temperature was also recorded. The preferred maximum temperature should be maintained at less than 40° C. The solution was filtered through a 10 μm filter.

c. Reverse Order of Addition:

Acidulent was added to water and cooled to room temperature. The sodium oxybate was dissolved in the diluted acidulent solution. The temperature of solution was monitored and recorded during addition of sodium oxybate. The solution was filtered through a 10 μm filter.

d. Sodium Oxybate Control

Sodium oxybate was dissolved in water to a concentration of 500 mg/cc with no added acidulent. The final pH was

recorded and the solution was filtered through a 10 μm (micron or micrometer) filter.

3. Solution Data:

Data was recorded for each solution which included: 1) date of preparation 2) date of analysis, 3) amount of acidulent required to achieve target pH, 4) length of time for dissolution of sodium oxybate, 5) temperature profile of solution over time of solution preparation to be recorded at 15 minute intervals, 6) final pH of solution.

4. Testing Requirements:

The following methods were used to test the prepared solutions: pH, HPLC (High Pressure Liquid Chromotography) for potency (sodium oxybate), and for impurities. Time 0 analysis was performed immediately (within 24 h). RRT= (relative retention time).

B. Summary of Part I:

1. Preliminary Evaluation of Sodium Oxybate Formulations

Tables 13, 14 and 15 provide test results for the three methods of preparation of sodium oxybate formulations.

TABLE 13

Formulation Study/PR98068
Results of Formulation Study - Time Zero determinations of Sodium Oxybate, GBL and Unspecified Impurities
Preparation Method A

Addition of Concentrated Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/cc % [95–105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (Apr. 23, 1998)					
(10 drops over 2 minutes)	pH 9.0	9.0	509 mg/cc 101%	0.009%	RRT 4.88 = 0.01%
(2.5 ml/4 minutes)	pH 7.5	7.5	507 mg/cc 101%	0.01%	RRT 4.89 = 0.02%
(45 ml/34 minutes)	pH 6.0	6.0	504 mg/cc 101%	0.033%	RRT 4.89 = 0.33%
Malic Acid (Apr. 24, 1998)					
(0.12 gm)	pH 9.0	9.1	498 mg/cc 99.6%	0.009%	RRT 4.89 = 0.01%
(1.6 gm)	pH 7.5	7.6	506 mg/cc 101%	0.009%	RRT 4.89 = 0.01%
(25 gm)	pH 6.0	6.2	493 mg/cc 98.6%	0.011%	RRT 4.89 = 0.01%
H_3PO_4 (Apr. 24, 1998)					
(2 drops)	pH 9.0	9.0	493 mg/cc 98.6%	0.009%	RRT 4.89 = 0.01%
(1.0 ml)	pH 7.5	7.5	493 mg/cc 98.6%	0.009%	RRT 4.89 = 0.02%
(17.3 ml)	pH 6.0	6.1	497 mg/cc 99.4%	0.063%	RRT 4.89 = 0.02%
Sodium Oxybate Control No Acidulent	n.a.	9.8	500 mg/cc 100%	0.009%	RRT 4.89 = 0.04%

*Method A = Mix Method with Concentrated Acidulent and Temperature Monitoring

TABLE 14

Preparation Method B

Addition of Diluted Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95–105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (25%) (Apr. 28, 1998)					
(20 drops)	pH 9.0	9.1	500 mg/cc 100%	0.009%	RRT 4.88 = 0.01%
(8.0 ml)	pH 7.5	7.6	499 mg/cc 99.8%	0.009%	RRT 4.88 = 0.01%
(175 ml)	pH 6.0	6.0	502 mg/cc 101%	0.016%	RRT 4.88 = 0.02%
H_3PO_4 (25%) (Apr. 29, 1998)					
(0.3 ml)	pH 9.0	8.9	499 mg/cc 99.8%	0.007%	RRT 4.92 = 0.02%
(4.0 ml)	pH 7.5	7.5	497 mg/cc 99.4%	0.008%	RRT 4.89 = 0.02%
(120 ml)	pH 6.0	6.0	499 mg/cc 99.8%	0.019%	RRT 4.89 = 0.01%
Malic Acid (500 mg/cc) (Apr. 30, 1998)					
(0.115 gm/0.23 ml)	pH 9.0	9.0	495 mg/cc 99%	0.008%	RRT 4.92 = 0.02%
(1.75 gm/3.5 ml)	pH 7.5	7.4	488 mg/cc 97.5%	0.009%	RRT 4.92 = 0.01%
(35 gm/70 ml)	pH 6.0	6.0	487 mg/cc 97.0%	0.013%	RRT 4.92 = 0.01%

*Acidulent added slowly at the rate of 2–3 drops/second

TABLE 15

Preparation Method C

Reverse Order of Addition* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95–105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (May 1, 1998)					
(20 drops)	pH 9.0	9.0	497 mg/cc 99.4%	0.006%	RRT 4.92 = 0.03%
(2.4 ml)	pH 7.5	7.6	504 mg/cc 101%	0.004%	RRT 4.92 = 0.04%
(45 ml)	pH 6.0	6.0	493 mg/cc 98.6%	0.044%	RRT 4.92 = 0.04%
H_3PO_4 (May 4, 1998)					
(0.08 ml)	pH 9.0	8.9	496 mg/cc 99.2%	0.005%	RRT 4.91 = 0.03%
(1.0 ml)	pH 7.5	7.6	496 mg/cc 99.2%	0.004%	RRT 4.91 = 0.04%
(30 ml)	pH 6.0	6.1	489 mg/cc 97.8%	0.023%	RRT 4.91 = 0.04%
Malic Acid (May 5, 1998)					
(0.12 gm)	pH 9.0	9.0	495 mg/cc 99%	0.006%	RRT 4.93 = 0.02%
(1.6 gm)	pH 7.5	7.6	497 mg/cc 99.4%	0.004%	RRT 4.93 = 0.04%
(35 gm)	pH 6.0	6.2	495 mg/cc 99%	0.044%	RRT 4.93 = 0.04%

*Acidulent added to water first, GHB added second.

Review of the data indicated that the optimum method for preparation of sodium oxybate with minimal impurity levels is Method B: Controlled mixing with diluted acidulent. Method 2b resulted in formulations with lowest levels of GBL.

2. Conclusions

Additional evaluations were carried out on selected formulations: 1) sodium oxybate with HCl as acidulent, at pH 7.5, and 2) sodium oxybate with malic acid as acidulent, pH 6.0, 7.5, and 9.0.

III. Study Design-Part II

Microbial Challenge and Stability Tested to determine the most preferred embodiments, the number of formulations was limited to three based on the data prepared from the above experiments.

A. Kinetic Stability Study with Selected Formulations

Samples of formulations are stored in tightly closed containers. Storage Conditions were 25° C., 40° C., and 60° C. Time points in brackets were tested at the inventor's discretion. The samples were tested according to the following schedule: at 25° C. storage temperature, the assay points will be 0, 14, 28, 45, 60 days and 120 days; at 40° C. storage temperature, the assay points will be 0, 7, 14, 28, 45, 60 days; at 60° C. storage temperature, the assay points will be at 0, 3, 7, 14, 28, 45 days, and, 60 days.

The testing requirements included pH, HPLC for sodium oxybate (duplicate injections of single sample preparation), and impurities, specified and unspecified.

B. Preservative Effectiveness Testing of Selected Formulations

Microbial challenge testing of formulations was preformed according to USP XXIII, <51>, Eighth Supplement. Solutions are determined to "Pass or Fail" based upon the USP criteria for perservative effectivness which states: For Bacteria, "Not less than 1 log reduction from the initial microbial count at 14 days and no increase from the 14 days count at 28 days;" and for yeast and molds, "No increase from the initial calculated count at 14 and 28 days." Solutions which met these criteria were designated as "Pass" and those that did not meet these criteria were designated as "Fail".

C. Summary Stability Results:

1. Formulations Prepared with Malic Acid as Acidulents:

a. Malic Acid, pH 6.0 formulation (250), GBL and impurity A levels were very low on Day 0, however, by Day 45 GBL levels had reached 2.8%. Impurity A increased from 0.01 to 1.0%, and pH increased from 6.0 to 6.3 by day 45. This formulation stored at 40° C. and 60° C. showed GBL levels up to 5.4%, impurity A levels increased to 2.3%, and pH increased to 6.3 by Day 14.

b. Malic Acid, pH 7.5 formulation (25° C.), GBL levels were 0.009% on Day 0, and increased to 0.17% by day 45. Impurity A increased from 0.01% to 0.1% and pH increased from 7.5 to 7.9. Malic acid, pH 7.5 GBL levels are reached (40° C.) and 60° C. a maximum of 0.22%. Impurity A levels reached 0.1% and pH increased to 8.0. Under accelerated conditions, all parameters reached an apparent maximum by Day 7 and did not increase significantly thereafter.

c. Malic Acid, pH 9.0 formulation (25° C.,) GBL levels measure 0.008% on Day 0, and increased slightly to 0.013% on Day 45. Impurity A did not increase nor did pH increase. Under accelerated conditions, GBL increased from 0.008% to a maximum of 0.018% by Day 14. Impurity A increased slightly from 0.10 to 0.014% by Day 14.

2. Formulations Prepared with HCl as Acidulents

HCl, pH 6.0 formulation (25°) GBL levels measured 2.8% by Day 30, and impurity A 0.004%, and pH 6.0. Accelerated storage conditions (40° C.) GBL levels were measured at 6.6%, and impurity A measured 3.1% by Day 30.

HCl, pH 7.5 formulation (25%) GBL levels measured 0 041% on Day 0, Impurity A measured 0.02%, and by Day 18 GBL measured to 0.12% and impurity A to 0.07%. Under

accelerated conditions (40° C. and 60° C.), GBL increased to a maximum of 0.21%, impurity A increased from 0.02% to 0.1%, and pH increased from 7.5 to 8.0. As with Malic Acid at pH 7.5, the measured parameters reached maximum by Day 7 and did not increase significantly thereafter.

HCl, pH 9.0 formulation (25° C.) GBL levels reached 0.022% by Day 18. Impurity A stayed constant at 0.01% for 18 days. Under accelerated conditions (40° C.) GBL levels were equivalent to 25° C. storage (0.21%). Impurity A showed no increase over 25° C. conditions.

3. Conclusions.

Formulations selected for microbial challenge testing were the following: HCl, pH 7.5, and malic acid, pH 7.5. The rationale for this decision was twofold. First, the formulations were selected based on minimal formation of GBL and impurity A. Second, the formulations were selected to maintain a pH in the neutral range.

EXAMPLE 5

Further Evaluation of Sodium Oxybate Formulations

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of gamma-hydroxybutyrate.

Scope: Various formulations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple pH levels. Solutions were prepared and tested at Neo-Pharm Laboratories, Blainville, Quebec. All formulations successfully prepared were placed on limited stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Conditions of varying pH and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Procedures: Solutions were prepared as summarized and microbial challenge testing carried out as follows:

I. Evaluation of Sodium Oxybate Formulations

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of gamma-hydroxybutyrate.

Scope: Various formulations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple pH levels. Selected formulations were studied for limited stability. Earlier studies demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Conditions of varying pH and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Responsibility: It was the responsibility of Neo-Pharm Laboratories to prepare selected formulations and perform testing per this protocol. Orphan Medical, New Medicine Development and Quality Assurance were responsible for reviewing raw data at the defined decision point, defining which formulations will be included in stability testing. Orphan Medical was also responsible for reviewing final results (raw data) and the final report.

Procedure: The following formulations were prepared by scientists at Neo-Pharm following the steps listed below and dispensed into containers (amber PET 240 ml bottle, OMI CS-460) and closures (Clic-Loc III, 24-400, OMI CS-470) to a volume of 200 ml each bottle. The bottles were tested by 28-day microbial challenge and by limited stability testing at 25° C. including, appearance, pH, potency, and impurity profile on day 1 (day of preparation) and day 28.

A. Formulations Prepared and Evaluated Using Sodium Oxybate:

TABLE 16

Formulations Prepared and Evaluated Using Sodium Oxybate

Formulation ID No.	Sodium Oxybate Concentration	Acidulent	Final pH
1	500 mg/cc	Malic Acid	7.5
2	250 mg/cc	Malic Acid	7.5
3	350 mg/cc	Malic Acid	7.5
4	450 mg/cc	Malic Acid	7.5
5	550 mg/cc	Malic Acid	7.5
6	650 mg/cc	Malic Acid	7.5
7	500 mg/cc	Citric Acid	7.5
8	500 mg/cc	Malic Acid	5.0

1. Preparation: Method for preparation of various formulations: As previously determined in PR98068, the method of choice for preparation of liquid formulations of sodium oxybate was the following:
   a. For a one liter quantity of product, add the sodium oxybate in 500 ml of purified and stir until dissolved. Prepare a 10% solution of the acid (Malic or Citric) and add slowly to the solution of sodium oxybate. The solution should be monitored for pH and temperature and both variables recorded at reasonable intervals (every 10 or 15 minutes). When the target pH is attained, the solution will be Q. S. to 1 liter, and pH rechecked and recorded.
   b. The final solutions will be filtered through 10 μm filters and 200 mL dispensed into 5 amber PET bottles with closures (provied by Orphan Medical, Inc.). Two bottles will be used for microbial challenge studies and the remaining three bottles will be placed on limited stability.
2. Testing: Formulations were tested by two methods of evaluation:
   a. Limited stability evaluation:
      (1) Storage Conditions: 25° C.
      (2) Pull Points: Day 0 (day of preparation), and day 28
      (3) Testing Requirements:

Test	Method
Appearance	Visual
Potency	HPLC Neopharm 764
Impurities	HPLC Neopharm 793DT
pH	USP <791>

   b. Microbial challenge:
      (1) Storage Conditions: Microbial challenge studies of above formulations were set up with 5 microorganisms and stored for 28 days at 20-25° C., per USP <51> Eighth Supplement.
      (2) Microorganisms: After a sufficient quantity of each formulation is prepared, aliquots were inoculated with 5 microorganisms at a concentration of at least 10^5 microorganisms/cc:

(a) *Escherichia coli*, ATCC 8739

(b) *Pseudomonas aeruginosa*, ATCC 9027

(c) *Staphylococcus aureus*, ATCC 6538

(d) *Aspergillus niger*, ATCC 18404

(e) *Candida albicans*, ATCC 10231

(3) Time Points: A determination of the viable cell concentration in each inoculated container was performed after 0, 1, 3, 7, 14, 21 and 28 days.

B. Formulations To Be Prepared From Alternative Salts of Gamma-Hydroxybutyrate: This work may be staged to take place at a later time than the work described above.

TABLE 17

Formulation Detail				
Formulation ID No.	Salt of GHB	Concentration of Salt of GHB	Acidultent	Final pH
9	Calcium salt	500 mg/cc (Or maximum possible*)	Malic Acid (If compatible)	7.5

1. Solubility determination: Little information is available about the solubility of this alternative salt of gamma-hydroxybutyrate and a determination of solubility was done in advance of efforts to prepare formulations for evaluation by stability and microbial challenge. Maximum solubility is evaluated for pH unadjusted soluations and within the pH range desired for this formulation (pH 6.0-8.0). If solubility is limited, the formulation will be changed to accommodate the solubility limitations. The preferred acidulent for this work is Malic acid. If acid is not compatible with the salt, then an alternative acid can be selected.
2. Preparation: Method for preparation of alternative salt formulations:
   a. The previously described method (Part A) is used for preparation of formulations of calcium gamma-hydroxybutyrate at the concentrations and specified pH determined by solubility experiments.
   b. The final solutions were filtered through 10 μm filters and dispensed into 5 amber PET bottles with closures (provided by Orphan Medical, Inc.). Two bottles are used for microbial challenge studies and two bottles are placed on limited stability. The remaining bottles are retained for any additional studies at a future time.
3. Testing: Formulations are tested as described above.

C. Reporting of Results: The results will be reported for the Stability and Microbial Challenge results in standard format as defined by the described Orphan Medical Development. Copies of HPLC chromatograms and any raw data from these studies will be provided with results.

D. Acceptance Criteria: Specific acceptance criteria for this study can be described analogous to those for sodium oxybate.

Results: Summarized as follows in Tables 18, 19 and 20 for various studies.

TABLE 18

Result Summary
Results of Protocol 98126 Microbial Challenge Study

	0	Day 1	Day 7	Day 14	Day 21	Day 28
Lot Number MCH1064-33 GHB, pH 7.50, 500 mg/cc Malic Acid						
E. coli	490,000	5,500	<100	<10	<10	<10
P. aeruginosa	141,000	21,600	<100	<10	<10	<10
S. aureus	1,035,000	405,000	79,500	8,300	1,645	375
C. albicans	835,000	147,000	<100	<10	<10	<10
A. niger	370,000	285,000	120,500	246,500	148,500	183,000
Lot Number MCH1064-35 GHB, pH 7.50, 250 mg/cc Malic Acid						
E. coli	705,000	229,500	<100	<10	<10	<10
P. aeruginosa	224,500	5,200	<100	<10	<10	<10
S. aureus	1,135,000	390,000	262,500	31,500	4,250	155
C. albicans	705,000	435,000	52,000	850	<10	<10
A. niger	510,000	515,000	155,500	176,000	147,500	184,000
Lot Number MCH1064-37 GHB, pH 7.50, 350 mg/cc Malic Acid						
E. coli	365,000	310,000	13,400	<10	<10	<10
P. aeruginosa	205,000	15,600	50	<10	<10	<10
S. aureus	1,170,500	605,000	67,500	<60	60	<10
C. albicans	870,000	355,000	8,300	<10	<10	<10
A. niger	540,000	525,000	172,000	155,500	155,500	163,500
Lot Number MCH1064-43 GHB, pH 7.50, 550 mg/cc Malic Acid						
E. coli	425,000	63,500	700	<10	<10	<10
P. aeruginosa	171,500	211,550	250	<10	<10	<10

TABLE 18-continued

Result Summary
Results of Protocol 98126 Microbial Challenge Study

	0	Day 1	Day 7	Day 14	Day 21	Day 28
S. aureus	1,020,000	520,000	41,500	1,050	180	10
C. albicans	880,000	157,500	800	<10	<10	<10
A. niger	545,000	505,000	131,000	156,500	205,000	187,500
Lot Number MCH1064-45 GHB, pH 7.50, 550 mg/cc Malic Acid						
E. coli	660,000	58,500	450	<10	<10	<10
P. aeruginosa	896,000	14,450	900	<10	<10	<10
S. aureus	860,000	132,000	19,750	935	110	45
C. albicans	1,125,000	166,000	<100	<10	<10	<10
A. niger	530,000	530,000	105,500	153,000	157,500	177,000
Lot Number MCH1046-47 GHB, pH 7.50, 650 mg/cc Malic Acid						
E. coli	630,000	119,000	1,350	<10	<10	<10
P. aeruginosa	183,500	5,900	50	<10	<10	<10
S. aureus	890,000	650,000	76,000	14,550	510	1,150
C. albicans	675,000	145,500	<100	<10	<10	<10
A. niger	535,000	385,000	103,000	162,000	187,000	173,000
Lot Number MCH1064-85 Ca-Oxybate, pH 7.50, 500 mg/cc Malic Acid						
E. coli	425,000	121,000	1,650	<10	<10	<10
P. aeruginosa	420,000	22,000	300	<10	<10	<10
S. aureus	265,000	2,000	<100	<10	<10	<10
C. albicans	565,000	440,000	29,500	<1000	<10	<10
A. niger	1,310,000	965,000	370,000	640,000	690,000	675,000
Lot Number MCH1064-49 GHB, pH 7.50, 500 mg/cc Citric Acid						
E. coli	615,000	6,500	<100	<10	<10	<10
P. aeruginosa	69,500	14,600	<100	<10	<10	<10
S. aereus	650,000	305,000	1,700	<10	<10	<10
C. albicans	720,000	107,000	<100	<10	<10	<10
A. niger	375,000	380,000	99,500	178,500	212,500	165,500

TABLE 19

Result Summary
Data from Dec. 30, 1997

	(n = 3) Inoculu	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Results
GHB (pH 7.5) 750 mg/cc									
E. coli	470,000	160,000	64,500	4,300	420	<10	<10	<10	
P. aeruginos	437,500	152,000	3,500	10	<10	<10	<10	<10	
S. aureus	447,500	330,000	24,500	42,000	8,050	1,935	15	10	
C. albicans	375,000	234,500	28,000	1,950	<10	<10	10	<10	
A. niger	475,500	395,000	395,000	229,000	101,500	161,500	101,000	202,000	
750 mg/cc + 0.2% MP/PP, pH 7.50									
E. coli	470,000	127,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginos	437,500	61,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	350,000	3,000	4,050	<10	<10	<10	<10	
C. albicans	375,000	103,500	<1,000	<10	<10	<10	<10	<10	
A. niger	457,500	315,000	415,000	35,500	79,500	38,500	87,500	6,400	
750 mg/cc + 0.1% MP/PP,									

TABLE 19-continued

	Result Summary Data from Dec. 30, 1997								
	(n = 3) Inoculu	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Results
pH 7.5									
E. coli	470,000	157,000	7,000	<10	<10	<10	<10	<10	
P. aeruginos	437,500	90,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	239,000	5,500	16,950	600	<10	<10	<10	
C. albicans	375,000	169,000	<1,000	<100	<10	<10	<10	<10	
A. niger	457,500	335,000	425,000	34,500	168,500	90,500	95,500	99,000	
750 mg/cc + 0.2% Potassium sorbate, pH 7.5									
E. coli	470,000	180,000	735,000	6,200	475	<10	<10	<10	
P. aeruginos	437,500	152,000	1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	264,000	27,500	49,800	14,550	2,370	<10	<10	
C. albicans	375,000	300,000	41,500	3,800	<10	<10	<10	<100	
A. niger	457,500	325,000	360,000	25,000	202,000	500,000	345,000	425,000	
GHB (pH 6.0) 500 mg/cc									
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10	
P. aeruginosa	437,500	172,000	3,000	<10	<10	<10	<10	<10	
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10	
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10	
A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600	PASS
500 mg/cc + 0.2% MP/PP, pH 6.0									
E. coli	470,000	163,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	60,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	243,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	150,500	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	400,000	38,000	<10	<10	<10	<10	<10	PASS
500 mg/cc + 0.1% MP/PP, pH 6.0									
E. coli	470,000	206,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	118,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	330,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	221,000	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	355,000	93,500	59,000	8,700	315	35	<10	PASS
500 mg/cc + 0.2% Potassium sorbate, pH 6.0									
E. coli	470,000	222,000	46,500	150	<10	<10	<10	<10	
P. aeruginosa	437,500	136,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	410,000	<1,000	130	<10	<10	<10	<10	
C. albicans	375,000	395,000	28,500	<100	<10	<10	<10	<10	
A. niger	475,500	405,000	270,000	63,000	51,000	49,500	39,000	11,150	PASS

TABLE 20

	Result Summary							
	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
	Data from Study Dated Dec. 30, 1997							
GHB (pH 6.0) 500 mg/cc								
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10
P. aeruginosa	437,500	172,000	3,000	<10	<10	<10	<10	<10
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10

TABLE 20-continued

	Result Summary							
	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10
A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600
	Data From Study Begun Mar. 12, 1998							
GHB (pH 6.0) 500 mg/cc								
E. coli	500,000	370,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	198,500	nd	nd	<100	<10	<10	<10
S. aureus	280,000	480,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	340,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	445,000	nd	nd	9,050	20,500	9,450	1,120
GHB (pH 6.0) 500 mg/cc								
E. coli	500,000	199,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	192,500	nd	nd	<100	<10	<10	<10
S. aureus	280,000	300,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	370,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	445,000	nd	nd	10,100	22,750	3,800	4,050
GHB (pH 9.0) 500 mg/cc								
E. coli	500,000	320,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	12,000	nd	nd	<100	<10	<10	<10
S. aureus	280,000	530,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	510,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	345,000	nd	nd	13,800	158,500	315,000	110,500
GHB (pH 9.0) 500 mg/cc								
E. coli	500,000	305,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	20,000	nd	nd	<100	<10	<10	<10
S. aureus	280,000	495,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	380,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	355,000	nd	nd	12,550	157,500	365,000	365,000
GHB (pH 6.0 + Excipients) 500 mg/cc								
E. coli	500,000	96,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	26,000	nd	nd	<100	<10	<10	<10
S. aureus	280,000	155,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	205,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	131,500	nd	nd	6,250	1,825	870	370
GHB (pH 6.0 + Excipients) 500 mg/cc								
E. coli	500,000	93,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	30,500	nd	nd	<100	<10	<10	<10
S. aureus	280,000	185,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	135,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	121,500	nd	nd	5,400	1,785	795	505

TABLE 21

Result Summary

GHB (pH 7.50)	Initial	Jul. 2, 1998 Start Date						
500 mg/cc	Conc	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
	HCl							
E. coli	97000	82000	19200	nd	1000	<10	<10	<10
P. aeruginosa	48500	29500	520	nd	<10	<10	<10	<10
S. aureus	54500	58000	42350	nd	4950	245	<10	<10
C. albicans	58500	38500	1060	nd	<100	<10	<10	<10
A. niger	77500	48000	21450	nd	46000	46000	38000	54000
	Malic Acid							
E. coli	97000	83000	44450	nd	3050	70	<10	<10
P. aeruginosa	48500	15650	545	nd	<10	<10	<10	<10
S. aureus	54500	59500	48400	nd	17400	6500	820	505
C. albicans	58500	44000	6200	nd	500	<10	<10	<10
A. niger	77500	35500	24100	nd	28000	49000	44500	44000

GHB (pH 7.50)	Initial	Jul. 2, 1998 Start Date						
500 mg/cc	Co	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
	HCl							
E. coli	9.70E+04	8.20E+04	1.92E+04	nd	1.00E+03	<10	<10	<10
P. aeruginosa	4.85E+04	2.95E+04	5.20E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.80E+04	4.24E+04	nd	4.95E+03	2.45E+02	<10	<10
C. albicans	5.85E+04	3.85E+04	1.06E+03	nd	<100	<10	<10	<10
A. niger	7.75E+04	4.80E+04	2.15E+04	nd	4.60E+04	4.60E+04	3.80E+04	5.40E+04
	Malic Acid							
E. coli	9.70E+04	8.30E+04	4.45E+04	nd	3.05E+03	7.00E+01	<10	<10
P. aeruginosa	4.85E+04	1.57E+04	5.45E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.95E+04	4.84E+04	nd	1.74E+04	6.50E+03	8.20E+02	5.05E+02
C. albicans	5.85E+04	4.40E+04	6.20E+03	nd	5.00E+02	<10	<10	<10
A. niger	7.75E+04	3.55E+04	2.41E+04	nd	2.80E+04	4.90E+04	4.45E+04	4.40E+04

For Category 1C Products:
Bacteria: Not less that 1 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days.
Yeast and Molds: No increase from the initial calculated count at 14 and 28 days.

TABLE 22

pH Variable Result Summary

	Inoculum	0	Day 14	Day 28
GHB, pH 7.5 750 mg/cc Dec. 30, 1997				
E. coli	470,000	160,000	<10	<10
P. aeruginosa	437,500	152,000	<10	<10
S. aureus	447,500	330,000	1,935	10
C. albicans	375,000	234,500	<10	<10
A. niger	475,500	395,000	161,500	202,000
GHB, pH 7.5 750 mg/cc + 0.2% MP/PP Dec. 30, 1997				
E. coli	470,000	127,000	<10	<10
P. aeruginosa	437,500	61,000	<10	<10
S. aureus	447,500	350,000	<10	<10
C. albicans	375,000	103,500	<10	<10
A. niger	457,500	315,000	38,500	6,400
GHB, pH 7.5 750 mg/cc + 0.1% MP/PP				
E. coli	470,000	157,000	<10	<10
P. aeruginosa	437,500	90,000	<10	<10
S. aureus	447,500	239,000	<10	<10

TABLE 22-continued

pH Variable Result Summary

	Inoculum	0	Day 14	Day 28
C. albicans	375,000	169,000	<10	<10
A. niger	457,500	335,000	90,500	99,000
GHB, pH 7.5 750 mg/cc + 0.2% Potassium sorbate	xxxxx x			
E. coli				
P. aeruginosa				
S. aureus				
C. albicans				
A. niger				
GHB, pH 6.0 500 mg/cc + 0.2% Potassium sorbate Dec. 30, 1997				
E. coli	470,000	222,000	<10	<10
P. aeruginosa	437,500	136,000	<10	<10
S. aureus	447,500	410,000	<10	<10

TABLE 22-continued

	pH Variable Result Summary			
	Inoculum	0	Day 14	Day 28
C. albicans	375,000	395,000	<10	<10
A. niger	475,500	405,000	49,500	11,150
GHB, pH 6.0 500 mg/cc + Excipients Mar. 12, 1998				
E. coli	500,000	93,000	<10	<10
P. aeruginosa	350,000	30,500	<10	<10
S. aureus	280,000	185,000	<10	<10
C. albicans	450,000	135,000	<10	<10
A. niger	450,000	121,500	1,785	505
GHB, pH 9.0 500 mg/cc Mar. 12, 1998				
E. coli	500,000	320,000	<10	<10
P. aeruginosa	350,000	12,000	<10	<10
S. aureus	280,000	530,000	<10	<10
C. albicans	450,000	510,000	<10	<10
A. niger	450,000	345,000	158,500	110,500
GHB, pH 9.0 500 mg/cc Mar. 12, 1998				
E. coli	500,000	305,000	<10	<10
P. aeruginosa	350,000	20,000	<10	<10
S. aureus	280,000	495,000	<10	<10
C. albicans	450,000	380,000	<10	<10
A. niger	450,000	355,000	157,500	365,000
GHB, pH 6.0 500 mg/cc Dec. 30, 1997				
E. coli	470,000	221,000	<10	<10
P. aeruginosa	437,500	172,000	<10	<10
S. aureus	447,500	320,000	<10	<10
C. albicans	375,000	310,000	<10	<10
A. niger	475,500	270,000	48,500	8,600
GHB, pH 6.0 500 mg/cc + 0.2% MP/PP Dec. 30, 1997				
E. coli	470,000	163,000	<10	<10
P. aeruginosa	437,500	60,000	<10	<10
S. aureus	447,500	243,000	<10	<10
C. albicans	375,000	150,500	<10	<10
A. niger	475,500	400,000	<10	<10
GHB, pH 6.0 500 mg/cc + 0.1% MP/PP Dec. 30, 1997				
E. coli	470,000	206,000	<10	<10
P. aeruginosa	437,500	118,000	<10	<10
S. aureus	447,500	330,000	<10	<10

TABLE 22-continued

	pH Variable Result Summary			
	Inoculum	0	Day 14	Day 28
C. albicans	375,000	221,000	<10	<10
A. niger	475,500	355,000	315	<10
GHB, pH 6.0 500 mg/cc Mar. 12, 1998				
E. coli				
P. aeruginosa				
S. aureus				
C. albicans				
A. niger				
GHB, pH 6.0 500 mg/cc Mar. 12, 1998				
E. coli	500,000	199,000	<10	<10
P. aeruginosa	350,000	192,500	<10	<10
S. aureus	280,000	300,000	<10	<10
C. albicans	450,000	370,000	<10	<10
A. niger	450,000	445,000	22,750	4,050
GHB, pH 6.0 500 mg/cc + Excipients Mar. 12, 1998				
E. coli	500,000	96,000	<10	<10
P. aeruginosa	350,000	26,000	<10	<10
S. aureus	280,000	155,000	<10	<10
C. albicans	450,000	205,000	<10	<10
A. niger	450,000	131,500	1,825	370
GHB, pH 7.50 500 mg/cc, HCl Jul. 2, 1998				
E. coli	97000	82000	<10	<10
P. aeruginosa	48500	29500	<10	<10
S. aureus	54500	58000	245	<10
C. albicans	58500	38500	<10	<10
A. niger	77500	48000	46000	54,000
GHB, pH 7.5 500 mg/cc, Malic Acid Jul. 2, 1998				
E. coli	97000	83000	70	<10
P. aeruginosa	48500	15650	<10	<10
S. aureus	54500	59500	6500	505
C. albicans	58500	44000	<10	<10
A. niger	77500	35500	49000	44,000

Short term stability testing was carried out as described in Appendix A and results are summarized in—Results of Limited Stability Testing—Xyrem oral solution—are show as follows:

TABLE 23-A

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO.: 333198

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	512 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.068%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.021%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.02%	NPLC-793D
		RRT 3.79: 0.007%	
PH	Report	7.6	USP <791>
Challenge Test	Conforms to USP	Conforms	USP 23 <51> S.8
	(0, 1, 7, 14, 21, 28 days)		

COMMENTS:
Initial test
Formulation 1: 500 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328841

TABLE 23-B

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO.: 331347

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	510 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.36%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.23%	NPLC-793D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.1%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 days (25° C., 60% RH)
Formulation 1: 500 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.02%
RRT 3.93: 0.008%

TABLE 23-C

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO.: 333197

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	258 mg/ml (103%)	NPLC-793-D
Impurities total	≦2.0%	0.045%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.016%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.79: 0.009%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 2: 250 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328845

TABLE 23-D

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO.: 331346

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	256 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.18%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.13%	NPLC-793D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.03%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 2: 250 mg/cc; Malic acid; pH 7.5
*A: RRT 1.29: 0.007%
RRT 3.93: 0.008%

TABLE 23-E

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO.: 333196

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	360 mg/ml (103%)	NPLC-793
Impurities total	≦2.0%	0.050%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.017%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.006%	NPLC-793D
		RRT 3.79: 0.007%	
PH	Report	7.7	USP <791>
Challenge test	Conforms to USP	Conforms	USP 23 <51> S.8
	(0, 1, 7, 14, 21, 28 days)		

COMMENTS:

Initial test

Formulation 3: 350 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328847

TABLE 23-F

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO.: 331345

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULTAT/RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	363 mg/ml (104%)	NPLC-793-D
Impurities total	≦2.0%	0.21%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.14%	NPLC-793D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.05%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	8.0	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 3: 350 mg/cc; Malic acid; pH 7.5
*A: RRT 1.29: 0.009%
RRT 3.93: 0.008%

TABLE 23-G

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO.: 333195

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE: 1741
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	461 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.065%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.018%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.02%	NPLC-793D
		RRT 3.79: 0.007%	
PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 4: 450 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328875

TABLE 23-H

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO.: 331343

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	454 mg/ml (101%)	NPLC-793-D
Impurities total	≦2.0%	0.40%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.26%	NPLC-793D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.1%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 4: 450 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.03%
RRT 3.93: 0.008%

TABLE 23-I

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO.: 333194

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	563 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.077%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.020%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.29: 0.03%	NPLC-793D
		RRT 3.79: 0.007%	
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 5: 550 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328883

TABLE 23-J

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO.: 331341

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	561 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.56%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.31%	NPLC-793D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.2%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 5: 550 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.04%
RRT 3.93: 0.007%

TABLE 23-K

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO.: 333193

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	666 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.10%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.025%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.05%	NPLC-793D
		RRT 3.78: 0.007%	
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 6: 650 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328885

TABLE 23-L

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO.: 331336

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	660 mg/ml (102%)	NPLC-764
Impurities total	≦2.0%	0.81%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.43%	NPLC-793D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.3%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 6: 650 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.07%
RRT 3.93: 0.007%

TABLE 23-M

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO.: 333192

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	518 mg/ml (104%)	NPLC-793
Impurities total	≦2.0%	0.065%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.018%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.79: 0.007%	NPLC-793D
		RRT 5.99: 0.02%	
PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 7: 500 mg/cc; Citric acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 329033

TABLE 23-N

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO.: 331335

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	515 mg/ml (103%)	NPLC-793-D
Impurities total	≦2.0%	0.38%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.27%	NPLC-793D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.1%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.93: 0.007%	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 7: 500 mg/cc; Citric acid; pH 7.5

TABLE 23-O

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 09 Feb. 1999
NO.: 330721

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC

TABLE 23-O-continued

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 09 Feb. 1999
NO.: 330721

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Challenge Test	Conforms to USP (0, 1, 7, 14, 21 and 28 days)	Conforms	USP 23 <51> S.8
Potency	Report	501 mg/ml (100%)	NPLC-793
Impurities total	≦2.0%	1.2%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
Impurities specified	Gamma-Butyrolactone Report:	RRT 1.46: 0.013%	NPLC-793D
PH	Report	7.3	USP <791>
Solubility study	Report	*B	PR 98126 IIA

COMMENTS:
Initial test
500 mg/ml cc; Malic acid; pH 7.5
*A: RRT 1.31: 0.02% RRT 1.67: 0.008%
RRT 1.91: Interference with peak of dilution solvent cannot calculate.
RRT 3.47: 0.1% RRT 3.79: 0.009% RRT 3.84: 0.01%
RRT 4.18: 0.06% RRT 5.10: 0.008% RRT 5.35: 0.02%
RRT 6.74: 0.9% RRT 6.90: 0.08% RRT 7.41: 0.006%
*B: Maximum solubility: 700 mg/ml no pH adjustment.

TABLE 23-P

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Feb. 1999
NO.: 331307

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM LIQUID FORM.
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	508 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.70%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
Impurities specified	Gamma-Butyrolactone Report:	RRT 1.37: 0.054%	NPLC-793D
PH	Report	7.6	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
500 mg/cc; Malic acid; pH 7.5
*A: RRT 1.17: 0.03% RRT 3.47: 0.2%
RRT 5.46: 0.01% RRT 6.87: 0.3%
RRT 7.04: 0.007%
RRT 1.78: Can not calculate because it interfere with a dilution solvant peak.

This report summarizes the results of the above described study and provides a summary of previous development work which evaluated conditions other than those evaluated in this study. The purposes of this information is to define the scope and limitations of the self-preserving properties of Xyrem® oral solution for completion of patent application.

II. Summary of Results

A. Preparation of Various Formulations of Sodium Oxybate and Formulations Using an Alternative Salt of GHB.

1. Various formulations of sodium oxybate were prepared as directed in the above Protocol. Sodium oxybate, 500 mg/cc with Malic Acid was not soluble at pH 5.0, and further evaluation of this solution was discontinued. All other solutions were successfully prepared as described.
2. The preparation of an alternative salt of gamma-hydroxybutyrate was described as the calcium salt, prepared at 500 mg/cc (or maximum possible) with Malic Acid at pH 7.5.
   a. The calcium salt of gamma-hydroxybutyrate was prepared by Toronto Research and shipped to NeoPharm for determination of solubility and evaluation according to the Protocol. The absolute limit of

solubility, without pH adjustment, was determined to be 700 mg/cc. The pH of this solution was 8.4. Solutions of lower pH were more difficult to prepare at 500 mg/cc using Malic acid as acidulant. When pH was adjusted to 6.0 with Malic acid, the solubility of the calcium oxybate was limited (longer stirring required to solubilize). The desired solution of 500 mg/cc, pH 7.5 was prepared with Malic acid as acidulant without difficulty. Appearance of the final solution was slightly yellow in color. Copies of the laboratory record for preparation of these solutions is available.

B. Microbial Challenge Testing of the Various Formulations Parepared by MDS NeoPharm.

The microbial challenge testing was carried as specified in the Protocol and the following table summarizes the results of microbial challenge testing of various formulations of sodium oxybate and the single calcium oxybate formulation prepared.

TABLE 24

Testing of Sodium and Calcium GHB Salts

		pH of Solution	Microbial Challenge Result
Sodium Oxybate Concentration			
1.	500 mg/cc	7.5 (Malic acid)	Pass
2.	250 mg/cc	7.5 (Malic acid)	Pass
3.	350 mg/cc	7.5 (Malic acid)	Pass
4.	450 mg/cc	7.5 (Malic acid)	Pass
5.	550 mg/cc	7.5 (Malic acid)	Pass
6.	650 mg/cc	7.5 (Malic acid)	Pass
7.	500 mg/cc	7.5 (Citric acid)	Pass
Calcium Oxybate Conctration			
	500 mg/cc	7.5	Pass

C. Short Term Stability Evaluation of Various Formulations of Sodium Oxybate and a Formulation of Calcium Oxybate.

Solutions were tested on day zero (preparation day) and day 28 according to the described Protocol. The results of the stability evaluation are summarized in Table 25 below:

TABLE 25

Sodium and Calcium GHB Evaluation

Sodium oxybate solution	Potency mg/cc (%)	Impurities (Total)	Impurities (Unspecified)	Impurities (Specified - GLB)	pH
500 mg/cc pH 7.5 Malic Acid Day 0	512 mg/cc (102%)	0.68%	0.041%	0.027%	7.6
Day 28	510 mg/cc (103%)	0.36%	0.33%	0.028%	7.9
250 mg/cc pH 7.5 Malic Acid Day 0	258 mg/cc (103%)	0.045%	0.009%	0.026%	7.6
Day 28	256 mg/cc (102%)	0.18%	0.015%	0.16%	7.9
350 mg/cc pH 7.5 Malic Acid	360 mg/cc (103%)	0.050%	0.013%	0.037%	7.7

TABLE 25-continued

Sodium and Calcium GHB Evaluation

Sodium oxybate solution	Potency mg/cc (%)	Impurities (Total)	Impurities (Unspecified)	Impurities (Specified - GLB)	pH
Day 0					
Day 28	363 mg/cc (104%)	0.21%	0.017%	0.19%	8.0
450 mg/cc pH 7.5 Malic Acid Day 0	461 mg/cc (102%)	0.065%	0.027%	0.038%	7.5
Day 28	454 mg/cc (101%)	0.40%	0.038%	0.36%	7.8
550 mg/cc pH 7.5 Malic Acid Day 0	563 mg/cc (102%)	0.077%	0.037%	0.040%	7.6
Day 28	561 mg/cc (102%)	0.56%	0.047%	0.51%	7.9
650 mg/cc pH 7.5 Malic Acid Day 0	666 mg/cc (102%)	0.10%	0.057%	0.045%	7.6
Day 28	660 mg/cc (102%)	0.81%	0.077%	0.73%	7.8
500 mg/cc pH 7.5 Citric Acid Day 0	518 mg/cc (104%)	0.065%	0.027%	0.038%	7.5
Day 28	515 mg/cc (103%)	0.38%	0.007%	0.37%	7.9
500 mg/cc pH 7.5 Malic Acid Day 0	501 mg/cc (100%)	1.2%	>0.1% (See C of A Attached)	0.013%	7.3
Day 28	508 mg/cc (102%)	0.70%	>0.1% (See C of A)	0.054%	7.6

D. Summary of Pertinent Solubility and Microbial Challenge Data are Shown in Tables 26 and 27.

TABLE 26

Limits of Solubility

Maximum Solubility	pH of Solution	Comments
Sodium oxybate		
450 mg/cc	pH 4 (HCl)	25°
500 mg/cc	pH 5 (HCl)	25°
600 mg/cc	pH 6 (HCl)	25°
750 mg/cc	pH 6.8 (HCl)	25°
750 mg/cc +	pH 10.3	25°
1000 mg/cc	pH (unadjusted)	65° Soluble, 25° Gel
Calsium oxybate		
700 mg/cc	pH 8.4 (unadjusted)	25°
500 mg/cc	pH 6.0	25°

TABLE 27

Microbial Challenge Results		
	pH of Solution	Microbial Challenge Result
Sodium oxybate Concentration (Date)		
750 mg/cc (Dec. 1997)	7.5 (HCl)	pass
500 mg/cc (Dec. 1997)	6.0 (HCl)	pass
500 mg/cc + Excipients (Xylitol) (March 1998)	6.0 (Malic Acid)	pass
500 mg/cc (March 1998)	9.0 (HCl)	pass (Borderline *aspergillus*)
150 mg/cc (BDL 1995)	5.0 (HCl)	fail (*aspergillus* only)
150 mg/cc (BDL 1995)	7.0 (HCl)	fail (*aspergillus* and *staph*)
150 mg/cc (BDL 1995)	3.0 (HCl)	fail (*aspergillus* only)
150 mg/cc (BDL 1995)	10.3 (unadjusted)	fail (*aspergillus* and *staph*)
500 mg/cc (May 1998)	6.0 (Malic Acid)	discontinued
500 mg/cc (May 1998)	7.5 (Malic Acid)	pass
500 mg/cc (May 1998)	9.0 (Malic Acid)	discontinued
500 mg/cc (May 1998)	7.5 (HCl)	pass
500 mg/cc	7.5 (Malic Acid)	pass
250 mg/cc	7.5 (Malic Acid)	pass
350 mg/cc	7.5 (Malic Acid)	pass
450 mg/cc	7.5 (Malic Acid)	pass
550 mg/cc	7.5 (Malic Acid)	pass
650 mg/cc	7.5 (Malic Acid)	pass
500 mg/cc	7.5 (Citric Acid)	pass
Calcium oxybate Concentration (Date)		
500 mg/cc	7.5 (Malic Acid)	pass

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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Yamada et al., 1967.

What is claimed is:

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.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,262,219 B2
APPLICATION NO. : 10/841709
DATED : August 28, 2007
INVENTOR(S) : Cook et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 10, line 33, delete "4.3,.about" and insert -- 4.3, about --, therefor.

In column 17, line 36, delete "preparations.may" and insert -- preparations may --, therefor.

In column 17, line 46, after "phosphate;" delete "sa" and insert -- a --, therefor.

In column 28, line 5, delete "I" and insert -- 1 --, therefor.

In column 33, lines 9–10, delete "constricted" and insert -- constructed --, therefor.

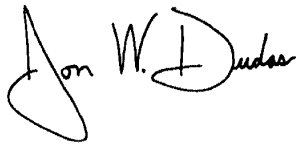
In column 34, line 54, delete "GH1B" and insert -- GHB --, therefor.

In column 40, line 35, delete "(250)" and insert -- (25°) --, therefor.

In column 72, line 63, delete "Calsium" and insert -- Calcium --, therefor.

Signed and Sealed this

Nineteenth Day of August, 2008



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT D

US007851506B2

(12) **United States Patent**
Cook et al.

(10) **Patent No.: US 7,851,506 B2**
(45) **Date of Patent: Dec. 14, 2010**

(54) **MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY**

(75) Inventors: **Harry Cook**, Eden Prairie, MN (US); **Martha Hamilton**, St. Paul, MN (US); **Douglas Danielson**, Otsego, MI (US); **Colette Goderstad**, St. Paul, MN (US); **Dayton Reardan**, Excelsior, MN (US)

(73) Assignee: **Jazz Pharmaceuticals, Inc.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **11/777,877**

(22) Filed: **Jul. 13, 2007**

(65) **Prior Publication Data**

US 2007/0270491 A1 Nov. 22, 2007

Related U.S. Application Data

(62) Division of application No. 10/841,709, filed on May 7, 2004, now Pat. No. 7,262,219, which is a division of application No. 10/194,021, filed on Jul. 11, 2002, now Pat. No. 6,780,889, which is a division of application No. 09/470,570, filed on Dec. 22, 1999, now Pat. No. 6,472,431.

(60) Provisional application No. 60/113,745, filed on Dec. 23, 1998.

(51) **Int. Cl.**
A61K 31/19 (2006.01)

(52) **U.S. Cl.** **514/557**

(58) **Field of Classification Search** 514/557
See application file for complete search history.

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Primary Examiner—Raymond J Henley, III
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg & Woessner, P.A.

(57) **ABSTRACT**

Disclosed are formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial growth. Also disclosed are formulations of gamma-hydroxybutyrate that are also resistant to the conversion into GBL. Disclosed are methods to treat sleep disorders, including narcolepsy, with these stable formulations of GHB. The present invention also provides methods to treat alcohol and opiate withdrawal, reduced levels of growth hormone, increased intracranial pressure, and physical pain in a patient.

3 Claims, 1 Drawing Sheet

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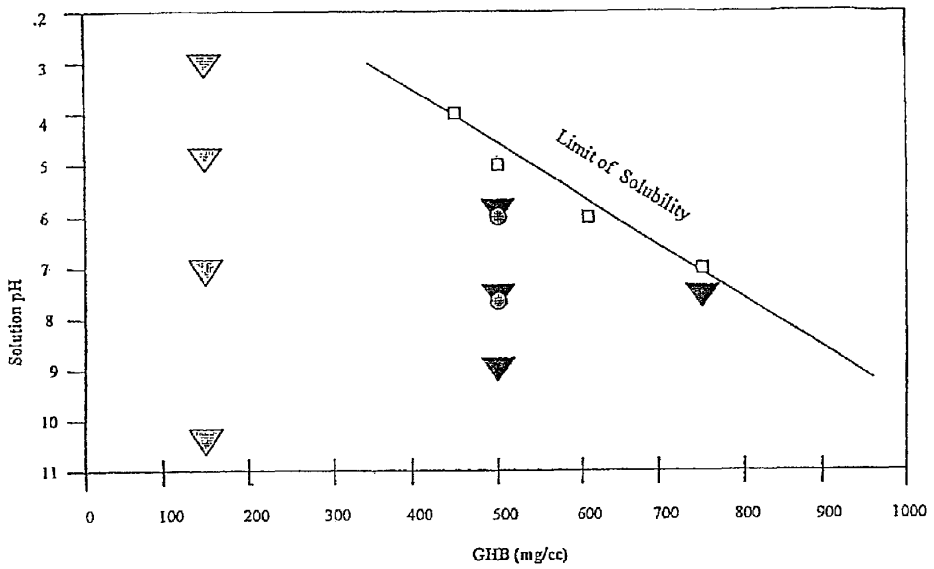
Figure 1.



□ Data points indicating limit of solubility of GHB as a function of concentration and pH, see Table 1.

Solutions susceptible to microbial growth, .designated "Fail".
(All solutions demonstrated activity against Pseudomonas aeruginosa. Some reduction of aspergillus niger mold occurred in 7 days of contact time.)

Solutions resistant to microbial growth, designated "Pass". (Rate of reduction of microorganism counts was slightly higher at pH 7.5 and 6.0 than pH 9.0. The rate of reduction of formulations at 750mg/cc GHB were slightly lower than formulations at 500 mg/cc GHB.)

Solutions resistant to microbial growth, designated "Pass". Results were similar for Malic Acid and HCl. Taste variations has implications for development of flavor systems.

Indicates pH adjustment with HCl.

Indicates pH adjustment with Malic Acid.

Note: Solutions with pH at 9.0 are not palatable or safe for oral consumption.

MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY

RELATED APPLICATIONS

This application is a divisional of U.S. application Ser. No. 10/841,709, filed on May 7, 2004 now U.S. Pat. No. 7,262,219, which is a divisional of U.S. patent application Ser. No. 10/194,021, filed Jul. 11, 2002 now U.S. Pat. No. 6,780,889, which is a divisional of U.S. patent application Ser. No. 09/470,570, filed Dec. 22, 1999 now U.S. Pat. No. 6,472,431, which claims priority from U.S. Provisional Patent Application Ser. No. 60/113,745, filed Dec. 23, 1998. These applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention relates generally to the fields of pharmaceutical compositions to be used in treatments, such as, sleeping disorders, such as, e.g., narcolepsy (particularly cataplexy), drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or for an increased level of intracranial pressure or the like. The present 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, e.g.

II. Description of Related Art

GHB is an endogenous compound with hypnotic properties that is found in many human body tissues. GHB is present, for example, in the mammalian brain and other tissues. In brain the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter (Snead and Morley, 1981). The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB is converted to succinate and then metabolized via the Krebs cycle. Clinical trials have shown that GHB increases delta sleep and improves the continuity of sleep (Ladinsky et al., 1983; Anden and Stock, 1973; Stock et al., 1973; Laborit, 1973; Lapierre et al., 1988; Lapierre et al., 1990; Yamda et al., 1967; Grove-White and Kelman, 1971; Scharf, 1985).

GHB has typically been administered in clinical trials as an oral solution (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993). GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e. daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency (Mamelak et al, 1973; Yamada et al., 1967; Bedard et al., 1989), reduces sleep apnea (Series et al, 1992; Scrima et al., 1987), and improves general anesthesia (Hasenbos and Gielen, 1985).

GHB has several clinical applications other than narcolepsy and sleep disorders. GHB has been reported to reduce alcohol craving, the number of daily drinks consumed, and the symptoms of alcohol withdrawal in patients (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992). GHB has been used to decrease the symptoms of opiate withdrawal, including both heroin and methadone withdrawal (Gallimberti et al, 1994; Gallimberti et al., 1993). It has analgesic effects that make it suitable as a pain reliever (U.S. Pat. No. 4,393,236). Intravenous administration of GHB has been reported to reduce intracranial pressure in patients (Strong, A. 1984). Also, administration of GHB was reported to increase growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970).

A good safety profile for GHB consumption, when used long term for treatment of narcolepsy, has been reported. Patients have been safely treated for many years with GHB without development of tolerance (Scharf, 1985). Clinical laboratory tests carried out periodically on many patients have not indicated organ or other toxicities (Lammers, 1993; Scrima, 1990; Scharf, 1985; Mamelack, 1977; Mamelak, 1979; Gallimberti, 1989; Gallimberti, 1992; Gessa, 1992). The side effects of GHB treatment have been minimal in incidence and degree of severity, though they include sleepwalking, enuresis, headache, nausea and dizziness (Broughton and Mamelak, 1979; Mamelak et al., 1981; Mamelak et al., 1977; Scrima et al., 1989; Scrima et al., 1990; Scharf et al., 1985).

The pharmacokinetics of GHB have been investigated in alcohol dependent patients (Ferrara et al., 1992) and in normal healthy males (Palatini et al., 1993) after oral administration. GHB possesses a rapid onset and short pharmacological effect (Ferrara et al., 1992; Palatine et al., 1993; Lee, C., 1977; van der Bogert; Gallimberti, 1989; Gallimberti, 1992; Lettieri and Fung, 1978; Arena and Fung, 1980; Roth and Giarman, 1966; Vickers, 1969; Lee, 1977). In alcohol dependent patients, GHB absorption into and elimination from the systemic circulation were fast processes. Virtually no unchanged drug could be recovered in the urine. There were preliminary indications that the pharmacokinetics of GHB might be non-linear or dose-dependent (Ferrara et al., 1992). In the healthy volunteers study, the pharmacokinetics of three rising GHB doses (12.5, 25, and 50 mg/kg) were investigated. These findings indicate that both the oral absorption and elimination processes of GHB were capacity-limited though the degree of dose dependency was moderate (Palatini et al., 1993).

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). 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.

SUMMARY OF THE INVENTION

The present invention overcomes deficiencies in the prior art by providing compositions of GHB in an aqueous medium that are resistant to microbial growth. These compositions are also resistant to the uncontrolled degradation of GHB into GBL or other substances. The compositions of the present

invention are stable compositions of GHB that improve shelf-life, and provide a titratable formulation of GHB for easy dose measurement. In addition, the concentrated solutions embodied in this invention reduce shipping and storage requirements and allow patients to carry more drugs for their convenience. The present invention provides methods to treat a number of conditions treatable by GHB, referred to herein as "therapeutic categories." Therapeutic categories for the present invention include, but are not limited to, sleeping disorders, drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders, such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or an increased level of intracranial pressure or other conditions treatable with GHB.

The invention first provides a pharmaceutical composition of GHB rendered chemically stable and/or resistant to microbial growth in an aqueous medium. Preferred GHB salts of the present invention include sodium, ammonium and calcium. As used herein in certain embodiments, "stable" may mean resistant to degradation of GHB into its known or unknown decomposition elements. The level of GBL that is acceptable can be up to 0.1% of the formulation as per the ICH guidelines for shelf-life determination. As used herein in certain embodiments, "resistant to microbial growth" or "resistant to microbial challenge" means that the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days. As used herein in certain embodiments, an "aqueous medium" may mean a liquid comprising more than about 50% water. In certain preferred embodiments, an "aqueous medium" may be a solution, suspension, gel or emulsion of GHB, with a solution of GHB being most preferred. Preferred gels are thixotropic gels. Compositions that are resistant to microbial growth are created by dissolving or mixing GHB in an aqueous medium to a concentration or content of greater than of about 150 mg/ml GHB to the maximal solubility of GHB. The solubility of GHB is up to about 750 mg/ml at room temperature (20° C. to about 25° C.), however, heating the aqueous medium during preparation up to 100° C. will increase GHB solubility to at least about 1000 mg/ml. A preferred concentration or content of GHB is about 500 mg/ml.

The amount of GHB that may be mixed or dissolved into an aqueous medium and still be resistant to microbial growth depends upon the pH of the aqueous medium. In certain embodiments the presence of a preservative may allow the amount of GHB contained in the compositions of the present invention to be increased and still maintain resistance to chemical degradation and/or microbial growth. In one embodiment of the present invention, the pH of the aqueous medium of the pharmaceutical composition is about 3 to about 10.

In a preferred embodiment, the pH of said aqueous medium is about 6 to about 7.5. The pH may be from about 3.0 to about 10.3, namely of about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6; about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0, about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, about 10.0, about 10.1, about 10.2, or about 10.3, and all pH values between each of the listed pH values, of the aqueous media. This will produce a GHB composition that is resistant to microbial growth as defined by the test described herein. As used herein, the term "about" generally means within about 10-20%.

These pH values will produce compositions resistant to microbial growth in an aqueous medium if the amount of GHB added, admixed, or dissolved is from above about 150 mg/ml to about 450 mg/ml, namely, above about 150 mg/ml, about 160 mg/ml, about 170 mg/ml, about 180 mg/ml, about 190 mg/ml, about 200 mg/ml, about 210 mg/ml, about 220 mg/ml, about 230 mg/ml, about 240 mg/ml, about 250 mg/ml, about 260 mg/ml, about 270 mg/ml, about 280 mg/ml, about 290 mg/ml, about 300 mg/ml, about 310 mg/ml, about 320 mg/ml, about 330 mg/ml, about 340 mg/ml, about 350 mg/ml, about 360 mg/ml, about 370 mg/ml, about 380 mg/ml, about 390 mg/ml, about 400 mg/ml, about 410 mg/ml, about 420 mg/ml, about 430 mg/ml, about 440 mg/ml, to about 450 mg/ml, and all amounts of GHB between the values listed.

At the medium to high end of the concentration or content of GHB that may be dissolved or mixed in the aqueous medium, the maximal pH that may be used is reduced at room temperature. This is shown in FIG. **1**, a graphical presentation of acceptable formulation ranges. At a concentration or content of about 450 mg/ml GHB, the pH may be of about 3.9 to about 10.3. At a concentration or content of about 500 mg/ml GHB, the pH may be of about 4.75 to about 10.3. At a concentration or content of about 600 mg/ml GHB, the pH may be of about 6.1 to about 10.3. At a concentration or content of about 750 mg/ml GHB, the pH may be of about 7.0 to about 10.3. Of course, all pH and concentration or content values in between each of the listed pH and concentration or content values are encompassed by the invention.

Certain embodiments may be selected as sub-ranges from these values of GHB content and aqueous medium pH. For example, a specific embodiment may be selected as a content of about 170 mg/ml to about 440 mg/ml GHB in an aqueous medium, at a pH range of about pH 5.5 to about pH 8.7. Another example of how a range may be selected in an embodiment would be the selection of a content of about 155 mg/ml of GHB, which is a value between the above listed values, to a content of about 350 mg/ml of GHB, and the selection of a pH range of the aqueous medium, such as a pH range of about 8.87, which is a value between the listed pH values, to a pH of about 8.93, which is another value between the listed values of pH. A third example of ranges that may be selected for a specific embodiment would be selection of a single content or concentration of GHB, such as about 200 mg/ml of GHB, and the selection of a pH range, such as a pH of about 3.5 to about 8.2. A fourth example of ranges that may be selected for a specific embodiment would be selection of a content or concentration of GHB over a range, such as about 300 mg/ml to about 400 mg/ml, and the selection of a single pH value for the aqueous medium, such as a pH of about 3. Another example of a range selected for an embodiment may be the selection of a single content or concentration of GHB, such as 400 mg/ml GHB, and a single pH value of the aqueous medium, such as pH 7.7.

Other examples of how a range of an embodiment of GHB content or concentration may be selected include a range of GHB content or concentration from about 200 mg/ml to about 460 mg/ml GHB, encompassing the ranges for GHB

described herein, and a range of pH for the aqueous medium may be from about pH 4.3 to about pH 7, encompassing ranges for GHB in an aqueous medium at room temperature described herein. Another example would be the selection of a range of GHB content or concentration from about 153 mg/ml to about 750 mg/ml, and a pH range of about 7 to about 9, encompassing ranges between the listed values of GHB content and pH described herein. An example may be the selection as a GHB concentration or content of about 170 mg/ml to about 640 mg/ml in an aqueous medium, at a pH range of about pH 6.5 to about pH 7.7. Another example of how a range may be selected in an embodiment would be a content or concentration of about 185 mg/ml of GHB, which is a value between the listed values, to a content or concentration of about 750 mg/ml of GHB, at a pH range of about 7.87, which is a value between the listed pH values, to a pH of about 8.91, which is another value between the listed values of pH. An additional example of ranges that may be selected for a specific embodiment would be a content or concentration of about 200 mg/ml of GHB at a pH of about 7 to about 8.2. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 750 mg/ml to about 400 mg/ml at a pH of about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 300 mg/ml to about 750 mg/ml at a pH of about 8.5 to about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 400 mg/ml to about 600 mg/ml at a pH of about 9 to about 5.8. And so forth. Thus, all ranges of pH and GHB concentration or content that can be selected from the values herein and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

The chemical stability of GHB is affected by pH, with compositions of GHB in an aqueous medium with a pH below about 6 being less effective in maintaining the chemical stability of GHB. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, all concentrations or content of GHB in an aqueous medium, as described herein, and as would be understood by those of ordinary skill in the art, may be selected to produce compositions of the present invention.

Additionally, the ranges described above are for a composition at room temperature, which is defined herein as from about 20° C. to about 25° C., namely, about 20° C. about 21° C., about 22° C., about 23° C., about 24° C., to about 25° C. Within the values and ranges of pH described above, the ranges of concentration or content of GHB may increase at temperatures greater than room temperature. Thus, the maximal content or concentration of GHB in an aqueous medium at a temperature of from about 26° C. to about 100° C., namely about 26° C., about 27° C., about 28° C., about 29° C., about 30° C., about 31° C., about 32° C., about 33° C., about 34° C., about 35° C., about 36° C., about 37° C., about 38° C., about 39° C., about 40° C., about 41° C., about 42° C., about 43° C., about 44° C., about 45° C., about 46° C., about 47° C., about 48° C., about 49° C., about 50° C., about 51° C., about 52° C., about 53° C., about 54° C., about 55° C., about 56° C., about 57° C., about 58° C., about 59° C., about 60° C., about 61° C., about 62° C., about 63° C., about 64° C., about 65° C., about 66° C., about 67° C., about 68° C., about 69° C., about 70° C., about 71° C., about 72° C., about 73° C., about 74° C., about 75° C., about 76° C., about 77° C., about 78° C., about 79° C., about 80° C., about 81° C., about 82° C., about 83° C., about 84° C., about 85° C., about 86° C., about 87° C., about 88° C., about 89° C., about 90° C., about 91° C., about 92° C., about 93° C., about 94° C., about 95° C., about 96° C., about 97° C., about 98° C., about 99° C., to about 100° C. may be from about 750 to about 1 g/ml, namely to about 751 mg/ml, about 760 mg/ml, about 770 mg/ml, about 780 mg/ml, about 790 mg/ml, about 800 mg/ml, about 810 mg/ml, about 820 mg/ml, about 830 mg/ml, about 840 mg/ml, about 850 mg/ml, about 860 mg/ml, about 870 mg/ml, about 880 mg/ml, about 890 mg/ml, about 900 mg/ml, about 910 mg/ml, about 920 mg/ml, about 930 mg/ml, about 940 mg/ml, about 950 mg/ml, about 960 mg/ml, about 970 mg/ml, about 980 mg/ml, about 990 mg/ml, to about 1000 mg/ml. At temperatures below room temperature, the solubility of GHB may decrease, and compositions at lower temperature and solubility of GHB at the pH values and ranges described herein are also encompassed by the invention. Additionally, differences of atmospheric pressure may also increase or decrease the solubility of GHB within the ranges described, and embodiments of the invention with an increased or decreased content of GHB due to changes in pressure are also encompassed by the invention. Of course, it is understood that the present invention encompasses embodiments of GHB concentration or content in an aqueous medium at higher or lower temperature within the values described herein, such as about 980 mg/ml to about 200 mg/ml at 95° C. GHB at a pH of about 9 to about 7.5. Or about 150 mg/ml GHB at about 17° C. at about pH 6 to about pH 7. And so forth. Thus, all ranges of pH and GHB content that can be selected at various temperatures and pressures from the values above, and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

In certain other embodiments of the present invention, the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids, bases, or combinations thereof. In certain embodiments, the acid may be an organic acid, preferably a carboxylic acid or alphahydroxy carboxylic acid. In certain other embodiments, the acid is selected from the group including, but not limited to, acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like. In a preferred embodiment, the acid is malic or hydrochloric acid. In certain other embodiments, the pH adjusting agent may be a base selected from the group including, but not limited to, acetanilide, ammonia, apomorphine, atropine, benzocaine, caffeine, calcium hydroxide, cocaine, codeine, ephedrine, morphine, papaverine, physostigmine, pilocarpine, potassium bicarbonate, potassium hydroxide, procaine, quinine, reserpine, sodium bicarbonate, sodium dihydrogen phosphate, sodium citrate, sodium taitrate, sodium carbonate, sodium hydroxide, theobromine, thiourea or urea. 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.

In certain embodiments, the composition may contain one or more salts. A "salt" is understood herein to mean certain embodiments to mean a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base. Various salts, includ-

ing salts of GHB, are also encompassed by the invention, particularly as pH adjusting or buffering agents. Pharmaceutically acceptable salts, include inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as malic, acetic, oxalic, tartaric, mandelic, and the like. Salts formed can also be derived from inorganic bases such as, for example, sodium, potassium, silicates, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Alkali metal salts, such as lithium, potassium, sodium, and the like may be used, preferably with an acid to form a pH adjusting agent. Other salts may comprise ammonium, calcium, magnesium and the like. In one embodiment, a salt of GHB comprising an alkali metal may be combined with an acid to create a composition that achieves the desired pH when admixed with an aqueous medium. In another embodiment, a weak base may be combined with GHB to create a composition that achieves the desired pH when admixed with an aqueous solution. Of course, other salts can be formed from compounds disclosed herein, or as would be known to one of ordinary skill in the art, and all such salts are encompassed by the invention.

In certain embodiments, excipients may be added to the invention. An "excipient" as used herein shall mean certain embodiments which are more or less inert substances added as diluents or vehicles or to give form or consistency when the remedy is in a solid form, though they may be contained in liquid form preparations, e.g. syrups, aromatic powders, honey, and various elixirs. Excipients may also enhance resistance to microbial growth, and thus act as a preservative. Such excipients include, but are not limited to, xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, cellulose derivatives, magnesium carbonate and the like.

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, propyl gallate BP, sorbic acid, chlorobutanol, dihydroacetic acid, monothioglycerol, potassium benzoate, propylparaben, benzoic acid, benzalkonium chloride, alcohol, benzoic acid, benzalkonium chloride, benzethonium chloride, benzyl alcohol, butylparaben, cetylpyridinium chloride, ethylenediamine, ethylparaben, ethyl vanillin, glycerin, hypophosphorus acid, methylparaben, phenol, phenylethyl alcohol, phenylmercuric nitrate, propylparaben, sassafras oil, sodium benzoate, sodium propionate, thimerosal and potassium sorbate. Preferred preservatives may be selected from the group comprising, but not limited to, xylitol, sodium benzoate, methylparaben, propylparaben and potassium sorbate. Xylitol is particularly preferred in certain compositions of the invention, because it acts as an preservative and a sweetener, is a caries preventative, is less laxative than other sweeteners, and is recommended for diabetics.

In certain embodiments, the pharmaceutical composition may also contain an antioxidant. An "antioxidant" is understood herein to mean certain embodiments which are substances that inhibits oxidation. Such antioxidants include, but are not limited to, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, potassium metabisulfite, sodium metabisulfite, anoxomer and maleic acid BP.

In certain embodiments, the pharmaceutical composition may also contain a flavoring agent. A "flavoring agent" is understood herein to mean certain embodiments which are substances that alters the flavor of the composition during oral consumption. A type of "flavoring agent" would be a sweetener. Preferred sweeteners or flavoring agents would be microbially non-metabolizable. Especially preferred sweeteners or flavoring agents would be carbohydrates such as xylitol and sorbitol. Such flavoring agents include, but are not limited to, acacia syrup, anethole, anise oil, aromatic elixir, benzaldehyde, benzaldehyde elixir-compound, caraway, caraway oil, cardamom oil, cardamom seed, cardamom spirit, cardamom tincture-compound, cherry juice, cherry syrup, cinnamon, cinnamon oil, cinnamon water, citric acid, citric acid syrup, clove oil, coca, coca syrup, coriander oil, dextrose, eriodictyon, eriodictyon fluidextract, eriodictyon syrup-aromatic, ethyl acetate, ethyl vanillin, fennel oil, ginger, ginger fluidextract, ginger oleoresin, glucose, glycerin, glycyrrhiza, glycyrrhiza elixir, glycyrrhiza extract, glycyrrhiza extract-pure, glycyrrhiza fluidextract, glycyrrhiza syrup, honey, non-alcoholic elixir, lavender oil, citrus extract or oil, lemon oil, lemon tincture, mannitol, methyl salicylate, nutmeg oil, orange-bitter-elixir, orange-bitter-oil, orange flower oil, orange flower water, orange oil, orange peel-bitter, orange-peel-sweet-tincture, orange spirit-compound, compound, orange syrup, peppermint, peppermint oil, peppermint spirit, peppermint water, phenylethyl alcohol, raspberry juice, raspberry syrup, rosemary oil, rose oil, rose water, saccharin, saccharin calcium, saccharin sodium, sarsaparilla syrup, sorbitol solution, spearmint, spearmint oil, sucrose, syrup, thyme oil, tolu balsam, tolu balsam syrup, vanilla, vanilla tincture, vanillin or wild cherry syrup.

Salts, excipients, pH adjusting agents such as acids, bases and buffering agents, flavoring agents, and other agents that may be combined with the compositions of the present invention, or may be used to prepare the compositions of the present invention, are well known in the art, (see for example, "Remington's Pharmaceutical Sciences" 8th and 15th Editions, and Nema et al., 1997, incorporated herein in their entirety), and are encompassed by the invention.

In certain other embodiments, the pharmaceutical composition comprises GHB, a pH adjusting or buffering agent, and an aqueous medium, wherein the components are admixed (sequentially or simultaneously) to prepare said pharmaceutical composition. The pH adjusting or buffering agent and aqueous medium may be any described herein.

The invention also provides a method of preparing a chemically stable and microbial growth-resistant pharmaceutical composition for the treatment of a condition responsive to GHB, comprising admixing GHB and a pH-adjusting or buffering agent in an aqueous medium. In certain embodiments, the method of preparing the pharmaceutical composition further comprises admixing a preservative with the pharmaceutical composition. Other components, such as flavoring agents, salts, and the like, may be added to the composition. The pH adjusting or buffering agent, aqueous medium, preservative, flavoring agents, salts, or other ingredient may be any described herein.

In certain other embodiments, the method of preparing the pharmaceutical composition comprises admixing GHB, a pH adjusting or buffering agent, and an aqueous medium soon before administration to a patient suspected of having a condition responsive to GHB.

The invention also provides a method of treating any therapeutic category of disorder responsive to GHB, comprising administering to a patient suspected of having such a condition a therapeutic amount of a pharmaceutical composition comprising chemically stable GHB (e.g. 1-10 gms.) in an aqueous medium resistant to microbial growth. In certain embodiments, the method of treating a condition responsive to GHB comprises a patient taking a first dosage of from

about 0.1 g to about 10 g, namely about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1-9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0, about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, to about 10 grams of GHB, or as needed by the patient as would be recognized by one of skill in the art. Of course, it will be understood that all values in between those listed, such as 9.45 grams, 6.32 grams, etc. may be administered, and those values are encompassed well. In preferred embodiments, the first dose is administered within an hour of sleep. In preferred embodiments, a second dose of GHB within the values described above may be administered. This second dose is administered preferably within about 2.0 to about 5.0 hrs, namely about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, to about 5.0 hours after the first dose, though it may be administered at a time outside of the preferred range.

In certain embodiments, a second pharmaceutical may be administered with the composition of GHB. Such a second pharmaceutical may be e.g., a stimulant administered within the same 24 hour period as the first dose of GHB. The stimulant may be, e.g., but not limited to, methylphenidate or pemoline to counter the residual effects of GHB treatment during periods of wakefulness. In certain embodiments, the method of treating a sleep disorder may include the discontinuation of other second pharmaceuticals used to control a sleep disorder. Such second pharmaceuticals may include, but are not limited to, a tricyclic antidepressant.

In certain embodiments, the invention provides a method of treating any appropriate therapeutic category of disorder, by administration of GHB compositions of the present invention as described above for the treatment of sleep disorders. When GHB is used in methods of treating any therapeutic category of disorder, the GHB composition of the present invention may be mixed with the aqueous medium, and optionally pH adjusting or buffering agent or other additives, by the patient or administrator soon before consumption. The patient may prepare the composition within a few minutes to hours before administration. Alternatively, one or more of the components may be premixed for ready use. The components of the GHB composition of the present invention, GHB, an aqueous medium, pH adjusting or buffering agent, excipients, preservatives, flavoring agents, and/or other components or additives may be stored in a container means suitable to aid preservation. Preferably, the container means is in the form of a set. A "set" as used herein certain embodiments is one or more components of the composition packaged in a container or other suitable storage means.

The present invention also provides a set for the treatment of a condition responsive to GHB comprising, in suitable storage means, GHB and a pH adjusting or buffering agent. In certain embodiments, the GHB and the pH adjusting or buffering agent are separately packaged. In certain other embodiments the GHB and the pH-adjusting or buffering agent may be mixed. The set may contain an aqueous medium. In certain other embodiments, at least one component selected from the group including, but not limited to, GHB, the pH-adjusting or buffering agent and/or an aqueous medium is separately, packaged. In certain other embodiments, at least two of the components selected from the group comprising GHB, a pH adjusting or buffering agent and an aqueous medium are mixed together. In some embodiments, the set further contains a preservative. Such a set may have one, two, or more components from the group comprising, GHB, a pH-adjusting or buffering agent, an aqueous medium or a preservative packaged separately. Such a set may have two or more components mixed together. Thus, both liquid and dry formulations of GHB and other components may be packaged in a set for mixing before administration, or one or more components may be premixed and packaged together with other components, or all the components may be premixed and packaged in a set.

It is understood that the compositions of the present invention, including those in a set, may be dispersed in a pharmaceutically acceptable carrier solution as described below. Such a solution would be sterile or aseptic and may include water, co-solvent vehicle buffers, isotonic agents, pharmaceutical aids or other ingredients known to those of skill in the art that would cause no allergic or other harmful reaction when administered to an animal or human subject. Therefore, the present invention may also be described as a pharmaceutical composition of GHB with increased stability in a pharmaceutically acceptable carrier solution.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also as used herein, the term "a" "an" or "the" is understood to include the meaning "one or more". Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. **1**. The Range of Gamma-Hydroxybutyrate's Resistance to Microbial Growth and Chemical Stability in Aqueous Solution. The ordinate is the pH of solutions of GHB. The axis is the concentration (mg/ml) of GHB in aqueous solution. The region below the diagonal line [/] is the range of GHB solubility at room temperature. Greater solubility can be achieved, up to 1 g/ml, by heating the solution up to 100° C.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

I. Formulations of Gamma-Hydroxybutyrate

A. Microbial Growth and Gamma-Butyrolactone Formation

The present invention arises from the discovery of chemically stable and microorganism resistant formulations of

GHB in an aqueous medium, preferably a solution, and the efficacy of these formulations in the treatment of therapeutic categories of disorders, such as narcolepsy and other sleep disorders. Specifically, GHB is prepared at a concentration greater than about 150 mg/ml in an aqueous medium, up to the limits of GHB's solubility or retention in an aqueous medium, to produce the compositions of the present invention.

The maximum solubility of GHB is affected by the pH of the aqueous medium. At about pH 4, the maximum amount of sodium-GHB that can be dissolved is about 450 mg/ml. The value of pH that is conducive to GHB solubility increases, as is shown at FIG. **1**, so that the minimal pH that will dissolve 750 mg/ml GHB was found to be about pH 6.8. This is shown in Table 1.

TABLE 1

	Limits of Sodium Oxybate Solubility		
ID A	Sodium Oxybate Maximum Solubility	pH of Solution	Temperature
B	450 mg/cc	pH 4 (HCl)	25°
C	500 mg/cc	pH 5 (HCl)	25°
D	600 mg/cc	pH 6 (HCl)	25°
E	750 mg/cc	pH 6.8 (HCl)	25°
F	750 mg/cc+	pH 10.3	25°
G	1000 mg/cc	pH unadjusted	65° Soluble, 25° Gel

The pH of the aqueous medium also affects the resistance of the composition to microbial growth at about 500 mg/ml GHB. GHB at this concentration in an aqueous medium that is between about pH 5 and pH 9 is resistant to microbial growth, with compositions at about pH 6 to about pH 7.5 being particularly resistant to microbial growth. However, at concentrations of GHB greater than about 750 mg/ml above about pH 7.5, the resistance to microbial growth is reduced. This is shown at Table 2.

TABLE 2

ID	Microbial Challenge Data Summary		
H	Sodium Oxybate Concentration	pH of Solution	Microbial Challenge Result
I	750 mg/cc	7.5 (HCl)	pass
J	500 mg/cc	6.0 (HCl)	pass
K	500 mg/cc + Excipients (Xylitol)	6.0 (Malic Acid)	pass
L	500 mg/cc	9.0 (HCl)	pass (borderline aspergillus)
M	150 mg/cc (BDL 1995)	5.0 (HCl)	fail (aspergillus only)
N	150 mg/cc (BDL 1995)	7.0 (HCl)	fail (aspergillus & staph)
O	150 mg/cc (BDL 1995)	3.0 (HCl)	fail (aspergillus only)
P	150 mg/cc (BDL 1995)	10.3 (unadjusted)	fail (aspergillus and staph)
Q	500 mg/cc	6.0 (Malic Acid)	discontinued
R	500 mg/cc	7.5 (Malic Acid)	pass
S	500 mg/cc (May '98)	9.0 (Malic Acid)	discontinued
T	500 mg/cc (May '98)	7.5 (HCl)	pass*
U	Others: 200 mg/cc—800 mg/cc	5.0-9.0	pending

*pass is generally defined as:

TABLE 2-continued

ID	Microbial Challenge Data Summary
	For Category 1C Products
Bacteria:	Not less than 1.0 log reduction no from the initial cout at 14 days, and increase from the 14 days' count at 28 days.

Yeast and Molds: No increase from the initial calculated count at 14 and 28 days.

The data from Table 1 and Table 2 are graphically shown in FIG. **1**. The concentration of GHB in the composition, when evaluated in relationship to the pH, affects the resistance of the GHB composition to microbial challenge. Compositions of GHB at or below 150 mg/ml are poorly resistant to microbial challenge from a pH range of about pH 3 to about pH 9. However, concentrations of GHB of greater than about 150 mg/ml, up to about 1000 mg/ml of GHB, are believed to be suitably resistant to microbial contamination at these pH ranges.

The chemical stability of GHB is affected by pH. Accordingly, the method for preparing GHB, as described herein, particularly as disclosed in the specific examples, varies with pH. GBL begins to form if the pH is about 6 or less. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, any pH or range of pH values where a clinically acceptable amount of GBL is produced is also contemplated as being preferred, and is encompassed by the present invention. The range of GBL could be regulatorily broadened with availability of sufficient toxicological data.

In certain embodiments of the invention, a pH-adjusting agent may be added to the composition. The choice of a pH adjusting agent may affect the resistance to microbial challenge and/or the stability of GHB, as measured by the reduction in assayable GHB. Compositions of GHB, pH adjusted with malic acid are resistant to both microbial growth and chemical degradation of GHB, and are preferred. Other pH adjusting or buffering agents may be selected. Agents that adjust pH that are selected on this basis will undergo a taste testing study. However, any pH adjusting agent disclosed herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the invention. Of course, any salt, flavoring agent, excipient, or other pharmaceutically acceptable addition described herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the invention.

Any of the above formulations may be prepared and/or packaged as a powdered or dry form for mixing with an aqueous medium before oral administration, or they may be prepared in an aqueous medium and packaged. After mixing with an aqueous medium, preferably to prepare a solution, these formulations are resistant to both microbial growth and chemical conversion of GHB to GBL, thereby increasing the shelf-life of therapeutic formulations of GHB in an aqueous medium. These formulations-then provide an easily titratable liquid medium for measuring the dosage of GHB to be administered to a patient. Additional embodiments of the composition and methods of preparation are described below and in the examples.

B. Pharmaceutical Compositions

1. Pharmaceutically Acceptable Carriers

Aqueous compositions of the present invention comprise an effective amount of GHB dissolved or dispersed in a pharmaceutically acceptable carrier and/or an aqueous medium. The phrases "pharmaceutically or pharmacologically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is not appropriate. Supplementary compatible active ingredients can be incorporated into the compositions. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by the Food and Drug Administration (FDA).

The GHB may be lyophilized for more ready formulation into a desired vehicle where appropriate. The active compounds may be formulated for parenteral administration, e.g., formulated for injection via intravenous, intraarterial, intramuscular, sub-cutaneous, intralesional, intraperitoneal or other parenteral routes. The preparation of an aqueous composition that contains a GHB agent as an active component or ingredient will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for using to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including, e.g., aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

Solutions of the active compounds as free acid or pharmacologically acceptable salts can be prepared in water suitably mixed with hydroxypropylcellulose and/or a pharmaceutically acceptable surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof as well as in oils. Under ordinary conditions of storage and use, these preparation may best contain a preservative to further prevent the growth of microorganisms.

A GHB composition of the present invention can be formulated into a composition in a neutral or salt form. Such salts can be formed from any of the acids and bases described herein particularly depending on the particular GHB or GHB salt used, or as would be known to one of ordinary skill in the art.

The carrier can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, or the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a substance, such as lecithin (e.g. a coating), by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by any of the preservatives described herein, or as would be known to one of ordinary skill in the art, including various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The preparation of more, or highly, concentrated solutions for direct injection is also contemplated, where the use of DMSO as solvent (although DMSO may not now be a permitted human drug) is envisioned to result in extremely rapid penetration, delivering high concentrations of the active agents to a small area.

Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above, but drug release capsules and the like can also be employed.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The active GHB may be formulated within a therapeutic mixture to comprise about 100 to about 10,000 milligrams per dose. Multiple doses can also be administered.

In addition to the compounds formulated for parenteral administration, such as intravenous or intramuscular injection, other pharmaceutically acceptable forms include, e.g., tablets or other solids; liposomal formulations; time release capsules; and any other form currently used, including cremes, which then may be admixed with an aqueous medium for oral administration.

One may also use nasal solutions or sprays, aerosols or inhalants in the present invention. Nasal solutions are usually aqueous solutions designed to be administered to the nasal passages in drops or sprays. Nasal solutions, are prepared so that they are similar in many respects to nasal secretions, so that normal ciliary action is maintained. Thus, the aqueous nasal solutions usually are isotonic and slightly buffered to maintain a pH of 5.5 to 6.5, though other pH ranges disclosed herein the specific examples, such as pH 3 to about pH 9, or pH 6 to about 7.5, are contemplated. In addition, preserva-

tives, similar to those used in ophthalmic preparations, and appropriate drug stabilizers, if required, may be included in the formulation. Various commercial nasal preparations are known and include. for example, antibiotics and antihistamines and are used for asthma prophylaxis.

The preferred oral formulations may include such normally employed excipients, as, for example, pharmaceutical grades of xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate and the like. These compositions can take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders to be admixed with an aqueous medium. In certain defined embodiments, oral pharmaceutical compositions will comprise an inert diluent or assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsule, or they may be compressed into tablets, or the GHB may be packaged separately from or in combination with the excipients, salts, flavorings or any other components described herein, to be admixed with an aqueous medium for oral or injectable formulations, or they may be incorporated directly with the food (i.e. a beverage) of the diet.

For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of tablets, buccal tablets or tabs, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. to be admixed with an aqueous medium. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 75% of the weight of thle unit, or preferably between 25-60%. The amount of active compounds in such therapeutically useful compositions is such that a suitable dosage will be obtained.

The tablets, troches, pills, capsules and the like may also contain the following: a binder, natural as gum tragacanth, acacia, cornstarch, or gelatin or synthetic as polyvinyl acetate; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a natural or synthetic flavoring agent. When the dosage unit form is a capsule for admixing with a specific volume of an aqueous medium, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with sugar, natural or synthetic polymers, or both. A syrup or elixir may contain the active compounds, sucrose as a sweetening agent, a preservative, a dye and/or a flavoring.

Additionally, any excipient, salt, acid, pH-mediating, adjusting or buffering compound or agent, flavoring, solution, solvent, dispersion, glycerol, glycol. oil, antibacterial and antifungal agents, antibiotics and antihistamines, binders, disintegrating agents, lubricants, sweetening agents, or any other additive or ingredient from those enumerated above or in the examples, or in any pharmaceutically acceptable composition or carrier described herein, or as would be known by one of skill in the art, is contemplated for use in aqueous mediums or solid forms of the GHB compositions of the invention. One or more of these compositions may be packaged with GHB or packaged separately from GHB prior to consumption. If packaged separately, useful compositions of GHB may be obtained by mixing GHB with the other components with an aqueous medium prior to consumption. Such components may be packaged in a set, described below.

2. Sets

Therapeutic sets of the present invention are sets comprising GHB. Such sets will generally contain, in suitable container, a pharmaceutically acceptable formulation of GHB. The set may have a single container, or it may have distinct container for each component, or distinct container for various combinations of components.

When the components of the set are provided in one or more liquid formulations, the liquid formulation is an aqueous medium, with a sterile aqueous solution being particularly preferred. The GHB compositions may also be formulated into a syringeable composition. In which case, the container means may itself be a syringe, pipette, vial, ampule or other such like apparatus, from which the formulation may be applied to an infected area of the body, injected into an animal, or even applied to and mixed with the other components of the set.

However, the components of the set may be provided as dried powder(s). When reagents or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent. It is envisioned that the solvent may also be provided in another container means.

The container means will generally include at least one vial, test tube, flask, bottle, pouch syringe or other container means, into which the GHB formulation or components thereof are placed, preferably, suitably allocated. The sets may also comprise a second container means for containing a sterile, pharmaceutically acceptable buffer or other diluent.

The sets of the present invention will also typically include a means for containing the vials in close confinement for commercial sale, such as, e.g., injection or blow-molded plastic containers into which the desired vials are retained.

Irrespective of the number or type of containers, the sets of the invention may also comprise, or be packaged with, an instrument for assisting with the injection/administration or placement of the GHB composition within the body of an animal. Such an instrument may be a drinking cup, syringe, pipette, or any such medically approved delivery vehicle.

II. Methods of Treatment with the GHB Compositions

Because GHB has been shown to be effective in treating narcolepsy and sleep disorders (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993), reducing alcohol craving and alcohol withdrawal symptoms, (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992), reducing opiate withdrawal symptoms (Gallimberti et al, 1994; Gallimberti et al., 1993), reducing pain (U.S. Pat. No. 4,393,236), reducing intracranial pressure in patients (Strong, A. 1984), and increasing growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970), the formulations of the present invention are also contemplated to be useful in the treatment of any of these disorders or conditions in patients. GHB has also been used alone as a narcotic in patients with a terminal carcinomatous state. GHB has been used with other analgesics, neuroleptics, or with a subliminal barbiturate dose for use as an anesthesia. GHB has been used in closed craniocerebral trauma and as a soporific (U.S. Pat. No. 5,380,937). The inventors contemplate the use of the GHB compositions of the present invention as a narcotic, hypnotic, or as a soporific. The inventors also contemplate the use of the GHB compositions of the present invention in combination with analgesics, neuroleptics or barbiturates for use as an anesthesia. The GHB compositions of the present invention may be prepared and administered by any of the means described herein, particularly those described in the section "Pharmaceutical Compositions" and the examples, or by any means as would be known to those of skill in the art.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

Preferred Embodiments

XYREM™ Clinical Trials

The inventors developed a liquid formulation composed of GHB, xylitol, and preservative in water (XYREM™). Subsequent instability of the preservative in this formulation and a desire to initiate clinical trials in a timely manner led to a change in the formulation to a foil pouch. One clinical trial utilized a twin-pouch dosage form, with one side (pouch 1) of the foil packet containing GHB and the other side (pouch 2) containing the flavoring agents (Xylitol, [NF]; Malic Acid, NF.

Patients were instructed to open the twin-pouch with a scissors, empty the contents into a dosing cup, add 2 ounces of water, snap the lid on the dosing cup, shake to dissolve, and drink the entire contents of the cup. Clinical trials conducted by the inventors have been performed using the twin-pouch dosage form.

However, the inventors have continued development of a liquid solution and have now overcome inherent problems with particular formulations and/or preservatives. The inventors have converted patients currently enrolled in a GHB open-label trial to a liquid solution composed of GHB, malic acid, and water—that is diluted with water immediately prior to oral administration.

The need for a liquid solution dosage form is further evidenced by the range of doses being used in a subsequent GHB open-label trial. Three sizes of pouches were prepared for the GHB open-label trial: 1.5 grams, 3.0 grams, and 4.5 grams. The initial dose for all patients in the GHB open-label trial was 6 grams of GHB nightly in divided doses. Dosage adjustments were permitted in the first two weeks of the trial as indicated for intolerance or lack of efficacy. The investigator was permitted to decrease the dose of GHB to 3 grams or 4.5 grams, or increase the dose to 7.5 grams or 9 grams nightly. After two weeks, further dosage adjustments were made if clinically indicated.

Thirty-five patients had their dose increased, and 16 patients had their dose decreased. Patients in the lowest dose group were disproportionately female and weighed 15 kg less than patients in the other two groups. Current dosing levels are noted below:

TABLE 3

Dosing Levels in the GHB Open-Label Trial

	Total	1.5 gram	3.0 gram	4.5 gram	6.0 gram	7.5 gram	9.0 gram
Number of Patients	95	0	4	10	39	12	30
Per Cent of Patients	100%	0%	4%	10%	41%	13%	32%

TABLE 3-continued

Dosing Levels in the GHB Open-Label Trial

	Total	1.5 gram	3.0 gram	4.5 gram	6.0 gram	7.5 gram	9.0 gram

To achieve these individualized doses, it has been necessary to provide a combination of different dose strengths. This complexity would be very difficult to achieve with a marketed product. In addition, a month's supply of twin-pouches is quite bulky. A liquid formulation allows for ease in dosing adjustment with one dosage form. In addition "child-resistant" packaging has been developed with the liquid formulation.

A number of patients have also complained about the flavor with the twin-pouches. As follow-up the inventors sent questionnaires to participants in the inventors' clinical trial, and performed taste testing in normal volunteers. The questionnaire responses, taste testing results, and the clinical experience in narcolepsy patients of the study administrator have all confirmed that unflavored solutions were acceptable.

The concentration and volume of the GHB solution that the patient administers will be the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. This is illustrated in Chart 1 and Table 4:

Chart 1 Comparison of Liquid Solution to Twin-Pouch

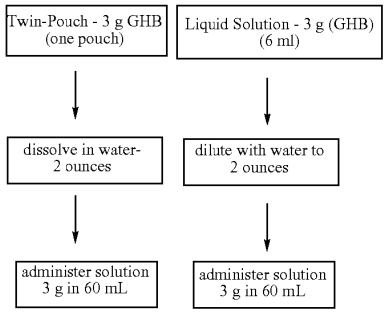


TABLE 4

Comparison of Liquid Solution to Twin-Pouch

	Twin-Pouch	Liquid Solution
Amount of GHB	3 grams (1 pouch)	3 grams (6 mL)
Inactive Components	malic acid Xylitol lemon/lime flavor Orange flavor	malic acid
Final Concentration	50 mg/mL	50 mg/mL*
Final Volume	60 mL	60 mL

*Final concentration outside the range of the most stable formulation. This formulation strength may be only stable at short periods of time such as 48 hours. The twin pouch version could be solubilized at a concentration within the preferred range of pH and GHB concentration for longer term storage.

Apart from the elimination of the sweetener (xylitol) and flavoring, the two formulations result in identical solutions.

CONCLUSIONS

The concentration and volume of the GHB solution that the patient administers is the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. Either method may be used to produce acceptably stable solutions of GHB.

EXAMPLE 2

Preferred Embodiments

Self Preserving Formulations of Gamma-Hydroxybutyrate

Summary of Formulation Studies—Liquid XYREM™

I. Maximum Solubility Range

As seen in FIG. **1** and Table 1, the solubility of GHB varies with pH levels at room temperature (25° C.). Additional amounts of GHB can be solubilized in a gel if heat is applied, in which case a 1000 mg/ml concentration can be achieved. The inventors contemplate that though the concentrations or contents of GIIB shown in FIG. **1** and Table 1 are preferred for use, due to the ease of preparing and consuming unheated preparations, higher concentrations of GHB in aqueous medium may also be made, up to 1000 mg/ml.

II. Microbial Testing

The inventors used a three factor analysis involving pH, concentrations of GHB and the pH adjuster used. As seen in FIG. **1**, and Table 2, unacceptably low resistance to microbial challenge was seen at 150 mg/ml GHB at pH 3, 5, 7, and 9.0, using HCl as the pH adjusting agent. 150 mg/ml GHB at pH 10.3 without a pH adjusting agent also proved unacceptably resistant to microbial challenge. Borderline acceptable microbial preservativeness was seen in a solution pH adjusted with HCl at 500 mg/ml GHB at pH 9. At a concentration of 500 mg/ml at pH 6.0 or 7.5, adjusted with either malic acid or HCl, and 500 mg/ml at pH 9.0 adjusted with HCl, the formulation is very effective in a microbial challenge test. The inventors contemplate that a concentration of greater than about 150 mg/ml of GHB, up to the maximal solubility in aqueous solution of GHB, will be suitably resistant to microbial challenge from about pH 3 to pH 10.3. Preferably, the aqueous medium will contain a pH-adjusting or buffering agent.

III. Gamma-Butyrolactone Degradation Range

GBL begins to form if the pH is about 6 or less with the formulation tested thus far.

A. Liquid Formulation Development

The objective of these experiments was to develop a commercial formulation for sodium gamma hydroxybutyric acid. The initial formulation for sodium gamma hydroxybutyric acid (GHB) was intended to be an aqueous liquid formulation containing 150 mg/mL GHB, preservatives and flavoring agents. To develop this formulation, studies were conducted to establish the: solubility of the drug in water and as a function of pH, type and concentrations of suitable preservatives, type and concentrations of flavor ingredients, and stability of the formulations.

1. Solubility

The feasibility of preparing formulations containing 150 mg/mL of GHB at pH 3, 5 and 7 was established. Solutions containing 150 mg/mL GHB were prepared. The initial pH was greater than pH 7.5 and the final pH was adjusted to 3, 5 or 7 with hydrochloric acid. The solutions were observed for precipitation and assayed by HPLC for GHB content. The results showed that no precipitation was observed and the drug concentration was found to be 150 mg/mL by HPLC. This information was used as the basis for additional formulation development studies.

2. Preservatives

Preservative effectiveness studies were conducted to identify a suitable preservative for the GHB liquid formulation. The following formulations shown in Table **5** were prepared and tested using *Staphylococcus aureus* (ATCC #6538), *Pseudomonas aeruginosa* (ATCC #9027) and *Aspergillus niger* (ATCC #16404).

TABLE 5

Liquid Formulations Used in Preservative Effectiveness Testing

Formulation	pH	Sodium Benzoate	Methylparaben Propylparaben	Potassium Sorbate	Control
1	3	X			
2	5	X			
3	7	X			
4	3		X		
5	5		X		
6	7		X		
7	3			X	
8	5			X	
9	7			X	
10	3				X
11	5				X
12	7				X
13	no pH adjustment				X

The preservative used in each formulation is marked with an X. The results showed that formulations #3, 4, 6 and 9 reduced all three challenge microorganisms by >99.99% in 48 h of contact time. Formulations #1, 5 and 7 reduced all three challenge microorganism by >99.99% in 7 days of contact time. Formulations #2, 8, 10, 11, 12 and 13 did not reduce *Aspergillus niger* mold to >99.99%, although some reduction occurred in 7 days of contact time. Controls #10, 11, 12 and 13 demonstrated activity against *Pseudomonas aeruginosa.*

3. Stability

Based on the results of the preservative effectiveness testing, five formulations were selected for stability testing. Table 6 shows the composition of the formulations.

TABLE 6

Liquid Formulations Used in Informal Stability Program

Chemical	1	2	3	4	5
Potassium Sorbate	0.4 gm	0.4 gm			
Sodium Benzoate			1.0 gm		
Methyl-paraben				0.36 gm	0.36 gm
Propyl-paraben				0.04 gm	0.04 gm
GHB	30 gm	30 gm	30 gm	30 gm	30 gm
Xylitol	40 gm	40 gm	40 gm	40 gm	40 gm
Water q.s.	200 mL	200 mL	200 mL	200 mL	200 mL

TABLE 6-continued

Liquid Formulations Used in Informal Stability Program

Chemical	1	2	3	4	5
Initial pH	8.68	8.68	9.30	7.75	7.75
Formulation Adjusted pH	3.01	5.00	3.00	2.98	4.98

The formulations were packaged in 125 mL, amber PET bottles with safety lined child-resistant caps and stored upright and inverted at 60° C., 40° C./75% relative humidity (RH) and 25° C./60% relative humidity. Samples were removed from the stability chambers after 1, 2 and 3 months and assayed by high performance liquid chromatography (HPLC) for GHB-content. Appearance and pH were also monitored.

Table 7 shows the results for the 3 month time point. Samples stored at 60° C. changed color but samples at all other conditions remained unchanged in color.

The pH of all formulations migrated upward over the three month stability period at 60° C. The percent increase in pH from initial to 3 months, was greater for the formulations which were initially adjusted to lower values.

For example, the migration of pH in formulations 1, 3 and 4 (adjusted down to pH 3) were 21-30 percent across all conditions in three months. The migration of pH in formulations 2 and 5 (adjusted down to pH 5) were 4.2-12 percent across all conditions in 3 months. Maintenance of pH becomes important for long term storage since preservatives are known to degrade in formulations having pH levels above approximately pH 6.

Additionally, development of flavor systems to mask the negative taste of preservatives is difficult.

flavor system development and organoleptic testing. A pH 3 formulation containing potassium sorbate was selected as the back-up formulation.

B. Dry Powder Formulation Development

Developing a flavor system for the primary and back-up liquid formulations proved to be difficult and a decision was made to develop a dry powder formulation for reconstitution with water before consumption. This approach removed the need for a preservative system, the requirement to adjust pH to levels below pH 6, and allowed the development of a suitable flavor system.

1. Dry Powder Formulation Organoleptic Testing

To develop a flavor system for the powder formulation, several parameters were evaluated. The flavor attributes of a GHB solution was characterized by a professional sensory panel. A mimic base containing similar sensory properties as a GHB solution for flavor system was developed. Generally Recognized As Safe (GRAS) excipients for flavor system development were selected. Different excipients (flavorings, sweeteners, acidulants and flow agents) in the mimic base were screened. Three flavor systems for the focus group test were selected. A preferred flavor system was optimized based on comments obtained from the focus group testing. This final formulation with GHB was optimized.

Based on the above activities, the following formulations in Table 8 were selected for stability studies:

TABLE 8

Composition of Prototype Dry Powder Formulation

Ingredient	Composition (grams)	Purpose
GHB	3	Active
Xylitol	5.5	non-cariogenic sweetener

TABLE 7

Table 7
Results of Liquid Formulation Informal Stability Study at Three Months

Formulation # (See Table 6)	Attribute	25° C./60% RH Upright	25° C./60% RH Inverted	40° C./75% RH Upright	40° C./75% RH Inverted	60° C. Upright
1	% t = 0	100.7	101.6	101.2	NA	NA
Potassium	pH	3.63	3.64	3.84	3.82	3.91
Sorbate (pH) at 3 months storage	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light yellow
2	% t = 0*	102.1	105.0	104.0	102.0	99.6
Potassium	pH	5.21	5.28	5.55	5.56	5.61
Sorbate (pH5)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light brown
3	% t = 0	102.4	104.1	99.1	102.6	97.0
Sodium	pH	3.60	3.74	3.78	3.75	3.79
Benzoate (pH3)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, colorless
4	% t = 0	101.5	102.7	100.6	101.2	93.7
4 Methyl &	pH	3.63	3.71	3.81	3.80	3.83
Propyl Parabens (pH3)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, colorless
5	% t = 0	103.1	105.8	101.9	103.1	95.6
4 methyl &	pH	5.22	5.55	5.55	5.56	5.60
Propyl Parabens (pH5)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light yellow

*% GHB at t = 0 percent of label claim

**initial time (t = 0)

4. Liquid Formulation Organoleptic Testing

Based on the above stability data and preservative effectiveness testing, a pH 5 formulation containing potassium sorbate was selected as the primary base formulation for

TABLE 8-continued

Composition of Prototype Dry Powder Formulation

Ingredient	Composition (grams)	Purpose
Malic acid	0.2	Acidulant
Flavor 1	0.2	Flavor ingredient
Flavor 2	0.04	Flavor ingredient
Silicon Dioxide (Cab-O-Sil ®)	0.03	Flow enhancer

2. Dry Powder Formulation Stability

A study was initiated to evaluate the stability of the above prototype formulation in two types of foil packages (high and moderate moisture resistant) as well as the stability of GHB alone in one type of foil package (high moisture resistant). Table 9 shows the Lots that were placed on stability. The foil packages were a high moisture resistant pouch and a moderate moisture resistant pouch. The study protocol, Table 10, required the samples to be stored at 40±2° C./75±5% relative humidity for six months, and 25±2° C./60±5% relative humidity for 12 months. Table 11 shows the tests, methods, number of packets/test and specifications for the study.

TABLE 9

Dry Powder Informal Stability Study Package Composition

Lot Number	Manufacture Date	Package Configuration	Special Comments
SPO #8018 A	Oct. 06, 1995	Foil Packet	Moderate moisture resistant pouch.
SPO #8018 B	Oct. 06, 1995	Foil Packet	Highest moisture protection pouch.
SPO #8018 C	Oct. 06, 1995	Foil Packet	Drug substance only. Highest moisture protection pouch.

TABLE 10

Dry Powder Informal Stability Study Protocol

	Stability Time in Months						
Storage Conditions	0	1	2	3	6	9	12
40 ± 2° C./75% ± 5% RH		X	X	X	X		
25 ± 2° C./60% ± 5% RH	X	X	C	C	R	R	R

X = Samples to be tested
C = Contingency Samples
R = Reduced testing; assay and H_2O only
RH = Relative Humidity

TABLE 11

Dry Powder Informal Stability Tests and Specifications

Test	Method	Packets/Test	Specification Limits
Appearance Dry Material	Visual	Use HPLC	White to off-white free flowing powder
Appearance Reconstituted Material	Visual	Use HPLC	Cloudy, off-white solution with visible particulates
Rate of Dissolution	Visual	Use HPLC	Material should dissolve completely in five min with mixing
Odor	Olfactory	Use HPLC	Characteristic Lemon/Lime odor
Assay: GHB	HPLC	3	90.0%-110.0%

TABLE 11-continued

Dry Powder Informal Stability Tests and Specifications

Test	Method	Packets/Test	Specification Limits
Assay: Malic Acid	HPLC	Use HPLC	90.0%-110.0%
Impurities/ Degradants	HPLC	Use HPLC	Not more than 1% for any individual impurity/degradant and Not more than 3% total impurity/degradants
Vacuum Leak test	Visual	3	No Appearance of Leaking
pH	USP <791>	Use HPLC	For Information
Moisture	Karl Fisher	3	Report Value - to be determined

After two months at 40±2° C./75±5% relative humidity, the potency (% label claim) of Lots SPO 8018A and SPO 8018B was less than 94.0%, the lower limit of the specification, whereas Lot SPO 8018C showed no loss in potency. Lots 8018A and 8018B showed approximately 96% potencies after 2 months at 25° C.±2° C./65%±5% relative humidity. Lot SPO 8018C again showed no loss in potency at this lower storage condition.

3. Appearance

After 2 months at 40° C.±2° C./75%±5% relative humidity, Lots SPO 8018A and SPO 8018B showed significant melting, whereas Lot 8018C showed no melting. Lots SPO 8018A and SPO 8018B also showed partial melting after 2 months at 25° C.±2° C./65%±5. % relative humidity. Lot SPO 8018C again showed no evidence of melting at this lower storage condition.

Based on the physical changes in state observed during the stability studies, it was apparent that a solid state interaction between GHB and the excipient blend had occurred. Since xylitol made up the majority of the excipient blend, it was assumed that xylitol was the primary source of the drug-excipient interaction. An alternative hypothesis was also proposed, based on the possibility that the package was mediating the interaction between GHB and xylitol. Three studies were initiated to test these hypotheses.

4. Stability of GHB Solids in a Set Container-System

In the first study, the samples that were stored at 25±20° C./60±5% relative humidity were transferred to glass vials and then stored at 40±2° C./7±5% relative humidity. In the second study, mixtures of GHB and xylitol were gently rubbed between sheets of different types of foil packaging. The mixtures were observed for changes in physical appearance. In the third study, different mixtures of GHB and xylitol were prepared. Differential Scanning Calorimetry (DSC) thermograms were then done to look for changes in the thermograms. The results of these studies are summarized below.

Transfer to Glass: Samples of Lot 8018A and Lot 8018C that were previously stored at 25±2° C./60±5% relative humidity were transferred to amber screw cap vials and stored at 40±2° C./75±5% relative humidity. Analyses similar to those shown in Table 6 were done. After 1 month, the potency of Lot 8018A was 94.6% whereas the potency of Lot 8018C (GHB only) was 100%. In addition, Lot 8018A also showed evidence of melting. The results supported the hypothesis that GHB and xylitol were interacting in the solid state and the interaction appeared to be independent of packaging.

Foil Study: Mixtures of GHB and xylitol were placed between folded sheets of several different foil packaging materials. Slight adhesion of the mixed granules with the foil lining was observed for all of the foils examined. No direct

evidence of melting was observed, however, even when excessive force was applied to the outer foil surfaces. This data suggests that the packaging material was not responsible for the solid state interaction observed during the stability studies.

DSC thermographs were obtained for samples of GHB/xylitol containing GHB:xylitol mixtures of 33:66, 45:55 and 55 percent 45 respectively. The scans were conducted at a scan rate of 10° C./min. The thermograms showed that the sample containing GHB:xylitol 33:66 showed a broad endothermic transition starting at 35° C.-40° C. Samples with higher ratios of GHB:xylitol also showed broad endothermic transitions that started at temperatures of 45° C.-50° C. The changes seen in the thermograms supported the hypothesis that a solid state interaction may be occurring between GHB and xylitol that resulted in low potencies for formulations containing mixtures of these two agents.

As a result of the changes seen in the DSC thermograms for different mixtures of GHB:xylitol, a study was initiated to investigate the stability of a formulation containing GHB:xylitol excipient blend 55:45. A formulation containing GHB:xylitol excipient blend 33:66 was used as a control sample. The formulations were packaged in glass vials and stored at 50° C., 40±2° C./75±5% relative humidity and 25±2° C./60±5% relative humidity. The appearance and potency of the formulations were monitored through analyses of stability samples. The stability study also showed potency losses after 1 month at 40° C.±2° C./75%±5% relative humidity with both the 50/50 GHB:xylitol ratio as well as the original 33/66 ratio formulation. Partial evidence of melting was also observed in both formulations.

Studies with mixtures of GHB:xylitol excipient blend indicated that the mixture was incompatible in the solid state. However, when prepared as an aqueous solution, these mixtures were chemically compatible. Using this information, a decision was made to package the GHB formulation in dual pouches; one pouch containing GHB alone and the other containing a mixture of xylitol and the other flavor ingredients. The formulation will contain equal amounts of GHB and the excipient blend. This product will be prepared, packaged, and may be checked for stability.

EXAMPLE 3

The Pharmacokinetics of Gamma-Hydroxybutyrate

I. Study Objectives

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; patients generally ingested the first dose of this medication prior to bedtime and the second dose from 2.5 to 4.0 h later) to narcoleptic patients who are maintained on a chronic regimen of GHB.

II. Study Design

This pharmacokinetic study was conducted as an open-label, single-center investigation in 6 narcoleptic patients. The study design is summarized as follows:

TABLE 12

Screening/ Washout ⇒	Treatment/Blood Sampling ⇒	Follow-up
(1 or more days to dosing; washout, at least 8 h)	(Two 3 g GHB oral doses, 4 h apart; 21 blood samples)	(Within 48 h after last blood sample)

Narcoleptic patients, 18 years of age or older, who volunteered for this study were screened at least one day prior to the treatment phase. Each patient was determined to be in stable health and evaluated for the presence of narcolepsy, defined for the purposes of this example as one or more years of medical history of narcolepsy as evidenced by a recent nocturnal polysomnogram (PSG) and a valid score from a Multiple Sleep Latency Test (MSLT).

Patients maintained on GHB were allowed to participate. These patients had been weaned from antidepressants, hypnotics, sedatives, antihistamines, clonidine, and anticonvulsants though a stable regimen of methylphenidate (immediate release or sustained release) was allowed. Each patient passed a pre-study physical examination (which included hematology, blood chemistry, urinalysis, and vital signs measurements) prior to the commencement of the treatment phase.

Before oral administration of the first GHB dose, an indwelling catheter was placed in an arm vein and a baseline blood sample was collected. Each patient then ingested a 3 g dose of GHB before bedtime. Another 3 g GHB dose was administered 4 h after the first dose. Twenty-one sequential blood samples were collected over 12 h (starting at 10 min after the first dose and ending at 8 h after the second dose). Upon completion of the treatment phase, a follow-up physical examination which included the measurement of vital signs was performed on each patient within 48 h after the last blood sample. A detailed description of the trial methodology is presented in Section IV.

III. Inclusion Criteria

Patients were included in the study if they: had signed an informed consent prior to beginning protocol required procedures; had not participated in such a study at an earlier date; were willing and able to complete the entire study as described in the protocol; were 18 years of age or older at study entry; had not taken any investigational therapy other than GHB within the 30-day period prior to screening for this study; had an established diagnosis of narcolepsy for at least one year with documentation from a qualified laboratory by a nocturnal polysomnogram (PSG) and a Multiple Sleep Latency Test (MSLT) which demonstrated mean sleep latency to be less than 5 min and REM onset in at least 2 of 5 naps; had not been diagnosed with uncontrolled sleep apnea syndrome, defined as a sleep Apnea Index of 5 or an Apnea Hypopnea Index (AHI) greater than 10 per hour or any other cause of daytime sleepiness; and were free of any medication for their narcolepsy (including hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants) other than GHB and methylphenidate (IR or SR). Patients admitted to this study if they were not experiencing unstable cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, metabolic, neurological, pulmonary, and/or renal disease which would place them at risk during the study or compromise the protocol objective; did not have neurological or psychiatric disorders (including transient ischemic attacks, epilepsy, or multiple sclerosis) which, in the investigator's opinion, would preclude the patients' participation and completion of this study; did not have a current or recent (within one year) history of alcohol or drug abuse; did not have a serum creatinine greater than 2.0 mg/dL, abnormal liver function tests (SGOT or SGPT more than twice the upper limit of normal, or serum bilirubin more than 1.5 times normal). Female patients were entered into the study if they were either post-menopausal (i.e. no menstrual period for a minimum of 6 months), surgically sterilized or provided evidence of effective birth control. Females of childbearing potential must agree to continue to use an IUD, diaphragm, or take their oral contraceptives for the duration of the study.

Female patients of childbearing potential must have a negative pregnancy test upon entry into the study.

IV. Trial Methodology

A time and events schedule is presented in Table 12.

A. Screening Period/Washout

Six narcoleptic patients who were chronically being treated with GHB were recruited to participate in this pharmacokinetic study. The screening period was at least one day prior to the treatment phase. During the screening period each patient completed the following procedures for the assessment of their physical condition: medical history evaluation; physical examination evaluation; clinical laboratory evaluation; inclusion criteria review. Each patient's GHB and methylphenidate regimen also were recorded on an appropriate case report form (CRF). The investigator also ensured that there was at least an 8-hour washout period for GHB prior to the treatment.

B. Treatment Period/Blood Samples Collection

All patients were hospitalized from approximately four hours prior to first GHB dosing (around 6 p.m.) until the end of the treatment period (around 10 a.m. the next morning). Patients ate their dinner at the clinical research unit soon after arrival and fasted until breakfast next morning. At least three hours elapsed between the completion of dinner and the administration of the first GHB dose. An indwelling catheter was placed in an arm vein of each patient for blood sampling at approximately 30 min and 1 h before the first GHB dose and a baseline blood sample (5 mL) was collected.

The first GHB dose (3 g) was administered at around 10 p.m. Dosing of individual patients were staggered. The second GHB dose was administered at 4 h after the first GHB dose (i.e. immediately after the 4 h blood sample). The exact dosing times in each patient were recorded on appropriate CRF pages. Blood samples (5 mL each) were collected through the indwelling catheter into heparinized tubes at 0.2, 0.4, 0.6, 0.8, 1, 1.5, 2, 3, 4, 4.2, 4.4, 4.6, 4.8, 5, 5.5, 6, 7, 8, 10, and 12 h after the first GHB dose. Blood samples were processed according to the procedures described herein. Patients were monitored for adverse experiences throughout the study according to the specific procedures.

C. Follow-Up

Follow-up occurred within 48 h after the last blood sample had been collected. An abbreviated physical examination which included vital signs measurement was performed. Adverse experiences and concomitant medication use, if any, were assessed. Any ongoing adverse experiences and clinically important findings in a patient were followed to the investigator's and/or sponsor's satisfaction before the patient was discharged from the study.

D. Methods of Assessment

1. Medical History

The medical history was recorded during the screening period. The history included gender, age, race, height, prior reaction to drugs, use of alcohol and tobacco, history and treatment, if any, of cardiovascular pulmonary, gastrointestinal, hepatic, renal, immunologic, neurological, or psychiatric diseases and confirmation of inclusion criteria.

2. Physical Examination

Physical Examination included body system review as well as measurement of body weight and vital signs and a neurological examination.

3. Vital Signs

Vital signs measurements included recording of blood pressure, heart rate, respiration, and body temperature.

4. Clinical Laboratory

All clinical laboratory tests were performed at a local laboratory. The laboratory tests and analysis were required of each patient included: hematology, including hemoglobin, hematocrit, red blood cell count, white blood cell count and differential; fasting blood chemistries included blood urea nitrogen (BUN). uric acid, glucose, creatinine, calcium, phosphorus, total protein, albumin, sodium, potassium, SCOT (AST), SGPT (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), and total bilirubin; midstream catch urinalysis included specific gravity, pH, protein, occult blood, ketones and glucose by dipstick determination as well as a microscopic examination of urine sediment for RBC, WBC, epithelial cells or casts or crystals; and a urine pregnancy test, if applicable. Any laboratory parameter that was out of range and considered clinically significant excluded the patient from participation in this study. The investigator would provide an explanation of all observations that were significantly outside the reference range.

5. Concomitant Medication

The continued use of a fixed dose of methylphenidate immediate release or sustained release (IR or SR) is acceptable. The methylphenidate regimen was recorded on the appropriate case report form.

6. Adverse Experiences

An adverse experience are any undesirable event experienced by a patient or volunteer whether or not considered drug-related by the investigator. An undesirable event can be, but is not limited to, subjective symptoms experienced by a patient or, objective findings such as significant clinical laboratory abnormalities. Adverse experience is considered synonymous with the term "adverse event".

The investigators report in detail all adverse experiences and symptoms that occurred during or following the course of trial drug administration for up to 2 days. Included in the description was the nature of the sign or symptom; the date of onset; date or resolution (duration); the severity; the relationship to trial treatment or other therapy; the action taken, if any; and the outcome.

A serious adverse experience is defined as one that is fatal, life threatening, permanently disabling, or which results in or prolongs hospitalization. In addition, overdose, congenital anomaly and occurrences of malignancy are always considered to be serious adverse experiences. An unexpected adverse experience is one not previously reported.

Any serious or unexpected adverse experience (including death) due to any cause which occurs during the course of this investigation, whether or not it is related to the investigational drug, was reported within 24 h by telephone or facsimile. Appropriate authorities were to be informed if the serious or unexpected adverse experience, in the opinion of inventors, was likely to affect the safety of other patients or volunteers or the conduct of the trial.

7. Clinical Supplies-Study Medication

Formulation: Unit 3 g GHB doses (Lot PK1) were obtained from Orphan Medical Each unit dose comprised twin foil pouches: one pouch containing GHB and the other containing a flavor excipient blend. (Table 8 formulation)

Labeling: The clinical supplies for individual patients were packaged in separate containers. Each container included two unit doses, i.e. two twin-pouches. Clinical supplies for eight patients (including those for two replacement patients) were delivered to the investigator. Foil twin-pouches were identified with a two-part label.

Dose Administration: The investigator or designee prepared the oral solution for dosing within 30 min prior to the first oral administration to individual patients. The contents of

one twin-pouch was emptied into a dosing cup to which two ounces of water were added. After replacing the lid of the dosing cup, it 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 ingesting in its entirety at 4 h after the first GHB dose.

Investigational Drug Accountability: At the conclusion of the study, all clinical supplies were accounted for on the drug accountability form and unused drug supplies were returned for proper disposition.

8. Determination of Plasma GHB Concentrations

Plasma samples were analyzed for GHB by the Department of Bioanalytical Chemistry (Covance (previously known as Hazelton Corning), Madison, Wis.) A gas chromatographic method with mass selective detection (GC-MSD) was used in the analysis.

9. Data Management and Analysis

Data Base: An EXCEL data base (spreadsheet) was constructed from data recorded on Case Report Forms (CRF) and plasma GHB concentration data sets received from Covance (Coming Hazleton). Each entry in the EXCEL spreadsheet was checked against the CRFs and any data entry error found was corrected.

Pharmacokinetic Analysis: Pharmacokinetic parameters were determined for individual sets of plasma GHB concentration vs. time data using the non-compartmental routine in WinNonlin Version 1.1. The peak GHB concentrations (C_{max}) and the times of their respectively occurrences (t_{max}) were observed values. Terminal half-life ($T_{1/2}$) was obtained by log-linear regression analysis of the terminal phase of concentration vs. time curves. The area under the curve (AUC_{inf}) and the area under the first moment curve ($AUMC_{inf}$) were calculated by the linear trapezoidal rule up to the last determined concentration and included extrapolated areas to time infinity. Apparent oral clearance (CL/F) was calculated as Dose/AUC_{inf}. Volume of distribution (V_Z/F) was determined by taking the ratio between CL/F and λ_Z (elimination rate constant). Mean residence time (MRT) was estimated from the ratio between $AUMC_{inf}$ and AUC_{inf}.

Safety Analyses: Results of physical examinations, vital signs, clinical laboratory data were summarized in tabular form and presented by patient number. Adverse events also were tabulated in a similar fashion.

10. Results

Patient and Study Accountability: Six narcoleptic patients were enrolled and all six completed the study in its entirety.

Protocol Compliance: There were no inclusion criteria violations. All patients admitted into the study met the study entrance requirements and completed the screening phase at least one day before the treatment phase.

All six patients took non-study medications in addition to methylphenidate and GHB doses because none of their concomitant medications (Synthroid, Premarin, Lovastatin, Fluvastatin, furosemide, potassium, hydrochlorothiazide, Iansoprazole, and verapamil) were on the exclusion list (which included hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants). Adverse experience probes, vital sign measurements, and essentially all pharmacokinetic blood samples were performed at protocol specified times; the few deviations in blood sampling times should not have any impact on the outcome of the study since actual blood sampling times were used in the pharmacokinetic analysis.

The diagnosis of narcolepsy for at least one year in each patient was verified by a nocturnal polysomnogram (NSG) and a Multiple Sleep Latency Test (MSLT) conducted at a qualified laboratory. Five patients have been maintained on GHB nightly for over 10 years and one patient has been receiving GHB nightly for two years. One patient (Subject 101) also bad multiple sclerosis; however, the attending physician, judged that it would not interfere with the objective of this study. A few of the screening clinical laboratory results marginally fell outside the reference range but none was considered by the attending physician to be clinically significant.

Exposure to Study Drug: All patients ingested the two GHB doses as scheduled (immediately prior to bedtime). The GHB doses per kg body weight ranged from 26.4 to 52.4 mg/kg.

Plasma GHB Concentration Profiles: It was noted that, in certain cases, (Patients #103, and #106), plasma GHB concentrations did not decline from the first C_{max} to zero concentration at h 4. Upon achievement of the second C_{max}, the semi-logarithmic plots of concentration versus time data in Patients #102, #103, and #105 exhibited a convex decline profile. Such a decline pattern suggested non-linear pharmacokinetics. The highest plasma GHB concentration observed in the study was 125.0 μg/mL which occurred in Subject 101 after the second 3 g GHB dose.

Pharmacokinetic Parameter Estimates: The mean (±SD) showed that maximum GHB concentrations (C_{max}) were 62.8±27.4 μg/mL and 91.2±25.6 μg/mL for the first and second GHB doses, respectively. The corresponding mean observed times to maximum concentrations were 40±6 and 36±7 min after the first and second GHB doses, respectively. The mean AUC_{inf} was 17732±4603 μg/mL.h. The mean CL/F was 4.2±1 mL/min/kg and the mean V_Z/F was 307±96 mL/kg. The mean MRT_{inf} was 249±56 min. The mean GHB $T_{1/2}$, estimated by linear regression of log[C] vs. time data of the terminal phase of the second GHB dose was 53±19 min.

Adverse Experiences: No adverse experiences were reported in the study.

Follow-up Safety Assessments: Inspection of screen and follow-up physical examination results per individual patient did not identify any changes attributable to GHB.

11. Discussion

To the inventors' knowledge, the level of GHB in human systemic circulation has not been reported in the literature. Hence, baseline (0 h) plasma samples were analyzed for GHB concentrations. The GC-MSD method used in the present study had a limit of quantification (LOQ) of 7.02 μg/mL and analysis of the baseline plasma samples showed the endogenous levels of GHB are below this sensitivity limit. This finding was confirmed by adding known amounts of GHB (5, 10, and 25 μg per mL of plasma) to blank human plasma samples and subjected these samples to GC-MSD analysis. This method of standard addition allowed an estimation of the endogenous GHB level in human plasma which was found to average about 2.02 μg/mL, (i.e. approximately ⅔ of the Limit Of Quantitation (LOQ) for a validated assay. Hence, the endogenous GHB level was not subtracted from exogenous GHB concentrations prior to pharmacokinetic analysis.

Values of mean t_{max} (~40 min after dosing) and $t_{1/2}$ (~35 min) suggest that the GHB solution administered to narcoleptic patients in this study was readily absorbed and rapidly eliminated. In 3 out of 6 patients the drug was essentially gone from the systemic circulation by h 4 after the first GHB dose whereas in the remaining three patients residual GHB levels of ~15 μg/mL was still detected at h 4.

The convex nature of the decline of plasma GHB concentrations in three patients after achievement of the second C_{max} indicated that elimination of GHB from the systemic circulation in these three patients is capacity limited. Nevertheless,

it should be noted that plasma GHB concentrations were no longer detectable by h 6 after the second GHB dose (10 h after the first GHB dose). The mean apparent oral clearance found in this study was 4.2±1.0 mL/min/kg and appeared to be comparable to the apparent oral clearance of 5.3±2.2 mL/min/kg reported in the literature for a group of alcohol dependent patients who were administered a dose of 50 mg/kg (Ferrara, 1992). While it appeared that the GHB dose (ranging from 26.4 to 52.4 mg/kg with a mean of 36.5 mg/kg) in the present study was lower than the comparison GHB dose (50 mg/kg) administered to the alcohol dependent patients (Ferrara, 1992), it should be noted that each patient in the present study was administered two consecutive GHB doses at four-hour interval and residual GHB levels were detected in three out of six patients immediately prior to the second GHB dose. The GHB pharmacokinetic non-linearity in alcohol dependent patients easily can be observed from the apparent oral clearance which increased to 8.1±4.8 mL/min/kg when the GHB dose is reduced to 25 mg/kg dose (Ferrara, 1992). In the present study, the non-linearity was less obvious because each narcoleptic patient received two consecutive fixed 3 g doses regardless of body weight.

The mean elimination half-life of GHB in the six narcoleptic patients was determined to be 53±19 min, longer than that in alcohol dependent patients after a 50 mg/kg GHB dose (Ferrara, 1992). The lengthening of GHB elimination half-life observed in this study partially was caused by the wider spacing in sampling time points. However, capacity limited elimination of this drug in some of the narcoleptic patients also could have contributed to this prolongation.

GHB appears to have a shortcoming in that its elimination from the body is capacity limited in some patients when the drug is administered at a fixed regimen of 3 g twice nightly at four-hour interval. However, from a therapeutic perspective, GHB offers an advantage in the treatment of narcolepsy because by the time a patient wakes up in the morning (i.e. 8 to 10 h after the first GHB dose), all GHB, including that from the second dose, will have been eliminated from the systemic circulation. GHB was also well tolerated by narcoleptic patients in this study. No adverse experience was reported.

12. Conclusions

The capacity limited elimination kinetics was observed in three out of six patients who had been administered two consecutive 3 g oral doses of GHB, 4 h apart. From a pharmacokinetic perspective, dividing the nightly GHB dose into two portions and administering the two portions to narcoleptic patients at a 2.5- to 4-h interval was rational because the elimination half-life of GHB was short (<1 h). The pharmacokinetic profiles of GHB in narcoleptic patients who had been receiving this agent nightly for years appeared to be comparable to those in alcohol dependent patients (Ferrara, 1992).

EXAMPLE 4

Sodium Oxybate Formulation Study

I. Study Objectives

This example described ways that sodium oxybate may be prepared and tested for stability to determine preferred formulations. Various formulations of sodium oxybate in water were prepared under different conditions, of mixing and with addition of selected acidulents at multiple pH levels (Neo-Pharm Laboratories, Blainville, Quebec). Selected formulations were placed on real time and accelerated stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Therefore several acidulents across a range of 6.0-9.0 were evaluated.

II. Study Design-Part I

The following experimental work is designed to be performed in two stages. Initial studies were conducted to evaluate the impact of conditions of formulation, pH and acidulent on the resultant levels of impurities, specified and unspecified, and potency of sodium oxybate. Sodium oxybate was prepared (MDS Neo-Pharm Laboratories, Quebec Canada), under different conditions of mixing and with addition of selected acidulents at multiple pH levels. These formulations of sodium oxybate acidulent were then tested.

A. Preliminary Studies

1. Formulations Description

All formulations were prepared at a concentration of 500 mg/cc of sodium oxybate in water. Three acidulents (HCl, malic acid, and phosphoric acid), were selected and tested at pH 6.0, 7.5 and 9.0.

2. Method of Formulation

Solutions, were prepared using the described methods:

a. Rapid Mix Method:

Sodium oxybate was dissolved in water and concentrated acidulent was added immediately, without temperature control. Temperature of solution was monitored and recorded prior to and during addition of acidulent. The time of equilibration to room temperature was also recorded. After the solution reached ambient room temperature, it was filtered through a 10 μm filter.

b. Cool Mix Method:

Sodium oxybate was dissolved in water. Acidulent was diluted to 10% and slowly added. The solution was cooled by water with jacket or ice bath. Monitor and record the temperature of the solution was monitored and recorded during addition of acidulent. The time of equilibrium from room temperature was also recorded. The preferred maximum temperature should be maintained at less than 40° C. The solution was filtered through a 10 μm filter.

c. Reverse Order of Addition:

Acidulent was added to water and cooled to room temperature. The sodium oxybate was dissolved in the diluted acidulent solution. The temperature of solution was monitored and recorded during addition of sodium oxybate. The solution was filtered through a 10 μm filter.

d. Sodium Oxybate Control:

Sodium oxybate was dissolved in water to a concentration of 500 mg/cc with no added acidulent. The final pH was recorded and the solution was filtered through a 10 μm (micron or micrometer) filter.

3. Solution data:

Data was recorded for each solution which included: 1) date of preparation 2) date of analysis, 3) amount of acidulent required to achieve target pH, 4) length of time for dissolution of sodium oxybate, 5) temperature profile of solution over time of solution preparation to be recorded at 15 minute intervals, 6) final pH of solution.

4. Testing Requirements:

The following methods were used to test the prepared solutions: pH, HPLC (High Pressure Liquid Chromatography) for potency (sodium oxybate), and for impurities. Time 0 analysis was performed immediately (within 24 h). RRT= (relative retention time).

B. Summary of Part I:

1. Preliminary Evaluation of Sodium Oxybate Formulations

Tables 13, 14 and 15 provide test results for the three methods of preparation of sodium oxybate formulations.

TABLE 13

Preparation Method A

Addition of Concentrated Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/cc % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (Apr. 23, 1998)	pH 9.0	9.0	509 mg/cc	0.009%	RRT 4.88 = 0.01%
(10 drops over 2 minutes)			101%		
(2.5 ml/4 minutes)	pH 7.5	7.5	507 mg/cc	0.01%	RRT 4.89 = 0.02%
			101%		
(45 ml/34 minutes)	pH 6.0	6.0	504 mg/cc	0.033%	RRT 4.89 = 0.33%
			101%		
Malic Acid (Apr. 24, 1998)	pH 9.0	9.1	498 mg/cc	0.009%	RRT 4.89 = 0.01%
(0.12 gm)			99.6%		
(1.6 gm)	pH 7.5	7.6	506 mg/cc	0.009%	RRT 4.89 = 0.01%
			101%		
(25 gm)	pH 6.0	6.2	493 mg/cc	0.011%	RRT 4.89 = 0.01%
			98.6%		
H_3PO_4 (Apr. 24, 1998)	pH 9.0	9.0	493 mg/cc	0.009%	RRT 4.89 = 0.01%
(2 drops)			98.6%		
(1.0 ml)	pH 7.5	7.5	493 mg/cc	0.009%	RRT 4.89 = 0.02%
			98.6%		
(17.3 ml)	pH 6.0	6.1	497 mg/cc	0.063%	RRT 4.89 = 0.02%
			99.4%		
Sodium Oxybate Control	n.a.	9.8	500 mg/cc	0.009%	RRT 4.89 = 0.04%
No Acidulent			100%		

*Method A = Mix Method with Concentrated Acidulent and Temperature Monitoring

TABLE 14

Preparation Method B

Addition of Diluted Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (25%) (Apr. 28, 1998)	pH 9.0	9.1	500 mg/cc	0.009%	RRT 4.88 = 0.01%
(20 drops)			100%		
(8.0 ml)	pH 7.5	7.6	499 mg/cc	0.009%	RRT 4.88 = 0.01%
			99.8%		
(175 ml)	pH 6.0	6.0	502 mg/cc	0.016%	RRT 4.88 = 0.02%
			101%		
H_3PO_4 (25%) (Apr. 29, 1998)	pH 9.0	8.9	499 mg/cc	0.007%	RRT 4.92 = 0.02%
(0.3 ml)			99.8%		
(4.0 ml)	pH 7.5	7.5	497 mg/cc	0.008%	RRT 4.89 = 0.02%
			99.4%		
(120 ml)	pH 6.0	6.0	499 mg/cc	0.019%	RRT 4.89 = 0.01%
			99.8%		
Malic Acid (500 mg/cc)	pH 9.0	9.0	495 mg/cc	0.008%	RRT 4.92 = 0.02%
(Apr. 30, 1998)			99%		
(0.115 gm/0.23 ml)					
(1.75 gm/3.5 ml)	pH 7.5	7.4	488 mg/cc	0.009%	RRT 4.92 = 0.01%
			97.5%		
(35 gm/70 ml)	pH 6.0	6.0	487 mg/cc	0.013%	RRT 4.92 = 0.01%
			97.0%		

*Acidulent added slowly at the rate of 2-3 drops/second

TABLE 15

Preparation Method C					
Reverse Order of Addition* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (May 1, 1998)	pH 9.0	9.0	497 mg/cc	0.006%	RRT 4.92 = 0.03%
(20 drops)			99.4%		
(2.4 ml)	pH 7.5	7.6	504 mg/cc	0.004%	RRT 4.92 = 0.04%
			101%		
(45 ml)	pH 6.0	6.0	493 mg/cc	0.044%	RRT 4.92 = 0.04%
			98.6%		
H_3PO_4 (May 4, 1998)	pH 9.0	8.9	496 mg/cc	0.005%	RRT 4.91 = 0.03%
(0.08 ml)			99.2%		
(1.0 ml)	pH 7.5	7.6	496 mg/cc	0.004%	RRT 4.91 = 0.04%
			99.2%		
(30 ml)	pH 6.0	6.1	489 mg/cc	0.023%	RRT 4.91 = 0.04%
			97.8%		
Malic Acid (May 5, 1998)	pH 9.0	9.0	495 mg/cc	0.006%	RRT 4.93 = 0.02%
(0.12 gm)			99%		
(1.6 gm)	pH 7.5	7.6	497 mg/cc	0.004%	RRT 4.93 = 0.04%
			99.4%		
(35 gm)	pH 6.0	6.2	495 mg/cc	0.044%	RRT 4.93 = 0.04%
			99%		

*Acidulent added to water first, GHB added second.

Review of the data indicated that the optimum method for preparation of sodium oxybate with minimal impurity levels is Method B: Controlled mixing with diluted acidulent. Method 2b resulted in formulations with lowest levels of GBL.

2. Conclusions.

Additional evaluations were carried out on selected formulations: 1) sodium oxybate with HCl as acidulent, at pH 7.5, and 2) sodium oxybate with malic acid as acidulent, pH 6.0, 7.5, and 9.0.

III. Study Design-Part II

Microbial Challenge and Stability Tested to determine the most preferred embodiments, the number of formulations was limited to three based on the data prepared from the above experiments.

A. Kinetic Stability Study with Selected Formulations

Samples of formulations are stored in tightly closed containers. Storage Conditions were 25° C., 40° C., and 60° C. Time points in brackets were tested at the inventor's discretion. The samples were tested according to the following schedule: at 25° C. storage temperature, the assay points will be 0, 14, 28, 45, 60 days and 120 days; at 40° C. storage temperature, the assay points will be 0, 7, 14, 28, 45, 60 days; at 60° C. storage temperature, the assay points will be at 0, 3, 7, 14, 28, 45 days, and, 60 days.

The testing requirements included pH, HPLC for sodium oxybate (duplicate injections of single sample preparation), and impurities, specified and unspecified.

B. Preservative Effectiveness Testing of Selected Formulations

Microbial challenge testing of formulations was preformed according to USP XXIII, <51>, Eighth Supplement. Solutions are determined to "Pass or Fail" based upon the USP criteria for preservative effectiveness which states: For Bacteria, "Not less than 1 log reduction from the initial microbial count at 14 days and no increase from the 14 days count at 28 days;" and for yeast and molds, "No increase from the initial calculated count at 14 and 28 days." Solutions which met these criteria were designated as "Pass" and those that did not meet these criteria were designated as "Fail".

C. Summary Stability Results:

1. Formulations Prepared with Malic Acid as Acidulents:

a. Malic Acid, pH 6.0 formulation (25°), GBL and impurity A levels were very low on Day 0, however, by Day 45 GBL levels had reached 2.8%. Impurity A increased from 0.01 to 1.0%, and pH increased from 6.0 to 6.3 by day 45. This formulation stored at 40° C. and 60° C. showed GBL levels up to 5.4%, impurity A levels increased to 2.3%, and pH increased to 6.3 by Day 14.

b. Malic Acid, pH 7.5 formulation (25° C.), GBL levels were 0.009% on Day 0, and increased to 0.17% by day 45. Impurity A increased from 0.01% to 0.1% and pH increased from 7.5 to 7.9. Malic acid, pH 7.5 GBL levels are reached (40° C.) and 60° C. a maximum of 0.22%. Impurity A levels reached 0.1% and pH increased to 8.0. Under accelerated conditions, all parameters reached an apparent maximum by Day 7 and did not increase significantly thereafter.

c. Malic Acid, pH 9.0 formulation (25° C.,) GBL levels measure 0.008% on Day 0, and increased slightly to 0.013% on Day 45. Impurity A did not increase nor did pH increase. Under accelerated conditions, GBL increased from 0.008% to a maximum of 0.018% by Day 14. Impurity A increased slightly from 0.10 to 0.014% by Day 14.

2. Formulations Prepared with HCL as Acidulents.

HCL, pH 6.0 formulation (250) GBL levels measured 2.8% by Day 30, and impurity A 0.004%, and pH 6.0. Accelerated storage conditions (40° C.) GBL levels were measured at 6.6%, and impurity A measured 3.1% by Day 30.

HCl, pH 7.5 formulation (25%) GBL levels measured 0.041% on Day 0, Impurity A measured 0.02%, and by Day 18 GBL measured to 0.12% and impurity A to 0.07%. Under accelerated conditions (40° C. and 60° C.), GBL increased to a maximum of 0.21%, impurity A increased from 0.02% to 0.1%, and pH increased from 7.5 to 8.0. As with Malic Acid at pH 7.5, the measured parameters reached maximum by Day 7 and did not increase significantly thereafter.

HCl, pH 9.0 formulation (25° C.) GBL levels reached 0.022% by Day 18. Impurity A stayed constant at 0.01% for 18 days. Under accelerated conditions (40° C.) GBL levels

were equivalent to 25° C. storage (0.21%). Impurity A showed no increase over 25° C. conditions.

3. Conclusions.

Formulations selected for microbial challenge testing were the following: HCl, pH 7.5, and malic acid, pH 7.5. The rationale for this decision was twofold. First, the formulations were selected based on minimal formation of GBL and impurity A. Second, the formulations were selected to maintain a pH in the neutral range.

EXAMPLE 5

Further Evaluation of Sodium Oxybate Formulations

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of gamma-hydroxybutyrate.

Scope: Various formulations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple pH levels. Solutions were prepared and tested at Neo-Pharm Laboratories, Blainville, Quebec. All formulations successfully prepared were placed on limited stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Conditions of varying pH and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Procedures: Solutions were prepared as summarized and microbial challenge testing carried out as follows:

I. Evaluation of Sodium Oxybate Formulations

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of gamma-hydroxybutyrate.

Scope: Various formulations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple pH levels. Selected formulations were studied for limited stability. Earlier studies demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Conditions of varying pH and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Responsibility: It was the responsibility of Neo-Pharm Laboratories to prepare selected formulations and perform testing per this protocol. Orphan Medical, New Medicine Development and Quality Assurance were responsible for reviewing raw data at the defined decision point, defining which formulations will be included in stability testing. Orphan Medical was also responsible for reviewing final results (raw data) and the final report.

Procedure: The following formulations were prepared by scientists at Neo-Pharm following the steps listed below and dispensed into containers (amber PET 240 ml bottle, OMI CS-460) and closures (Clic-Loc III, 24-400, OMI CS-470) to a volume of 200 ml each bottle. The bottles were tested by 28-day microbial challenge and by limited stability testing at 25° C. including, appearance, pH, potency, and impurity profile on day 1 (day of preparation) and day 28.

A. Formulations Prepared and Evaluated Using Sodium Oxybate:

TABLE 16

Formulations Prepared and Evaluated Using Sodium Oxybate

Formulation ID No.	Sodium Oxybate Concentration	Acidulent	Final pH
1	500 mg/cc	Malic Acid	7.5
2	250 mg/cc	Malic Acid	7.5
3	350 mg/cc	Malic Acid	7.5
4	450 mg/cc	Malic Acid	7.5
5	550 mg/cc	Malic Acid	7.5
6	650 mg/cc	Malic Acid	7.5
7	500 mg/cc	Citric Acid	7.5
8	500 mg/cc	Malic Acid	5.0

1. Preparation: Method for preparation of various formulations: As previously determined in PR98068, the method of choice for preparation of liquid formulations of sodium oxybate was the following:
   a. For a one liter quantity of product, add the sodium oxybate in 500 ml of purified and stir until dissolved. Prepare a 10% solution of the acid (Malic or Citric) and add slowly to the solution of sodium oxybate. The solution should be monitored for pH and temperature and both variables recorded at reasonable intervals (every 10 or 15 minutes). When the target pH is attained, the solution will be Q.S. to 1 liter, and pH rechecked and recorded.
   b. The final solutions will be filtered through 10 μm filters and 200 mL dispensed into 5 amber PET bottles with closures (provided by Orphan Medical, Inc.). Two bottles will be used for microbial challenge studies and the remaining three bottles will be placed on limited stability.
2. Testing: Formulations were tested by two methods of evaluation:
   a. Limited Stability Evaluation:
      (1) Storage Conditions: 25° C.
      (2) Pull Points: Day 0 (day of preparation), and day 28
      (3) Testing Requirements:

Test	Method
Appearance	Visual
Potency	HPLC Neopharm 764
Impurities	HPLC Neopharm 793DT
pH	USP <791>

   b. Microbial Challenge:
      (1) Storage Conditions: Microbial challenge studies of above formulations were set up with 5 microorganisms and stored for 28 days at 20-25° C., per USP <51> Eighth Supplement.
      (2) Microorganisms: After a sufficient quantity of each formulation is prepared, aliquots were inoculated with 5 microorganisms at a concentration of at least 10' microorganisms/cc:
         (a) *Escherichia coli*, ATCC 8739
         (b) *Pseudomonas aeruginosa*, ATCC 9027
         (c) *Staphylococcus aureus*, ATCC 6538
         (d) *Aspergillus niger*, ATCC 18404
         (e) *Candida albicans*, ATCC 10231

(3) Time Points: A determination of the viable cell concentration in each inoculated container was performed after 0, 1, 3, 7, 14, 21 and 28 days.

B. Formulations To Be Prepared From Alternative Salts of Gamma-Hydroxybutyrate: This work may be staged to take place at a later time than the work described above.

TABLE 17

Formulation Detail				
Formulation ID No.	Salt of GHB	Concentration of Salt of GHB	Acidulent	Final pH
9	Calcium salt	500 mg/cc (Or maximum possible*)	Malic Acid (If compatible)	7.5

1. Solubility determination: Little information is available about the solubility of this alternative salt of gamma-hydroxybutyrate and a determination of solubility was done in advance of efforts to prepare formulations for evaluation by stability and microbial challenge. Maximum solubility is evaluated for pH unadjusted solutions and within the pH range desired for this formulation (pH 6.0-8.0). If solubility is limited, the formulation will be changed to accommodate the solubility limitations. The preferred acidulent for this work is Malic acid. If acid is not compatible with the salt, then an alternative acid can be selected.
2. Preparation: Method for Preparation of Alternative Salt Formulations:
   a. The previously described method (Part A) is used for preparation of formulations of calcium gamma-hydroxybutyrate at the concentrations and specified pH determined by solubility experiments.
   b. The final solutions were filtered through 10 μm filters and dispensed into 5 amber PET bottles with closures (provided by Orphan Medical, Inc.). Two bottles are used for microbial challenge studies and two bottles are placed on limited stability. The remaining bottles are retained for any additional studies at a future time,
3. Testing: Formulations are tested as described above.

C. Reporting of Results: The results will be reported for the Stability and Microbial Challenge results in standard format as defined by the described Orphan Medical Development. Copies of HPLC chromatograms and any raw data from these studies will be provided with results.

D. Acceptance Criteria: Specific acceptance criteria for this study can be described analogous to those for sodium oxybate.

Results: Summarized as follows in Tables 18, 19 and 20 for various studies.

TABLE 18

Result Summary Results of Protocol 98126 Microbial Challenge Study						
	0	Day 1	Day 7	Day 14	Day 21	Day 28
Lot Number MCH1064-33						
GHB, pH 7.50, 500 mg/cc Malic Acid						
E. coli	490,000	5,500	<100	<10	<10	<10
P. aeruginosa	141,000	21,600	<100	<10	<10	<10
S. aureus	1,035,000	405,000	79,500	8,300	1,645	375
C. albicans	835,000	147,000	<100	<10	<10	<10
A. niger	370,000	285,000	120,500	246,500	148,500	183,000
Lot Number MCH1064-35						
GHB, pH 7.50, 250 mg/cc Malic Acid						
E. coli	705,000	229,500	<100	<10	<10	<10
P. aeruginosa	224,500	5,200	<100	<10	<10	<10
S. aureus	1,135,000	390,000	262,500	31,500	4,250	155
C. albicans	705,000	435,000	52,000	850	<10	<10
A. niger	510,000	515,000	155,500	176,000	147,500	184,000
Lot Number MCH1064-37						
GHB, pH 7.50, 350 mg/cc Malic Acid						
E. coli	365,000	310,000	13,400	<10	<10	<10
P. aeruginosa	205,000	15,600	50	<10	<10	<10
S. aureus	1,170,500	605,000	67,500	<60	60	<10
C. albicans	870,000	355,000	8,300	<10	<10	<10
A. niger	540,000	525,000	172,000	155,500	155,500	163,500

TABLE 18-continued

Result Summary
Results of Protocol 98126 Microbial Challenge Study

	0	Day 1	Day 7	Day 14	Day 21	Day 28
			Lot Number MCH1064-43			
GHB, pH 7.50, 550 mg/cc Malic Acid						
E. coli	425,000	63,500	700	<10	<10	<10
P. aeruginosa	171,500	211,550	250	<10	<10	<10
S. aureus	1,020,000	520,000	41,500	1,050	180	10
C. albicans	880,000	157,500	800	<10	<10	<10
A. niger	545,000	505,000	131,000	156,500	205,000	187,500
			Lot Number MCH1064-45			
GHB, pH 7.50, 550 mg/cc Malic Acid						
E. coli	660,000	58,500	450	<10	<10	<10
P. aeruginosa	896,000	14,450	900	<10	<10	<10
S. aureus	860,000	132,000	19,750	935	110	45
C. albicans	1,125,000	166,000	<100	<10	<10	<10
A. niger	530,000	530,000	105,500	153,000	157,500	177,000
			Lot Number MCH1046-47			
GHB, pH 7.50, 650 mg/cc Malic Acid						
E. coli	630,000	119,000	1,350	<10	<10	<10
P. aeruginosa	183,500	5,900	50	<10	<10	<10
S. aureus	890,000	650,000	76,000	14,550	510	1,150
C. albicans	675,000	145,500	<100	<10	<10	<10
A. niger	535,000	385,000	103,000	162,000	187,000	173,000
			Lot Number MCH1064-85			
Ca-Oxybate, pH 7.50, 500 mg/cc Malic Acid						
E. coli	425,000	121,000	1,650	<10	<10	<10
P. aeruginosa	420,000	22,000	300	<10	<10	<10
S. aureus	265,000	2,000	<100	<10	<10	<10
C. albicans	565,000	440,000	29,500	<1000	<10	<10
A. niger	1,310,000	965,000	370,000	640,000	690,000	675,000
			Lot Number MCH1064-49			
GHB, pH 7.50, 500 mg/cc Citric Acid						
E. coli	615,000	6,500	<100	<10	<10	<10
P. aeruginosa	69,500	14,600	<100	<10	<10	<10
S. aureus	650,000	305,000	1,700	<10	<10	<10
C. albicans	720,000	107,000	<100	<10	<10	<10
A. niger	375,000	380,000	99,500	178,500	212,500	165,500

TABLE 19

Result Summary
Data from Dec. 30, 1997

	(n = 3) Inoculu	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Results
GHB (pH 7.5) 750 mg/cc									
E. coli	470,000	160,000	64,500	4,300	420	<10	<10	<10	
P. aeruginosa	437,500	152,000	3,500	10	<10	<10	<10	<10	
S. aureus	447,500	330,000	24,500	42,000	8,050	1,935	15	10	

TABLE 19-continued

Result Summary Data from Dec. 30, 1997									
	(n = 3) Inoculu	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Results
C. albicans	375,000	234,500	28,000	1,950	<10	<10	10	<10	
A. niger	475,500	395,000	395,000	229,000	101,500	161,500	101,000	202,000	
750 mg/cc + 0.20% MP/PP pH 7.50									
E. coli	470,000	127,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	61,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	350,000	3,000	4,050	<10	<10	<10	<10	
C. albicans	375,000	103,500	<1,000	<10	<10	<10	<10	<10	
A. niger	457,500	315,000	415,000	35,500	79,500	38,500	87,500	6,400	
750 mg/cc + 0.1% MP/PP, pH 7.5									
E. coli	470,000	157,000	7,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	90,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	239,000	5,500	16,950	600	<10	<10	<10	
C. albicans	375,000	169,000	<1,000	<100	<10	<10	<10	<10	
A. niger	457,500	335,000	425,000	34,500	168,500	90,500	95,500	99,000	
750 mg/cc + 0.2% Potassium sorbate, pH 7.5									
E. coli	470,000	180,000	735,000	6,200	475	<10	<10	<10	
P. aeruginosa	437,500	152,000	1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	264,000	27,500	49,800	14,550	2,370	<10	<10	
C. albicans	375,000	300,000	41,500	3,800	<10	<10	<10	<100	
A. niger	457,500	325,000	360,000	25,000	202,000	500,000	345,000	425,000	
GHB (pH 6.0) 500 mg/cc									
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10	
P. aeruginosa	437,500	172,000	3,000	<10	<10	<10	<10	<10	
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10	
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10	
A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600	
									PASS
500 mg/cc + 0.2% MP/PP, pH 6.0									
E. coli	470,000	163,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	60,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	243,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	150,500	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	400,000	38,000	<10	<10	<10	<10	<10	
									PASS
500 mg/cc + 0.1% MP/PP, pH 6.0									
E. coli	470,000	206,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	118,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	330,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	221,000	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	355,000	93,500	59,000	8,700	315	35	<10	
									PASS
500 mg/cc + 0.2% Potassium sorbate, pH 6.0									
E. coli	470,000	222,000	46,500	150	<10	<10	<10	<10	
P. aeruginosa	437,500	136,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	410,000	<1,000	130	<10	<10	<10	<10	
C. albicans	375,000	395,000	28,500	<100	<10	<10	<10	<10	
A. niger	475,500	405,000	270,000	63,000	51,000	49,500	39,000	11,150	
									PASS

TABLE 20

Result Summary

	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
Data from Study Dated Dec. 30, 1997								
GHB (pH 6.0) 500 mg/cc								
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10
P. aeruginosa	437,500	172,000	3,000	<10	<10	<10	<10	<10
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10
A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600
Data From Study Begun Mar. 12, 1998								
GHB (pH 6.0) 500 mg/cc								
E. coli	500,000	370,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	198,500	nd	nd	<100	<10	<10	<10
S. aureus	280,000	480,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	340,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	445,000	nd	nd	9,050	20,500	9,450	1,120
GHB (pH 6.0) 500 mg/cc								
E. coli	500,000	199,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	192,500	nd	nd	<100	<10	<10	<10
S. aureus	280,000	300,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	370,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	445,000	nd	nd	10,100	22,750	3,800	4,050
GHB (pH 9.0) 500 mg/cc								
E. coli	500,000	320,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	12,000	nd	nd	<100	<10	<10	<10
S. aureus	280,000	530,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	510,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	345,000	nd	nd	13,800	158,500	315,000	110,500
GHB (pH 9.0) 500 mg/cc								
E. coli	500,000	305,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	20,000	nd	nd	<100	<10	<10	<10
S. aureus	280,000	495,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	380,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	355,000	nd	nd	12,550	157,500	365,000	365,000
GHB (pH 6.0 + Excipients) 500 mg/cc								
E. coli	500,000	96,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	26,000	nd	nd	<100	<10	<10	<10
S. aureus	280,000	155,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	205,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	131,500	nd	nd	6,250	1,825	870	370
GHB (pH 6.0 + Excipients) 500 mg/cc								
E. coli	500,000	93,000	nd	nd	<100	<10	<10	<10
P. aeruginosa	350,000	30,500	nd	nd	<100	<10	<10	<10
S. aureus	280,000	185,000	nd	nd	<100	<10	<10	<10
C. albicans	450,000	135,000	nd	nd	<100	<10	<10	<10
A. niger	450,000	121,500	nd	nd	5,400	1,785	795	505

TABLE 21

Result Summary

GHB (pH 7.50)	HCl	Jul. 2, 1998 Start Date						
500 mg/cc	Initial Conc	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	97000	82000	19200	nd	1000	<10	<10	<10
P. aeruginosa	48500	29500	520	nd	<10	<10	<10	<10
S. aureus	54500	58000	42350	nd	4950	245	<10	<10
C. albicans	58500	38500	1060	nd	<100	<10	<10	<10
A. niger	77500	48000	21450	nd	46000	46000	38000	54000
GHB (pH 7.50)	Malic Acid							
500 mg/cc	Initial Conc	0	Day1	Day 3	Day7	Day 14	Day 21	Day 28
E. coli	97000	83000	44450	nd	3050	70	<10	<10
P. aeruginosa	48500	15650	545	nd	<10	<10	<10	<10
S. aureus	54500	59500	48400	nd	17400	6500	820	505
C. albicans	58500	44000	6200	nd	500	<10	<10	<10
A. niger	77500	35500	24100	nd	28000	49000	44500	44000
GHB (pH 7.50)	HCl	Jul. 2, 1998 Start Date						
500 mg/cc	Initial Co	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	9.70E+04	8.20E+04	1.92E+04	nd	1.00E+03	<10	<10	<10
P. aeruginosa	4.85E+04	2.95E+04	5.20E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.80E+04	4.24E+04	nd	4.95E+03	2.45E+02	<10	<10
C. albicans	5.85E+04	3.85E+04	1.06E+03	nd	<100	<10	<10	<10
A. niger	7.75E+04	4.80E+04	2.15E+04	nd	4.60E+04	4.60E+04	3.80E+04	5.40E+04
GHB (pH 7.50)	Malic Acid							
500 mg/cc	Initial Co	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	9.70E+04	8.30E+04	4.45E+04	nd	3.05E+03	7.00E+01	<10	<10
P. aeruginosa	4.85E+04	1.57E+04	5.45E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.95E+04	4.84E+04	nd	1.74E+04	6.50E+03	8.20E+02	5.05E+02
C. albicans	5.85E+04	4.40E+04	6.20E+03	nd	5.00E+02	<10	<10	<10
A. niger	7.75E+04	3.55E+04	2.41E+04	nd	2.80E+04	4.90E+04	4.45E+04	4.40E+04

For Category 1C Products:

Bacteria: Not less than 1 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days.

Yeast and Molds: No increase from the initial calculated count at 14 and 28 days.

TABLE 22

pH Variable Result Summary

GHB, pH 7.5 750 mg/cc Dec. 30, 1997	Inoculum	0	Day 14	Day 28	GHB, pH 6.0 500 mg/cc Dec. 30, 1997	Inoculum	0	Day 14	Day 28
E. coli	470,000	160,000	<10	<10	*E. coli*	470,000	221,000	<10	<10
P. aeruginosa	437,500	152,000	<10	<10	*P. aeruginosa*	437,500	172,000	<10	<10
S. aureus	447,500	330,000	1,935	10	*S. aureus*	447,500	320,000	<10	<10
C. albicans	375,000	234,500	<10	<10	*C. albicans*	375,000	310,000	<10	<10
A. niger	475,500	395,000	161,500	202,000	*A. niger*	475,500	270,000	48,500	8,600
GHB, pH 7.5 750 mg/cc + 0.2% MP/PP Dec. 30, 1997					GHB, pH 6.0 500 mg/cc + 0.2% MP/PP Dec. 30, 1997				
E. coli	470,000	127,000	<10	<10	*E. coli*	470,000	163,000	<10	<10
P. aeruginosa	437,500	61,000	<10	<10	*P. aeruginosa*	437,500	60,000	<10	<10
S. aureus	447,500	350,000	<10	<10	*S. aureus*	447,500	243,000	<10	<10
C. albicans	375,000	103,500	<10	<10	*C. albicans*	375,000	150,500	<10	<10
A. niger	457,500	315,000	38,500	6,400	*A. niger*	475,500	400,000	<10	<10
GHB, pH 7.5 750 mg/cc + 0.1% MP/PP					GHB, pH 6.0 500 mg/cc + 0.1% MP/PP Dec. 30, 1997				

TABLE 22-continued

pH Variable Result Summary

E. coli	470,000	157,000	<10	<10	*E. coli*	470,000	206,000	<10	<10
P. aeruginosa	437,500	90,000	<10	<10	*P. aeruginosa*	437,500	118,000	<10	<10
S. aureus	447,500	239,000	<10	<10	*S. aureus*	447,500	330,000	<10	<10
C. albicans	375,000	169,000	<10	<10	*C. albicans*	375,000	221,000	<10	<10
A. niger	457,500	335,000	90,500	99,000	*A. niger*	475,500	355,000	315	<10
GHB, pH 7.5 750 mg/cc + 0.2% Potassium sorbate	xxxxxx				GHB, pH 6.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coil					*E. coil*				
P. aeruginosa					*P. aeruginosa*				
S. aureus					*S. aureus*				
C. albicans					*C. albicans*				
A. niger					*A. niger*				
GHB, pH 6.0 500 mg/cc + 0.2% Potassium sorbate Dec. 30, 1997					GHB, pH 6.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coli	470,000	222,000	<10	<10	*E. coli*	500,000	199,000	<10	<10
P. aeruginosa	437,500	136,000	<10	<10	*P. aeruginosa*	350,000	192,500	<10	<10
S. aureus	447,500	410,000	<10	<10	*S. aureus*	280,000	300,000	<10	<10
C. albicans	375,000	395,000	<10	<10	*C. albicans*	450,000	370,000	<10	<10
A. niger	475,500	405,000	49,500	11,150	*A. niger*	450,000	445,000	22,750	4,050
GHB, pH 6.0 500 mg/cc + Excipients Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 6.0 500 mg/cc + Excipients Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	93,000	<10	<10	*E. coli*	500,000	96,000	<10	<10
P. aeruginosa	350,000	30,500	<10	<10	*P. aeruginosa*	350,000	26,000	<10	<10
S. aureus	280,000	185,000	<10	<10	*S. aureus*	280,000	155,000	<10	<10
C. albicans	450,000	135,000	<10	<10	*C. albicans*	450,000	205,000	<10	<10
A. niger	450,000	121,500	1,785	505	*A. niger*	450,000	131,500	1,825	370
GHB, pH 9.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 7.50 500 mg/cc, HCl Jul. 2, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	320,000	<10	<10	*E. coli*	97000	82000	<10	<10
P. aeruginosa	350,000	12,000	<10	<10	*P. aeruginosa*	48500	29500	<10	<10
S. aureus	280,000	530,000	<10	<10	*S. aureus*	54500	58000	245	<10
C. albicans	450,000	510,000	<10	<10	*C. albicans*	58500	38500	<10	<10
A. niger	450,000	345,000	158,500	110,500	*A. niger*	77500	48000	46000	54,000
GHB, pH 9.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 7.5 500 mg/cc, Malic Acid Jul. 2, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	305,000	<10	<10	*E. coli*	97000	83000	70	<10
P. aeruginosa	350,000	20,000	<10	<10	*P. aeruginosa*	48500	15650	<10	<10
S. aureus	280,000	495,000	<10	<10	*S. aureus*	54500	59500	6500	505
C. albicans	450,000	380,000	<10	<10	*C. albicans*	58500	44000	<10	<10
A. niger	450,000	355,000	157,500	365,000	*A. niger*	77500	35500	49000	44,000

Short term stability testing was carried out as described in Appendix A and results are summarized in—Results of Limited Stability Testing—XYREM® oral solution—are show as follows:

TABLE 23-A

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Jan. 26, 1999
NO.: 333198

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	512 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.068%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.45: 0.021%	NPLC-793D
GBL-RRT 1.6	Impurity A (RRT 4.3): ≦0.5%	RRT 4.17: 0.02%	
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.02% RRT 3.79: 0.007%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge Test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:
Initial test
Formulation 1: 500 mg/cc; Malic acid; pH 7.5
THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328841

TABLE 23-B

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: Jan. 21, 1999
NO.: 331347

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	510 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.36%	NPLC-793D
Impurities specified	Gamma-Butyrolactone (RRT = 1.6): ≦0.5%	RRT 1.46: 0.23%	NPLC-793D
	Impurity A (RRT 4.3): ≦0.5%	RRT 4.31: 0.1%	
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:
28 days (25° C., 60% RH)
Formulation 1: 500 mg/cc; Malic acid; pH 7.5
*A: RRT 1.30: 0.02% RRT 3.93: 0.008%

TABLE 23-C

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305

DATE: Jan. 26, 1999
NO.: 333197

ARTIFACT SHEET

Enter artifact number below. Artifact number is application number + artifact type code (see list below) + sequential letter (A, B, C …). The first artifact folder for an artifact type receives the letter A, the second B, etc..
Examples: 59123456PA, 59123456PB, 59123456ZA, 59123456ZB

13592202VA

Indicate quantity of a single type of artifact received but not scanned. Create individual artifact folder/box and artifact number for each Artifact Type.

☐ CD(s) containing:
- computer program listing ☐
  Doc Code: Computer Artifact Type Code: P
- pages of specification and/or sequence listing and/or table ☐
  Doc Code: Artifact Artifact Type Code: S
- content unspecified or combined ☐
  Doc Code: Artifact Artifact Type Code: U

☐ Stapled Set(s) Color Documents or B/W Photographs
Doc Code: Artifact Artifact Type Code: C

☐ Microfilm(s)
Doc Code: Artifact Artifact Type Code: F

1 Video tape(s)
Doc Code: Artifact Artifact Type Code: V

☐ Model(s)
Doc Code: Artifact Artifact Type Code: M

☐ Bound Document(s)
Doc Code: Artifact Artifact Type Code: B

☐ Confidential Information Disclosure Statement or Other Documents marked Proprietary, Trade Secrets, Subject to Protective Order, Material Submitted under MPEP 724.02, etc.
Doc Code: Artifact Artifact Type Code X

☐ Other, description: _____
Doc Code: Artifact Artifact Type Code: Z

March 8, 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Dayton T. Reardan Ph.D et al.

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

Docket No.:	101.031US9	Serial No.:	13/592,202
Filed:	August 22, 2012	Due Date:	N/A
Examiner:	Lena Najarian	Group Art Unit:	3686
Customer No.:	21186	Confirmation No.:	5805

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

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

X Supplemental Information Disclosure Statement (2 pgs.); Form 1449 (1 pg.); CD-ROM disk (1).
X Return Postcard

If not provided for in a separate paper filed herewith, please consider this a PETITION FOR EXTENSION OF TIME for sufficient number of months to enter these papers and please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
Customer No.: 21186

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

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 6th day of March, 2013.

/Valerie Murphy/
Name

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Dayton T. Reardan Ph.D et al.	Examiner:	Lena Najarian
Serial No.:	13/592,202	Group Art Unit:	3686
Filed:	August 22, 2012	Docket:	101.031US9
Customer No.:	21186	Confirmation No.:	5805
Title:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD		

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

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

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

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

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

The following citation appears on the accompanying Form 1449:

- "Advisory Committee Video on Xyrem, Oral Solution", (5/29/01), 9 minutes, 8 seconds. The submission corresponding to this citation is a physical CD-ROM disk containing a video file.

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

Respectfully submitted,

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

Date March 5, 2013 By / /

David D'Zurilla
Reg. No. 36,776

DDZ:vam

Modified form PTO/SB/08A(04-07) OMB 651-0031
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Substitute for form 1449A/PTO	*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	**Application Number**	13/592,202
	Filing Date	August 22, 2012
	First Named Inventor	Dayton T. Reardan Ph.D
(Use as many sheets as necessary)	**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
	"Advisory Committee Video on Xyrem, Oral Solution", (5/29/01), 9 minutes, 8 seconds	

EXAMINER **DATE CONSIDERED**

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

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-8,457,988	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 **DATE CONSIDERED**

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/595,676	08/27/2012	INV001Dayton T. Reardan	101.031US10	1006

21186 7590 03/21/2013

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

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

NOTIFICATION DATE	DELIVERY MODE
03/21/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@slwip.com
SLW@blackhillsip.com

Office Action Summary	Application No.	Applicant(s)	
	13/595,676	REARDAN ET AL.	
	Examiner	Art Unit	
	LENA NAJARIAN	3686	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-25* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-25* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20121004; 20130214; 20130305*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 1-25 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Based upon consideration of all of the relevant factors with respect to the claims as a whole, claims 1-25 are held to claim an abstract idea, and are therefore rejected as ineligible subject matter under 35 U.S.C. §101. The rationale for this finding is explained below:

Based on Supreme Court precedent and recent Federal Circuit decisions, the Office's guidance to examiners is that a §101 process should ordinarily at least (1) be tied to a particular machine or apparatus or (2) transform underlying subject matter (such as an article or materials) to a different state or thing. *Diamond v. Diehr,* 450 U.S. 175, 184 (1981); *Parker* v. *Flook,* 437 U.S. 584, 588 n.9 (1978); *Gottschalk v. Benson,* 409 U.S. *63,* 70 (1972); *Cochrane* v. *Deener,* 94 U.S. 780,787-88 (1876). If neither of these requirements is met by the claim, the method is likely not a patent eligible process under §101 and should be rejected as being directed to nonstatutory subject matter.

The recited steps of independent claim 1, for example, of receiving, entering, maintaining, and using information are not tied to a machine or apparatus and do not transform underlying subject matter (such as an article or

materials) to a different state or thing. Furthermore, it appears as though the steps are being performed by a human. Therefore, claims 1-25 are deemed to be directed to non-statutory subject matter.

Claim Rejections - 35 USC § 112

3. The following is a quotation of 35 U.S.C. 112(b):

(B) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 3, 10, 16, and 21 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

5. The term "controls" in claims 3, 10, 16, and 21 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.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, 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. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keresman, III et al (US 2001/0047281 A1) in view of Lilly et al. (US 2004/0176985 A1), and further in view of Talk About Sleep ("An Interview with Orphan Medical about Xyrem").

(A) Referring to claim 1, Keresman discloses a method of treatment of a patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising (abstract of Keresman):

receiving into a single computer database all 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 (para. 15 of Keresman);

entering into the single computer database information sufficient to identify the patient for whom the company's prescription drug is prescribed (para. 15 of Keresman);

entering into the single computer database 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 (para. 15 of Keresman).

Keresman does not expressly disclose: entering and maintaining in the single computer database information that indicates that the narcoleptic patient or prescriber has abused, misused, or diverted the company's prescription drug; and using the single computer database to authorize filling of the prescriptions for the company's prescription drug only if there is no record of incidents that indicate abuse, misuse, or diversion by the narcoleptic patient or prescriber, or if there is a record of such incidents, the single computer database indicates that such incidents have been investigated, and the single computer database indicates that such incidents do not involve abuse, misuse or diversion.

Lilly discloses entering and maintaining in the single computer database information that indicates that the patient or prescriber has abused, misused, or diverted the company's prescription drug (para. 54-58 of Lilly); and

using the single computer database to authorize filling of the prescriptions for the company's prescription drug only if there is no record of incidents that indicate abuse, misuse, or diversion by the patient or prescriber, or if there is a record of such incidents, the single computer database indicates that such incidents have been investigated, and the single computer database indicates that such incidents do not involve abuse, misuse or diversion (para. 54-58 and 39 of Lilly).

Talk About Sleep discloses patients with narcolepsy (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

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 Lilly and Talk

About Sleep within Keresman. The motivation for doing so would have been for less abuse-related healthcare costs, fewer erroneous prescriptions, more accountability, and better tracking and management of prescriptions (para. 12 of Lilly) and to help those with cataplexy safely obtain the necessary medication (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

(B) Referring to claims 2 and 3, Keresman and Lilly do not disclose delivering the prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the prescription drug and wherein an exclusive central pharmacy controls the single computer database.

Talk About Sleep discloses delivering the prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the prescription drug and wherein an exclusive central pharmacy controls the single computer database (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

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 Keresman and Lilly. The motivation for doing so would have been to provide the necessary medication to patients that need it in a safe and responsible manner (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

(C) Referring to claims 4 and 5, Keresman discloses selectively blocking shipment of the prescription drug to the patient (para. 66 of Keresman)

Keresman does not disclose wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the prescription drug is blocked based upon such association.

Lilly discloses wherein an abuse pattern is associated with the patient, and shipment of the prescription drug is blocked based upon such association (para. 58 of Lilly).

Talk About Sleep discloses patients with narcolepsy (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

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 Lilly and Talk About Sleep within Keresman. The motivation for doing so would have been for less abuse-related healthcare costs, fewer erroneous prescriptions, more accountability, and better tracking and management of prescriptions (para. 12 of Lilly) and to help those with cataplexy safely obtain the necessary medication (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

(D) Referring to claims 6 and 7, Keresman and Lilly do not disclose wherein the prescription drug comprises a gamma hydroxy butyrate (GHB) drug product and wherein said GHB drug product treats cataplexy in said narcoleptic patient.

Talk About Sleep discloses wherein the prescription drug comprises a gamma hydroxy butyrate (GHB) drug product and wherein said GHB drug product treats cataplexy in said narcoleptic patient (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

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 Keresman and Lilly. The motivation for doing so would have been to provide the necessary medication to patients that need it in a safe and responsible manner (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

(E) Referring to claim 8, Keresman discloses a method of treatment of a patient with a prescription drug that has the potential for misuse, abuse or diversion, comprising (abstract of Keresman):

receiving into a single computer database all prescriptions for a prescription drug with the potential for abuse, misuse or diversion (para. 15 of Keresman);

entering into the single database information sufficient to identify the patient for whom said prescription drug was prescribed (para. 15 of Keresman);

entering into the single database information sufficient to identify the physician or other prescriber of said prescription drug and information to show that the physician or other prescriber was authorized to prescribe said prescription drug (para. 15 of Keresman);

Keresman does not expressly disclose that drug is sold or distributed under a single trademark, entering and maintaining in the single database information which may suggest that the narcoleptic patient or prescriber has abused, misused, or diverted said prescription drug; using the single computer database to authorize filling of the prescriptions for said prescription drug only if

there is no record of incidents that may suggest abuse, misuse, or diversion by the narcoleptic patient or prescriber, or if there is a record of such incidents, the single computer database indicates that such incidents have been investigated, and the single computer database indicates that such incidents do not involve abuse, misuse or diversion.

Lilly discloses entering and maintaining in the single database information which may suggest that the patient or prescriber has abused, misused, or diverted said prescription drug; using the single computer database to authorize filling of the prescriptions for said prescription drug only if there is no record of incidents that may suggest abuse, misuse, or diversion by the patient or prescriber, or if there is a record of such incidents, the single computer database indicates that such incidents have been investigated, and the single computer database indicates that such incidents do not involve abuse, misuse or diversion (para. 54-58 and 39 of Lilly).

Talk About Sleep discloses patients with narcolepsy and that drug is sold or distributed under a single trademark (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

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 Lilly and Talk About Sleep within Keresman. The motivation for doing so would have been for less abuse-related healthcare costs, fewer erroneous prescriptions, more accountability, and better tracking and management of prescriptions (para. 12 of

Lilly) and to help those with cataplexy safely obtain the necessary medication (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

(F) Referring to claim 15, Keresman discloses a method of treatment of a patient with a prescription drug that has the potential for misuse, abuse or diversion, comprising (abstract of Keresman):

entering into the single database information sufficient to identify the patient for whom said prescription drug was prescribed (para. 15 of Keresman),

entering into the single database information sufficient to identify the physician or other prescriber of said prescription drug and information to show that the physician or other prescriber was authorized to prescribe said prescription drug (para. 15 of Keresman);

Keresman does not disclose receiving into a single computer database all prescriptions for a prescription drug that has been manufactured at a single manufacturing site with the potential for abuse, misuse or diversion; entering and maintaining in the single database information which may suggest that the narcoleptic patient or prescriber has abused, misused, or diverted said prescription drug; using the single computer database to authorize filling of the prescription for said prescription drug only if there is no record of incidents that may suggest abuse, misuse, or diversion by the narcoleptic patient or prescriber or if any such incidents have been investigated and found not to involve abuse, misuse or diversion; providing said prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the prescription drug; wherein the prescription drug that has the potential for misuse, abuse or diversion is a

gamma hydroxybutyrate (GHB) drug product; wherein said GHB drug product treats cataplexy in said narcoleptic patient.

Lilly discloses entering and maintaining in the single database information which may suggest that the patient or prescriber has abused, misused, or diverted said prescription drug; using the single computer database to authorize filling of the prescription for said prescription drug only if there is no record of incidents that may suggest abuse, misuse, or diversion by the patient or prescriber or if any such incidents have been investigated and found not to involve abuse, misuse or diversion (para. 54-58 and 39 of Lilly).

Talk About Sleep discloses receiving into a single computer database all prescriptions for a prescription drug that has been manufactured at a single manufacturing site with the potential for abuse, misuse or diversion; providing said prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the prescription drug; wherein the prescription drug that has the potential for misuse, abuse or diversion is a gamma hydroxybutyrate (GHB) drug product; wherein said GHB drug product treats cataplexy in said narcoleptic patient (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

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 Lilly and Talk About Sleep within Keresman. The motivation for doing so would have been for less abuse-related healthcare costs, fewer erroneous prescriptions, more accountability, and better tracking and management of prescriptions (para. 12 of

Lilly) and to help those with cataplexy safely obtain the necessary medication (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

(H) Referring to claim 19, Keresman discloses a method of treatment of a patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising (abstract of Keresman):

receiving into a single computer database all prescriptions for the prescription drug with the potential for abuse, misuse or diversion (para. 15 of Keresman),

entering into the single computer database information sufficient to identify the patient for whom the company's prescription drug is prescribed (para. 15 of Keresman);

entering into the single computer database 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 (para. 15 of Keresman).

Keresman does not disclose entering and maintaining in the single computer database information that indicates that the narcoleptic patient or prescriber has abused, misused, or diverted the company's prescription drug; and using the single computer database to authorize filling of the prescriptions for the company's prescription drug only if there is no record of incidents that indicate abuse, misuse, or diversion by the narcoleptic patient or prescriber, or if there is a record of such incidents, the single computer database indicates that such incidents have been investigated, and the single computer database

indicates that such incidents do not involve abuse, misuse or diversion and wherein the prescription drug inventory is owned by a company and is managed thorough said single computer database.

Lilly discloses entering and maintaining in the single computer database information that indicates that the patient or prescriber has abused, misused, or diverted the company's prescription drug; and using the single computer database to authorize filling of the prescriptions for the company's prescription drug only if there is no record of incidents that indicate abuse, misuse, or diversion by the patient or prescriber, or if there is a record of such incidents, the single computer database indicates that such incidents have been investigated, and the single computer database indicates that such incidents do not involve abuse, misuse or diversion (para. 54-58 and 39 of Lilly).

Talk About Sleep discloses wherein the prescription drug inventory is owned by a company and is managed thorough said single computer database and patients with narcolepsy (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

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 Lilly and Talk About Sleep within Keresman. The motivation for doing so would have been for less abuse-related healthcare costs, fewer erroneous prescriptions, more accountability, and better tracking and management of prescriptions (para. 12 of Lilly) and to help those with cataplexy safely obtain the necessary medication (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

(G) Claims 9-14, 16-18, and 20-25 repeat the same limitations as claims 2-7, and are therefore rejected for the same reasons given above.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LENA NAJARIAN whose telephone number is (571)272-7072. The examiner can normally be reached on Monday - Friday, 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jerry O'Connor can be reached on (571) 272-6787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LENA NAJARIAN/
Primary Examiner, Art Unit 3686
3/8/13

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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	13/595,676
	Filing Date	August 27, 2012
	First Named Inventor	Dayton T. Reardan Ph.D
	Group Art Unit	3626
	Examiner Name	Unknown
Sheet 1 of 5	Attorney Docket No: 101.031U10	

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	Examiner Name	Unknown
Sheet 2 of 5	Attorney Docket No: 101.031U10	

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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	13/595,676
	Filing Date	August 27, 2012
	First Named Inventor	Dayton T. Reardan Ph.D
	Group Art Unit	3626
	Examiner Name	Unknown
Sheet 4 of 5	Attorney Docket No: 101.031U10	

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. 11/097,985, Notice of Allowance mailed 03-10-10", 11 pgs	
	"Application Serial No. 11/097,985, Preliminary Amendment mailed 04-01-05", 7 pgs	
	"Application Serial No. 11/097,985, Response filed 11-03-09 to Non Final Office Action mailed 09-14-09", 15 pgs	
	"Application Serial No. 11/097,985, Supplemental Notice of Allowability mailed 06-29-10", 3 pgs	
	"Application Serial No. 12/704,097, Non-Final Office Action mailed 09-24-10", 5 pgs	
	"Application Serial No. 12/704,097, Notice of Allowance mailed 12-21-10", 8 pgs	
	"Application Serial No. 12/704,097, Response filed 11-04-10 to Non Final Office Action mailed 09-24-10", 12 pgs	
	"Application Serial No. 13/013,680, Response filed 06-12-12 to Restriction Requirement mailed 12-14-11", 9 pgs	
	"Application Serial No. 13/013,680, Restriction Requirement mailed 12-14-11", 7 pgs	
	"Application Serial No.13/013,680, Preliminary Amendment filed 06-13-12", 4 pgs	
	"Civil Docket", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 2:10-CV-06108-ES-CLW), (11/22/10), 15 pgs	
	"Complaint For Patent Infringement", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 10-6108 (ES) (CLW)), (11/22/10), 14 pgs	
	"Diversion Prevention Through Responsible Distribution", NADDI Regional Training, (May 2001), 12 pages	
	"Diversion Prevention Through Responsible Distribution", NADDI Regional Training Tennessee, (June 2001), 14 Pages	
	"Diversion Prevention Through Responsible Distribution", NADDI National Conference, (November 2001), 15 pages	
	"Jazz Pharmaceuticals, Inc.'s Opening Markman Brief", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., United States District Court, District of New Jersey Civil Action No. 10-6108 (ES) (CLW), (12/05/11), 34 pgs	
	"Jazz Pharmaceuticals, Inc.'s Responsive Markman Brief", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 10-6108 (ES) (CLW)), (02/21/12), 41 pgs	
	"Joint Claim Construction And Prehearing Statement", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 10-6108 (ES) (CLW)), (10/21/11), 31 pgs	
	"Letter dated 10-14-10 from Randall S. Wilson (Roxane Labs) to Bruce C. Cozadd (Jazz Pharmaceuticals)", Re: Patent Notice Pursuant to Section 505(b)(3)(B) [21 USC Sec. 355(b)(3)(B)], (10/14/10), 11 pgs	
	"Letter from Theodora McCormick to Magistrate Judge Cathy L. Waldor", (w/ Exhibits), (02/27/12), 60 pgs	

EXAMINER /Lena Najarian/ **DATE CONSIDERED** 03/08/2013

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	Group Art Unit	3626
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Sheet 5 of 5	Attorney Docket No: 101.031U10	

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
	"Letter from Theodora McCormick to Magistrate Judge Cathy L. Waldor", (w/ Exhibits), (03/19/12), 104 pgs	
	"Letter from Theodora McCormick to Magistrate Judge Cathy L. Waldor", (03/29/12), 4 pgs	
	"NASCSA National Conference", Orphan Medical, Inc., (November 2000), 8 pgs	
	"Peripheral and Central Nervous System Drugs Advisory Committee", Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, Holiday Inn, Bethesda, Maryland, (06/06/2001), 7 pages	
	"Preliminary Amendment pursuant to 37 CFR Sec. 1.115", Application Serial No. 11/104,013 filed 04-12-05, 3 pgs	
	"Reply To Counterclaims", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., United States District Court, District of New Jersey Civil Action No. 10-6108 (SDW) (MCA), (02/07/11), 37 pgs	
	"Reply To Counterclaims", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 11-660 (SDW) (MCA) Lead Action CV-10-6108), (04/18/11), 6 pgs	
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims To Plaintiff's Complaint", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 10-6108 (ES) (CLW), (12/29/10), 21 pgs	
	"Roxane Laboratories, Inc.'s Initial Invalidity And Noninfringement Contentions Pursuant To Local Patent Rule 3.6", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 2:10-cv-06108 (SDW) (MCA)), (04/14/11), 317 pgs	
	"Roxane Laboratories, Inc.'s Opening Markman Brief In Support Of Its Claim Constructions", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 2.10-cv-06108 (ES) (CLW)), (12/05/11), 37 pgs	
	"Roxane Laboratories, Inc.'s Responsive Markman Brief In Support Of Its Claim Constructions", Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc., (United States District Court, District of New Jersey Civil Action No. 2:10-cv-06108 (ES) (CLW)), (02/21/12), 27 pgs	
	"System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) Starter Kit", Celgene Corporation, (2001), 103 pgs.	
	UKENS, C., "Specialty Pharmacy", Drug Topics, 144, (June 5, 2000), 40-47	

EXAMINER	/Lena Najarian/	DATE CONSIDERED	03/08/2013

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	Filing Date	August 27, 2012
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	Group Art Unit	3626
	Examiner Name	Unknown
Sheet 1 of 1	Attorney Docket No: 101.031U10	

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. 13/592,202, Restriction Requirement mailed 01-16-13", 6 pgs	
	"Application Serial No. 13/595,757, Non Final Office Action mailed 01-17-13", 6 pgs	
	"Markman Opinion, filed September 14, 2012, in the case of Jazz Pharmaceuticals, Inc., Plaintiff, v. Roxane Laboratories, Inc., Defendant (United States District Court for the District of New Jersey, Civil 10-6108 ES)", 43 pgs.	
	"Roxane Laboratories, Inc.'s Answer and Affirmative Defenses to Plaintiff's Complaint", (January 4, 2013), 8 pgs.	
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint", (December 29, 2010), 21 pgs.	
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint", (March 9, 2011), 13 pgs.	
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint", (June 1, 2011), 12 pgs.	
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint", (November 9, 2012), 18 pgs.	

EXAMINER /Lena Najarian/ **DATE CONSIDERED** 03/08/2013

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	Application Number	13/595,676
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	Group Art Unit	3626
	Examiner Name	Unknown
Sheet 1 of 1	Attorney Docket No: 101.031U10	

US PATENT DOCUMENTS

Examiner Initial *	USP Document Number	Publication Date	Name of Patentee or Applicant of cited Document
	US-20030074225	4/17/2003	Borsand, Gerlad, et al.

OTHER DOCUMENTS – NON PATENT LITERATURE DOCUMENTS

Examiner Initial *	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T 1
	"Application Serial No. 13/592,202, Response filed 02-15-13 to Restriction Requirement mailed 01-16-13", 8 pgs	
	"Briefing Booklet for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting", Orphan Medical, Inc., (6/6/01), 353 pgs	
	"Civil Cover Sheet", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey, (1/18/13), 2 pgs	
	"Complaint for Patent Infringement", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey, (1/18/13), 17 pgs	
	"Controlled Substances Act", Drugs of Abuse, U.S. Department of Justice, Drug Enforcement Administration, (1997), 9 pgs	
	"Detailed Factual and Legal Basis of Non-Infringement and/or Invalidity", Amneal Pharmaceuticals, LLC, (12/12/12), 3 pgs	
	"Detailed Factual and Legal Basis of Non-Infringement and/or Invalidity", Amneal Pharmaceuticals, LLC, (12/7/12), 6 pgs	
	"Exhibits A-D", Jazz Pharmaceuticals v Amneal Pharmaceuticals, LLC, (1/18/2013), 151 pgs	
	"Exhibits D-G", Jazz Pharmaceuticals v Amneal Pharmaceuticals, LLC, (1/18/13), 123 pgs	
	"Fed. R. Civ. P. Rule 7.1 Disclosure Statement", (1/18/13), 2 pgs	
	"Making Good in Your Own Mail-Order Business", Changing Times - The Kiplinger Magazine, (October 1980), 66-68	
	"Notice of Electronic Filing: Civil Inital Pleadings (Attorney/Credit Card) USE CASE 33-1", US District Court, District of new Jersey [LIVE], (1/18/13), 2 pgs	
	"Notice of Paragraph IV Certification Concerning ANDA 203631 for Sodiium Oxybate Oral Solution, 500 mg/mL", Amneal Pharmaceuticals, LLC, (12/7/12), 4 pgs	
	"Notice of Paragraph IV Certification Concerning ANDA 203631 for Sodiium Oxybate Oral Solution. 500 mg/mL", Amneal Pharmaceuticals, LLC, (12/12/12), 4 pgs	
	"Peripheral and Central Nervous System Drugs Advisory Committee - Transcript", Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, Holiday Inn, Bethesda, Maryland, (6/6/01), 381 pgs	
	"Xyrem Prescription and Distribution Process-Video Script", (2/2/01), 10 pgs	
	DEUTSCH, SHERYL, "The Verification and Information-Gathering Process", The Credentialing Handbook, Aspen Publishers, Inc., (1999), 231-275	
	MANI, RANJIT, "Preliminary Clinical Safety Review of NDA No. 21196", Orphan Medical, Inc., (05/03/01), 122 pgs	

EXAMINER /Lena Najarian/ **DATE CONSIDERED** 03/08/2013

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/595,757	08/27/2012	Dayton T. Reardan	101.031US11	5359

21186 7590 03/12/2013

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

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

NOTIFICATION DATE	DELIVERY MODE
03/12/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@slwip.com
SLW@blackhillsip.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/595,757	REARDAN ET AL.	
	Examiner	Art Unit	
	LENA NAJARIAN	3686	

All participants (applicant, applicant's representative, PTO personnel):

(1) *LENA NAJARIAN*.

(2) *David D'Zurilla (Reg. No. 36,776)*.

(3) *Phil McGarrigle (Reg. No. 31,395)*.

(4)_____.

Date of Interview: *05 March 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☒112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *all*.

Identification of prior art discussed: *n/a*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Discussed 112 rejection and Applicant's newly filed IDS..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/LENA NAJARIAN/ Primary Examiner, Art Unit 3686	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

in every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

UNITED STATES PATENT AND TRADEMARK OFFICE

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NOTICE OF ALLOWANCE AND FEE(S) DUE

21186 7590 03/21/2013
SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

DATE MAILED: 03/21/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/595,757	08/27/2012	INV001Dayton T. Reardan	101.031US11	5359

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	$1780	$0	$0	$1780	06/21/2013

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.

PTOL-85 (Rev. 02/11)

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)

21186 7590 03/21/2013
SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
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.
13/595,757	08/27/2012	INV001Dayton T. Reardan	101.031US11	5359

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	$1780	$0	$0	$1780	06/21/2013

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

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(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 _____

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❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit 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 form 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.

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This collection of information 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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/595,757	08/27/2012	INV001Dayton T. Reardan	101.031US11	5359

21186 7590 03/21/2013

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

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

DATE MAILED: 03/21/2013

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.

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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. 13/595,757	Applicant(s) REARDAN ET AL.	
	Examiner LENA NAJARIAN	Art Unit 3686	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *terminal disclaimers filed 3/7/13*.

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 *1-15*. 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).
   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 20130305
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
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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	13/595,757
	Filing Date	August 27, 2012
	First Named Inventor	Dayton T. Reardan Ph.D
	Group Art Unit	3686
	Examiner Name	Lena Najarian
Sheet 1 of 2	Attorney Docket No: 101.031U11	

US PATENT DOCUMENTS

Examiner Initial *	USP Document Number	Publication Date	Name of Patentee or Applicant of cited Document
	US-20030074225	4/17/2003	Borsand, Gerlad, et al.

OTHER DOCUMENTS – NON PATENT LITERATURE DOCUMENTS

Examiner Initial *	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T 1
	"Application Serial No. 13/592,202, Response filed 02-15-13 to Restriction Requirement mailed 01-16-13", 8 pgs	
	"Application Serial No. 13/592,202, Restriction Requirement mailed 01-16-13", 6 pgs	
	"Briefing Booklet for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting", Orphan Medical, Inc., (6/6/01), 353 pgs	
	"Civil Cover Sheet", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey, (1/18/13), 2 pgs	
	"Complaint for Patent Infringement", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey, (1/18/13), 17 pgs	
	"Controlled Substances Act", Drugs of Abuse, U.S. Department of Justice, Drug Enforcement Administration, (1997), 9 pgs	
	"Detailed Factual and Legal Basis of Non-Infringement and/or Invalidity", Amneal Pharmaceuticals, LLC, (12/12/12), 3 pgs	
	"Detailed Factual and Legal Basis of Non-Infringement and/or Invalidity", Amneal Pharmaceuticals, LLC, (12/7/12), 6 pgs	
	"Exhibits A-D", Jazz Pharmaceuticals v Amneal Pharmaceuticals, LLC, (1/18/2013), 151 pgs	
	"Exhibits D-G", Jazz Pharmaceuticals v Amneal Pharmaceuticals, LLC, (1/18/13), 123 pgs	
	"Fed. R. Civ. P. Rule 7.1 Disclosure Statement", (1/18/13), 2 pgs	
	"Making Good in Your Own Mail-Order Business", Changing Times - The Kiplinger Magazine, (October 1980), 66-68	
	"Markman Opinion, filed September 14, 2012, in the case of Jazz Pharmaceuticals, Inc., Plaintiff, v. Roxane Laboratories, Inc., Defendant (United States District Court for the District of New Jersey, Civil 10-6108 ES)", (9/14/12), 43 pgs.	
	"Notice of Electronic Filing: Civil Inital Pleadings (Attorney/Credit Card) USE CASE 33-1", US District Court, District of new Jersey [LIVE], (1/18/13), 2 pgs	
	"Notice of Paragraph IV Certification Concerning ANDA 203631 for Sodiium Oxybate Oral Solution, 500 mg/mL", Amneal Pharmaceuticals, LLC, (12/7/12), 4 pgs	
	"Notice of Paragraph IV Certification Concerning ANDA 203631 for Sodiium Oxybate Oral Solution. 500 mg/mL", Amneal Pharmaceuticals, LLC, (12/12/12), 4 pgs	
	"Peripheral and Central Nervous System Drugs Advisory Committee - Transcript", Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, Holiday Inn, Bethesda, Maryland, (6/6/01), 381 pgs	
	"Roxane Laboratories, Inc.'s Answer and Affirmative Defenses to Plaintiff's Complaint", (January 4, 2013), 8 pgs.	

EXAMINER /Lena Najarian/ **DATE CONSIDERED** 03/11/2013

* 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

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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	13/595,757
	Filing Date	August 27, 2012
	First Named Inventor	Dayton T. Reardan Ph.D
	Group Art Unit	3686
	Examiner Name	Lena Najarian
Sheet 2 of 2	Attorney Docket No: 101.031U11	

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**
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint", (December 29, 2010), 21 pgs.	
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint", (March 9, 2011), 13 pgs.	
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint", (June 1, 2011), 12 pgs.	
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint", (November 9, 2012), 18 pgs.	
	"Xyrem Prescription and Distribution Process-Video Script", (2/2/01), 10 pgs	
	DEUTSCH, SHERYL, "The Verification and Information-Gathering Process", The Credentialing Handbook, Aspen Publishers, Inc., (1999), 231-275	
	MANI, RANJIT, "Preliminary Clinical Safety Review of NDA No. 21196", Orphan Medical, Inc., (05/03/01), 122 pgs	

EXAMINER /Lena Najarian/ **DATE CONSIDERED** 03/11/2013

* 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./

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Dayton T. Reardan Ph.D et al.	Examiner: Lena Najarian
Serial No.: 13/595,757	Group Art Unit: 3686
Filed: August 27, 2012	Docket No.: 101.031U11
Customer No.: 21186	Confirmation No.: 5359

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

AMENDMENT & RESPONSE UNDER 37 C.F.R. § 1.111

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

In response to the Office Action dated January 17, 2013, please amend the application as follows.

IN THE CLAIMS

Please amend the claims as follows:

1. (Currently Amended) 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.

2. (Original) 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. (Original) 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.

4. (Original) 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. (Currently Amended) The method of claim 1, wherein the exclusive central pharmacy enters data into ~~controls~~ the exclusive computer database.

6. (Original) The method of claim 1, comprising selectively blocking shipment of the company's prescription drug to the narcoleptic patient.

7. (Original) 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. (Original) The computerized method of claim 1, wherein the company's prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

9. (Currently Amended) 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 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.

10. (Original) 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.

11. (Original) 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. (Original) 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. (Currently Amended) The method of claim 9, wherein the exclusive central pharmacy enters data into ~~controls~~ the exclusive computer database.

14. (Original) 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. (Original) The method of claim 9, wherein the company's prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

REMARKS

This communication responds to the Office Action dated January 17, 2013.

Claims 1, 5, 9, and 13 are currently amended, no claims are canceled, and no claims are added; as a result, claims 1-15 are now pending and subject to examination in this application.

Interview Summary

The Applicant expresses its gratitude to Examiner Najarian for the courtesies extended to its representatives Mr. David D'Zurilla and Mr. Philip McGarrigle during a telephonic interview on March 5, 2013.

Mr. D'Zurilla discussed proposed amendments to claims 1, 5, 9, and 13, and stated that a written response would be filed in the near future.

Mr. McGarrigle explained that a supplemental information disclosure statement has been filed and/or will be filed in the near future. Mr. McGarrigle also offered a brief summary of the litigations that involve U.S. Patent No. 7,668,730, which issued from the grandparent application of the current pending application.

No agreement on the claims was reached.

Double Patenting Rejection

Claims 1-15 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-11 of U.S. Patent No. 7,668,730 and claims 1-16 of U.S. Patent No. 7,895,059.

The Applicant does not admit that claims 1-15 are unpatentable over claims 1-11 of U.S. Patent No. 7,668,730 and/or claims 1-16 of U.S. Patent No. 7,895,059. However, to advance the prosecution of the present application, the Applicant is submitting a terminal disclaimer to obviate the double patenting rejection.

The Rejection of Claims Under § 112

Claims 1 -15 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim

the subject matter which the inventor or a joint inventor, or for a pre-AIA situation the applicant, regards as the invention.

In response to the rejections of the claims under section 112, the Applicant has made several amendments to the claims as outlined above and as described below to advance the prosecution of this application. However, the Applicant does not admit to the propriety of such rejections.

The Office Action stated that the term "various credentials" in claims 1 and 9 is a relative term and that the term renders those claims indefinite. The Applicant respectfully submits that the term "various credentials" is not relative or indefinite, since the specification states that such credentials of a medical doctor are checked to determine if the physician has a current DEA license to prescribe controlled substances and if the physician has any actions against him or her for misusing or misprescribing controlled drugs (Applicant's specification, page 7, lines 26-30). Additionally, the Applicant respectfully points out that U.S. Patent No. 7,668,730 includes the term "various credentials" in claim 1.

The Applicant therefore respectfully submits that the term "various credentials" does not render claims 1 or 9 indefinite, and the Applicant respectfully requests the withdrawal of the rejection of claims 1-15 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph.

Per the suggestion in the Office Action, the Applicant has further amended claims 1 and 9 by removing the terms "are unique in that they" and "the uniqueness of" from claims 1 and 9. The Applicant respectfully submits that these amendments to claims 1 and 9 overcome the rejection of the claims under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, and respectfully requests the withdrawal of the rejection of claims 1-15.

The Applicant has also amended claims 5 and 13 by deleting the term "controlling" and substituting therefore "enters data into." Support for the amendment can be found in the Applicant's specification at page 8, lines 3-4. The Applicant respectfully submits that these amendments to claims 5 and 13 overcome the rejection of claims 5 and 13 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, and respectfully requests the withdrawal of the rejection of claims 5 and 13.

CONCLUSION

The 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 the undersigned 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 March 7, 2013

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

EXHIBIT 2

Mark S. Olinsky
Theodora McCormick
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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **vs.** **ROXANE LABORATORIES, INC.,** **Defendant.**	**C.A. No. 2:12-cv-07459 (ES) (SCM)** **CONSOLIDATED WITH** **C.A. No. 2:10-cv-06108 (ES) (SCM)**

ROXANE LABORATORIES, INC.'S
AMENDED ANSWER AND AFFIRMATIVE DEFENSES
TO PLAINTIFF'S COMPLAINT REGARDING U.S. PATENT NO. 8,234,275

Defendant, Roxane Laboratories, Inc. ("Roxane"), for its Amended Answer and Affirmative Defenses to Plaintiff Jazz Pharmaceuticals, Inc.'s ("Jazz Pharmaceuticals") Complaint for Patent Infringement ("the Complaint"), states as follows:

Nature of the Action

1. Roxane admits that the Complaint purports to be a civil action for patent infringement. Roxane also admits that it filed an Abbreviated New Drug Application ("ANDA") No. 202090 with the United States Food and Drug Administration ("FDA"), seeking approval to

commercially market a generic version of Jazz Pharmaceuticals' XYREM® drug product prior to the expiration of United States Patent No. 8,324,275 ("the '275 patent"). Roxane denies all other allegations contained in paragraph 1 of the Complaint.

The Parties

2. Roxane admits on information and belief that Jazz Pharmaceuticals is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304. Roxane denies all other allegations contained in paragraph 2 of the Complaint.

3. Roxane admits the allegations contained in paragraph 3 of the Complaint.

4. Roxane admits that it is registered to do business in the State of New Jersey and maintains a registered agent for service of process in New Jersey. Roxane further admits that it sells generic drug products throughout the United States, including this judicial district. Roxane further admits that it has litigated patent cases in this district and that, in at least some of those actions, Roxane has asserted counterclaims. Roxane denies all other allegations contained in paragraph 4 of the Complaint.

Jurisdiction and Venue

5. Roxane denies the allegations contained in paragraph 5 of the Complaint.

6. For purposes of this action, Roxane consents to this Court's personal jurisdiction. Roxane denies all other allegations contained in paragraph 6 of the Complaint.

7. For purposes of this action, Roxane consents that venue is proper in this district. Roxane denies all other allegations contained in paragraph 7 of the Complaint.

The Patent in Suit

8. Roxane admits that what purports to be a copy of the '275 patent is attached to the Complaint as Exhibit A. Roxane further admits that Exhibit A (a) is entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," and (b) lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan as "Inventors." Roxane denies all other allegations contained in paragraph 8 of the Complaint.

The XYREM® Drug Product

9. Roxane admits that New Drug Application ("NDA") No. 21-196 was approved by the FDA and that Jazz Pharmaceuticals is listed as the applicant for that NDA. Roxane denies all other allegations contained in paragraph 9 of the Complaint.

10. Roxane admits that the '275 patent is listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to XYREM®, but denies that the '275 patent appeared in the Orange Book at the time the present complaint was filed. Roxane denies all other allegations contained in paragraph 10 of the Complaint.

Acts Giving Rise to this Suit

11. Roxane admits that it filed ANDA No. 202090. Roxane's ANDA speaks for itself as to its contents. Roxane denies all other allegations contained in paragraph 11 of the Complaint.

12. Roxane admits that in connection with its ANDA, it provided written certifications to the FDA pursuant to Section 505 of the Federal Food Drug and Cosmetics Act ("FFDCA"). Roxane's certifications speak for themselves as to its contents. Roxane has not

certified as to the '275 patent. Roxane denies all other allegations contained in paragraph 12 of the Complaint.

13. Roxane's ANDA speaks for itself as to its contents. Roxane denies all other allegations contained in paragraph 13 of the Complaint.

Count for Infringement of the '275 Patent

14. Roxane repeats, reasserts, and incorporates by reference its answers to paragraphs 1-13 of the Complaint above, as if fully set forth herein.

15. Roxane denies the allegations contained in paragraph 15 of the Complaint.

16. Roxane admits the allegations contained in paragraph 16 of the Complaint.

17. Roxane denies the allegations contained in paragraph 17 of the Complaint.

18. Roxane denies the allegations contained in paragraph 18 of the Complaint.

19. Roxane denies the allegations contained in paragraph 19 of the Complaint.

20. Roxane denies the allegations contained in paragraph 20 of the Complaint.

21. Roxane denies the allegations contained in paragraph 21 of the Complaint.

22. Roxane denies the allegations contained in paragraph 22 of the Complaint.

23. Roxane denies the allegations contained in paragraph 23 of the Complaint.

PRAYER FOR RELIEF

Roxane specifically denies that Jazz Pharmaceuticals is entitled to the general or specific relief requested against Roxane, or to any relief whatsoever, and prays for judgment in favor of Roxane dismissing this action with prejudice, and awarding Roxane its reasonable attorneys' fees pursuant to 35 U.S.C. § 285, interest, and costs of this action, and such other or further relief as this Court may deem just and proper.

AFFIRMATIVE DEFENSES

Without prejudice to the denials set forth in its Amended Answer and without admitting any allegations of the Complaint not otherwise admitted, Roxane avers and asserts the following Affirmative Defenses to the Complaint of Plaintiff Jazz Pharmaceuticals.

FIRST AFFIRMATIVE DEFENSE
(Noninfringement of U.S. Patent No. 8,324,275)

1. The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that is the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 8,324,275 ("the '275 patent") either literally or under the doctrine of equivalents.

SECOND AFFIRMATIVE DEFENSE
(Invalidity of U.S. Patent No. 8,324,275)

2. Upon information and belief, the claims of the '275 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

THIRD AFFIRMATIVE DEFENSE
(Failure to State a Claim)

3. Jazz Pharmaceuticals has failed to state a claim upon which relief can be granted.

FOURTH AFFIRMATIVE DEFENSE
(Lack of Subject Matter Jurisdiction)

4. Jazz Pharmaceuticals has failed to state a claim under 35 U.S.C. § 271(e)(2) and therefore the Court lacks subject matter jurisdiction over this matter.

FIFTH AFFIRMATIVE DEFENSE
(Prosecution Laches)

5. On information and belief, the '275 patent is unenforceable against Roxane because Jazz Pharmaceuticals committed prosecution laches by engaging in a course of conduct to unreasonably and inexcusably delay the presentation of claims directed to a sodium gamma hydroxybutyrate (sodium oxybate) solution having, for example, no pH adjusting agent or a specific pH range; claims directed to diluting a concentrated sodium oxybate solution prior to dosage administration to the patient; and claims directed to a single exclusive distribution system by a company or trademark. Such delay has and is causing material prejudice to Roxane.

6. On information and belief, on or about November 22, 2010, upon receiving Roxane's written notice of its written certification to the U.S. Food and Drug Administration ("FDA") as called for by Section 505 of the Federal Food Drug and Cosmetic Act ("Roxane's notice letter") alleging that United States Patent Nos. 6,780,889 ("the '889 patent"); 7,262,219 ("the '219 patent"); 7,668,730 ("the '730 patent"); 7,765,106; and 7,765,107 listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" ("the Orange Book") with respect to XYREM® are invalid, unenforceable and/or will not be infringed by Roxane's filing of its ANDA seeking approval to market and distribute a generic sodium oxybate product, Jazz Pharmaceuticals initiated a patent-infringement case against Roxane.

7. Jazz Pharmaceuticals' initial patent-infringement case against Roxane alleged infringement of the five Orange Book patents discussed in Roxane's notice letter. At that time, only those five patents were listed in the Orange Book.

8. On or about February 4, 2011, Jazz Pharmaceuticals initiated a second patent-infringement case against Roxane alleging infringement of United States Patent Nos. 6,472,431 ("the '431 patent") and 7,851,506 ("the '506 patent") based on Roxane's previous filing of its sodium oxybate ANDA.

9. On or about May 2, 2011, Jazz Pharmaceuticals initiated a third patent-infringement case against Roxane alleging infringement of United States Patent No. 7,895,059 based on Roxane's previous filing of its sodium oxybate ANDA.

10. Litigation regarding United States Patent Nos. 6,780,889; 7,262,219; 7,668,730; 7,765,106; 7,765,107; 6,472,431; 7,851,506; and 7,895,059 ("the original patents-in-suit") were consolidated into a single case, Civil Action No. 10-06108 (Docket Entries 27 and 49).

11. All of the patents-in-suit can be characterized as belonging to one of two families: "the '431 patent family" includes the patents stemming from the '431 patent and consist of composition or chemical/stability or methods of dosing patents regarding sodium gamma-hydroxybutyrate, also known as or sodium oxybate; and "the '730 patent family" includes patents stemming from the '730 patent, and generally relate to a distribution system for sodium oxybate and other drug products that are potentially subject to being abused.

12. On or about July 28, 2011, after motion practice because of Jazz's resistance to inclusion of a patent prosecution bar, the Court issued a Discovery Confidentiality Order with terms that had been negotiated between Roxane and Jazz Pharmaceuticals directed toward keeping Roxane confidential information out of the hands of Jazz Pharmaceuticals' patent prosecution counsel. (Docket Entry No. 54.)

13. Pursuant to the Discovery Confidentiality Order, Roxane produced to Jazz Pharmaceuticals its confidential ANDA, amendments to the ANDA, correspondences with FDA relating to the ANDA, and other production documents which disclosed information regarding the process Roxane uses for making, the composition of and the method of dosing its proposed sodium oxybate solution as well as the method of distributing it.

14. In the course of the litigation related to the original patents-in-suit, and pursuant to the Local Patent Rules of the United States District Court, District of New Jersey, Roxane provided invalidity and non-infringement contentions to Jazz Pharmaceuticals in Civil Action No. 10-cv-06108 on or about April 14, 2011 and on or about August 16, 2011.

15. Roxane's contentions included assertions that it did not infringe any of the patents-in-suit because, among other things, Roxane's proposed ANDA product did not contain a pH adjusting agent, required a dilution step in the dosing regimen, did not add sodium oxybate to an aqueous medium in order to make the final sodium oxybate product, and had a different distribution system than that claimed in the original patents-in-suit.

16. On information and belief, Jazz Pharmaceuticals has embarked on an abusive course of conduct in which it gleans information about Roxane's noninfringement positions, then runs to the Patent Office to obtain new, patent-counsel-invented patent claims by filing continuation applications of patent applications filed ten plus years ago, and then files in seriatim law suits against Roxane based on these unreasonably presented patent claims, to delay resolution of this action.

17. For example, all of the claims in the '506 patent required that the sodium oxybate solution be administered using a concentrated medium of 500 mg/ml of sodium oxybate.

18. Roxane alleged non-infringement of the '506 patent on the basis that administration of Roxane's sodium oxybate solution required dilution of the concentrated medium prior to patient administration.

19. On information and belief, having learned of Roxane's non-infringement defense to the '506 patent claims, Jazz Pharmaceuticals, on or about April 13, 2012, filed two United

States Patent Applications, Serial Nos. 13/446,940 and 13/446,942, which issued as U.S. Patent Nos. 8,263,650 ("the '650 patent") and 8,324,275 patents ("the '275 patent"), respectively.

20. Both the '650 and '275 patents contain claims calling for dilution of the sodium oxybate solution prior to patient administration.

21. On information and belief, at no time before or during prosecution of the applications did Jazz Pharmaceuticals or its prosecution counsel discuss the new claims for the '650 and '275 patents with the patent inventors.

22. The '219 and '889 patent recites claims to sodium oxybate solution formulations which require the inclusion of "a pH adjusting agent."

23. Roxane alleged non-infringement of the '219 and '889 patents because Roxane's sodium oxybate solution does not contain a "pH adjusting agent."

24. On information and belief, after having learned of Roxane's non-infringement defense, Jazz Pharmaceuticals filed, on or about April 13, 2012, United States Patent Application No. 13/446,940 seeking claims to compositions that do not require "a pH adjusting agent."

25. United States Patent Application No. 13/446,940 issued as the '650 patent on September 11, 2012.

26. On information and belief, at no time before or during the prosecution of Application No. 13/446,940 did Jazz or its patent prosecution counsel discuss the new claims in that application with any of the patent inventors.

27. Application No. 13/446,940 was filed fourteen years after the application for the parent '431 patent was filed.

28. All of the claims of the '431 patent require that sodium oxybate be "added" to an aqueous medium.

29. Roxane alleged non-infringement of the '431 patent-in-suit because Roxane makes its sodium oxybate solution without "adding" sodium oxybate to an aqueous medium.

30. On information and belief, after having learned of Roxane's non-infringement defense to the '431 patent, Jazz Pharmaceuticals, on or about July 13, 2011, filed United States Patent Application No. 13/182,324 seeking claims for "admixing" rather than "adding" sodium oxybate to an aqueous medium.

31. On information and belief, at no time before or during the prosecution of Application No. 13/182,324 did Jazz Pharmaceuticals or its patent prosecution counsel discuss the new claims in that application with any of the patent inventors.

32. The original patents-in-suit in the distribution family have claims directed to the distribution of sodium oxybate products by a single exclusive distribution system.

33. Roxane alleged non-infringement of the original patents-in-suit in the distribution family on the basis that Roxane uses a separate distribution systems.

34. On information and belief, after having learned of Roxane's noninfringement position to the distribution patent claims during the litigation, Jazz Pharmaceuticals, on or about January 25, 2011, filed United States Patent Application No. 2011/0119085 seeking claims requiring a single exclusive distribution system by a company or trademark.

35. On information and belief, at no time before or during prosecution of Application No. 2011/0119085 did Jazz Pharmaceuticals or its patent prosecution counsel discuss the new claims in that application with any of the patent inventors.

36. On information and belief, Jazz Pharmaceuticals improperly delayed filing patent applications to seek additional claims to cover Roxane's proposed product or to circumvent Roxane's noninfringement defenses to the claims of the original patents-in-suit and has

improperly kept and unreasonably delayed in keeping patent applications pending, not to claim additional inventions the inventors believed they had invented, but to glean information from Roxane to craft broader or different claims in an attempt to read on Roxane's sodium oxybate product and method of dosing and distributing same.

37. On information and belief, this serial and directed prosecution of patent applications has and does materially prejudice Roxane's development and market entry of its sodium oxybate product.

38. On information and belief, Jazz Pharmaceuticals has also used the additional new patents to try to serially consolidate new patent lawsuits with older patent lawsuits in order to delay resolution of these patent infringement litigations.

39. Roxane relied on Jazz Pharmaceuticals' list of five patents in the Orange Book when Roxane filed its ANDA in 2010. In particular, Roxane invested substantial time, money, and resources to develop its sodium oxybate product based on its conclusion that Jazz Pharmaceuticals' five patents listed in the Orange Book at that time were either invalid or not infringed.

40. On information and belief, Jazz Pharmaceuticals will continue to use Roxane's product information and specifications disclosed as part of this litigation to file additional patent applications claiming priority to the '431 or '730 patents and subsequently bring suit against Roxane on such patents.

41. Jazz Pharmaceuticals has five non-public continuation patent applications pending in the patent office, two from the '431 patent family and three from the '730 patent family.

42. On information and belief, as Jazz Pharmaceuticals continues to seek and obtain new patents, add patents to the Orange Book, bring patent infringement suits against Roxane,

and then seek consolidation of all suits related to sodium oxybate, Roxane will suffer material prejudice by being forced to continually defend itself against patents that were not invented by the named inventors but are based on information gleaned by patent attorneys during a litigation, causing Roxane to face an "at-risk" launch of its sodium oxybate product due to delayed resolution of this litigation.

SIXTH AFFIRMATIVE DEFENSE
(Unclean Hands)

43. Roxane repeats, reasserts and incorporates by reference paragraphs 1-42 above, as if fully set forth herein.

44. On information and belief, the claims of the '275 patent are unenforceable due to Jazz Pharmaceuticals' unclean hands in prosecuting the application that matured into the '275 patent in the United States Patent Office, including but not limited to, Jazz Pharmaceuticals' prosecution of the '275 patent application with prior and concurrent access to Roxane's confidential business and product specification information and Jazz Pharmaceuticals' use of that information to craft the '275 patent claims.

45. On information and belief, Jazz Pharmaceuticals has continued to file and prosecute patent applications as continuations to the '431 and '730 patent families, including the '275 patent, with claims based on information Jazz Pharmaceuticals has gleaned from Roxane before and during litigation about Roxane's sodium oxybate product, the method of dosing and the distribution of same.

46. On information and belief, Jazz Pharmaceuticals has continued to file and prosecute patent applications as continuations to the '431 and '730 patent families, including the '275 patent, with no claims based on what the inventors thought they invented.

47. On information and belief, Jazz Pharmaceuticals' misconduct in the prosecution of the '275 patent is directly related to the issues in this litigation.

ROXANE'S PRAYER FOR RELIEF

WHEREFORE, Roxane respectfully requests that the Court find in favor of Roxane based on any of its Affirmative Defenses.

Dated: _____, 2013

Respectfully Submitted,

s/_____

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EXHIBIT 1

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **vs.** **ROXANE LABORATORIES, INC.,** **Defendant.**	**C.A. No. 2:12-cv-06761 (ES) (SCM)** **CONSOLIDATED WITH** **C.A. No. 2:10-cv-06108 (ES) (SCM)**

ROXANE LABORATORIES, INC.'S AMENDED ANSWER, AFFIRMATIVE DEFENSES AND COUNTERCLAIMS TO PLAINTIFF'S COMPLAINT REGARDING U.S. PATENT NO. 8,263,650

Defendant, Roxane Laboratories, Inc. ("Roxane"), for its Amended Answer, Affirmative Defenses and Counterclaims to Plaintiff Jazz Pharmaceuticals, Inc.'s ("Jazz Pharmaceuticals") Complaint for Patent Infringement ("the Complaint"), states as follows:

Nature of the Action

1. Roxane admits that the Complaint purports to be a civil action for patent infringement. Roxane also admits that it filed an Abbreviated New Drug Application ("ANDA") No. 202090 with the United States Food and Drug Administration ("FDA"), seeking approval to commercially market a generic version of Jazz Pharmaceuticals' XYREM® drug product prior to

the expiration of United States Patent No. 8,263,650 ("the '650 patent"). Roxane denies all other allegations contained in paragraph 1 of the Complaint.

The Parties

2. Roxane admits on information and belief that Jazz Pharmaceuticals is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304. Roxane denies all other allegations contained in paragraph 2 of the Complaint.

3. Roxane admits the allegations contained in paragraph 3 of the Complaint.

4. Roxane admits that it is registered to do business in the State of New Jersey and maintains a registered agent for service of process in New Jersey. Roxane further admits that it sells generic drug products throughout the United States, including this judicial district. Roxane further admits that it has litigated patent cases in this district and that, in at least some of those actions, Roxane has asserted counterclaims. Roxane denies all other allegations contained in paragraph 4 of the Complaint.

Jurisdiction and Venue

5. Roxane admits the allegations contained in paragraph 5 of the Complaint.

6. For purposes of this action, Roxane consents to this Court's jurisdiction. Roxane denies all other allegations contained in paragraph 6 of the Complaint.

7. For purposes of this action, Roxane consents that venue is proper in this district. Roxane denies all other allegations contained in paragraph 7 of the Complaint.

The Patents in Suit

8. Roxane admits that what purports to be a copy of the '650 patent is attached to the Complaint as Exhibit A. Roxane further admits that Exhibit A (a) is entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy,"

and (b) lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan as "Inventors." Roxane denies all other allegations contained in paragraph 8 of the Complaint.

The XYREM® Drug Product

9. Roxane admits that New Drug Application ("NDA") No. 21-196 was approved by the FDA and that Jazz Pharmaceuticals is listed as the applicant for that NDA. Roxane denies all other allegations contained in paragraph 9 of the Complaint.

10. Roxane admits that the '650 patent is listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to XYREM®. Roxane denies all other allegations contained in paragraph 10 of the Complaint.

Acts Giving Rise to this Suit

11. Roxane admits that it filed ANDA No. 202090. Roxane's ANDA speaks for itself as to its contents. Roxane denies all other allegations contained in paragraph 11 of the Complaint.

12. Roxane admits that it provided a written certification to the FDA pursuant to Section 505 of the Federal Food Drug and Cosmetics Act ("FFDCA"). Roxane's certification speaks for itself as to its contents. Roxane denies all other allegations contained in paragraph 12 of the Complaint.

13. Roxane admits that by letter dated October 5, 2012 ("Roxane's Notice Letter"), Roxane notified Jazz Pharmaceuticals of its ANDA certification that the claims of the '650 patent are invalid, unenforceable, and/or will not be infringed by Roxane. Roxane's ANDA speaks for itself as to its contents. Roxane further admits that in Roxane's Notice Letter, Roxane informed Jazz Pharmaceuticals that Roxane seeks FDA approval for Roxane's sodium oxybate oral solution. Roxane denies all other allegations contained in paragraph 13 of the Complaint.

Count I: Infringement of the '650 Patent

14. Roxane repeats, reasserts and incorporates by reference its answers to paragraphs 1-13 of the Complaint above, as if fully set forth herein.

15. Roxane denies the allegations contained in paragraph 15 of the Complaint.

16. Roxane admits the allegations contained in paragraph 16 of the Complaint.

17. Roxane denies the allegations contained in paragraph 17 of the Complaint.

18. Roxane denies the allegations contained in paragraph 18 of the Complaint.

19. Roxane denies the allegations contained in paragraph 19 of the Complaint.

20. Roxane denies the allegations contained in paragraph 20 of the Complaint.

21. Roxane denies the allegations contained in paragraph 21 of the Complaint.

22. Roxane denies the allegations contained in paragraph 22 of the Complaint.

PRAYER FOR RELIEF

Roxane specifically denies that Jazz Pharmaceuticals is entitled to the general or specific relief requested against Roxane, or to any relief whatsoever, and prays for judgment in favor of Roxane dismissing this action with prejudice, and awarding Roxane its reasonable attorneys' fees pursuant to 35 U.S.C. § 285, interest, and costs of this action, and such other or further relief as this Court may deem just and proper.

AFFIRMATIVE DEFENSES

Without prejudice to the denials set forth in its Amended Answer and without admitting any allegations of the Complaint not otherwise admitted, Roxane avers and asserts the following Affirmative Defenses to the Complaint of Plaintiff Jazz Pharmaceuticals.

FIRST AFFIRMATIVE DEFENSE
(Noninfringement of U.S. Patent No. 8,263,650)

1. The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that is the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 8,263,650 ("the '650 patent") either literally or under the doctrine of equivalents.

SECOND AFFIRMATIVE DEFENSE
(Invalidity of U.S. Patent No. 8,263,650)

2. Upon information and belief, the claims of the '650 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

THIRD AFFIRMATIVE DEFENSE
(Inequitable Conduct)

3. Upon information and belief, the claims of the '650 patent are unenforceable because of Jazz Pharmaceutical's inequitable conduct, as alleged more specifically in Roxane's Counterclaim set forth below.

FOURTH AFFIRMATIVE DEFENSE
(Patent Misuse)

4. Upon information and belief, the claims of the '650 patent are unenforceable due to Jazz Pharmaceutical's inequitable conduct committed during its prosecution with unclean hands including, without limitation, the failure of the applicants, inventors, and/or those involved in the prosecution, with the intent to deceive the United States Patent and Trademark Office, to disclose prior art that was material to the examination of the '650 patent, as alleged more specifically in Roxane's Counterclaims set forth below.

FIFTH AFFIRMATIVE DEFENSE
(Prosecution Laches)

5. On information and belief, the '650 patent is unenforceable against Roxane because Jazz Pharmaceuticals committed prosecution laches by engaging in a course of conduct to unreasonably and inexcusably delay the presentation of claims directed to a sodium gamma hydroxybutyrate (sodium oxybate) solution having, for example, a specific pH range or no pH adjusting agent; claims directed to diluting a concentrated sodium oxybate solution prior to dosage administration to the patient; and claims directed to a single exclusive distribution system by a company or trademark. Such delay has and is causing material prejudice to Roxane.

6. On information and belief, on or about November 22, 2010, upon receiving Roxane's written notice of its written certification to the U.S. Food and Drug Administration ("FDA") as called for by Section 505 of the Federal Food Drug and Cosmetic Act ("Roxane's notice letter") alleging that United States Patent Nos. 6,780,889 ("the '889 patent"); 7,262,219 ("the '219 patent"); 7,668,730 ("the '730 patent"); 7,765,106; and 7,765,107 listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" ("the Orange Book") with respect to XYREM® are invalid, unenforceable and/or will not be infringed by Roxane's filing of its ANDA seeking approval to market and distribute a generic sodium oxybate product, Jazz Pharmaceuticals initiated a patent-infringement case against Roxane.

7. Jazz Pharmaceuticals' initial patent-infringement case against Roxane alleged infringement of the five Orange Book patents discussed in Roxane's notice letter. At that time, only those five patents were listed in the Orange Book.

8. On or about February 4, 2011, Jazz Pharmaceuticals initiated a second patent-infringement case against Roxane alleging infringement of United States Patent Nos. 6,472,431

("the '431 patent") and 7,851,506 ("the '506 patent") based on Roxane's previous filing of its sodium oxybate ANDA.

9. On or about May 2, 2011, Jazz Pharmaceuticals initiated a third patent-infringement case against Roxane alleging infringement of United States Patent No. 7,895,059 based on Roxane's previous filing of its sodium oxybate ANDA.

10. Litigation regarding United States Patent Nos. 6,780,889; 7,262,219; 7,668,730; 7,765,106; 7,765,107; 6,472,431; 7,851,506; and 7,895,059 ("the original patents-in-suit") were consolidated into a single case, Civil Action No. 10-06108 (Docket Entries 27 and 49).

11. All of the patents-in-suit can be characterized as belonging to one of two families: "the '431 patent family" includes the patents stemming from the '431 patent and consist of composition or chemical/stability or methods of dosing patents regarding sodium gamma-hydroxybutyrate, also known as or sodium oxybate; and "the '730 patent family" includes patents stemming from the '730 patent, and generally relate to a distribution system for sodium oxybate and other drug products that are potentially subject to being abused.

12. On or about July 28, 2011, after motion practice because of Jazz's resistance to inclusion of a patent prosecution bar, the Court issued a Discovery Confidentiality Order with terms that had been negotiated between Roxane and Jazz Pharmaceuticals directed toward keeping Roxane confidential information out of the hands of Jazz Pharmaceuticals' patent prosecution counsel. (Docket Entry No. 54.)

13. Pursuant to the Discovery Confidentiality Order, Roxane produced to Jazz Pharmaceuticals its confidential ANDA, amendments to the ANDA, correspondences with FDA relating to the ANDA, and other production documents which disclosed information regarding

the process Roxane uses for making, the composition of and the method of dosing its proposed sodium oxybate solution as well as the method of distributing it.

14. In the course of the litigation related to the original patents-in-suit, and pursuant to the Local Patent Rules of the United States District Court, District of New Jersey, Roxane provided invalidity and non-infringement contentions to Jazz Pharmaceuticals in Civil Action No. 10-cv-06108 on or about April 14, 2011 and on or about August 16, 2011.

15. Roxane's contentions included assertions that it did not infringe any of the patents-in-suit because, among other things, Roxane's proposed ANDA product did not contain a pH adjusting agent, required a dilution step in the dosing regimen, did not add sodium oxybate to an aqueous medium in order to make the final sodium oxybate product, and had a different distribution system than that claimed in the original patents-in-suit.

16. On information and belief, Jazz Pharmaceuticals has embarked on an abusive course of conduct in which it gleans information about Roxane's noninfringement positions, then runs to the Patent Office to obtain new, patent-counsel-invented patent claims by filing continuation applications of patent applications filed ten plus years ago, and then files in seriatim law suits against Roxane based on these unreasonably presented patent claims, to delay resolution of this action.

17. For example, all of the claims in the '506 patent required that the sodium oxybate solution be administered using a concentrated medium of 500 mg/ml of sodium oxybate.

18. Roxane alleged non-infringement of the '506 patent on the basis that administration of Roxane's sodium oxybate solution required dilution of the concentrated medium prior to patient administration.

19. On information and belief, having learned of Roxane's non-infringement defense to the '506 patent claims, Jazz Pharmaceuticals, on or about April 12, 2012, filed two United States Patent Applications, Serial Nos. 13/446,940 and 13/446,942, which issued as U.S. Patent Nos. 8,263,650 ("the '650 patent") and 8,324,275 patents ("the '275 patent"), respectively.

20. Both the '650 and '275 patents contain claims calling for dilution of the sodium oxybate solution prior to patient administration.

21. On information and belief, at no time before or during prosecution of the applications did Jazz Pharmaceuticals or its prosecution counsel discuss the new claims for the '650 and '275 patents with the patent inventors.

22. The '219 and '889 patent recites claims to sodium oxybate solution formulations which require the inclusion of "a pH adjusting agent."

23. Roxane alleged non-infringement of the '219 and '889 patents because Roxane's sodium oxybate solution does not contain a "pH adjusting agent."

24. On information and belief, after having learned of Roxane's non-infringement defense, Jazz Pharmaceuticals filed, on or about April 13, 2012, United States Patent Application No. 13/446,940 seeking claims to compositions that do not require "a pH adjusting agent."

25. United States Patent Application No. 13/446,940 issued as the '650 patent on September 11, 2012.

26. On information and belief, at no time before or during the prosecution of Application No. 13/446,940 did Jazz or its patent prosecution counsel discuss the new claims in that application with any of the patent inventors.

27. Application No. 13/446,940 was filed fourteen years after the application for the parent '431 patent was filed.

28. All of the claims of the '431 patent require that sodium oxybate be "added" to an aqueous medium.

29. Roxane alleged non-infringement of the '431 patent-in-suit because Roxane makes its sodium oxybate solution without "adding" sodium oxybate to an aqueous medium.

30. On information and belief, after having learned of Roxane's non-infringement defense to the '431 patent, Jazz Pharmaceuticals, on or about July 13, 2011, filed United States Patent Application No. 13/182,324 seeking claims for "admixing" rather than "adding" sodium oxybate to an aqueous medium.

31. On information and belief, at no time before or during the prosecution of Application No. 13/182,324 did Jazz Pharmaceuticals or its patent prosecution counsel discuss the new claims in that application with any of the patent inventors.

32. The original patents-in-suit in the distribution family have claims directed to the distribution of sodium oxybate products by a single exclusive distribution system.

33. Roxane alleged non-infringement of the original patents-in-suit in the distribution family on the basis that Roxane uses a separate distribution systems.

34. On information and belief, after having learned of Roxane's noninfringement position to the distribution patent claims during the litigation, Jazz Pharmaceuticals, on or about January 25, 2011, filed United States Patent Application No. 2011/0119085 seeking claims requiring a single exclusive distribution system by a company or trademark.

35. On information and belief, at no time before or during prosecution of Application No. 2011/0119085 did Jazz Pharmaceuticals or its patent prosecution counsel discuss the new claims in that application with any of the patent inventors.

36. On information and belief, Jazz Pharmaceuticals improperly delayed filing patent applications to seek additional claims to cover Roxane's proposed product or to circumvent Roxane's noninfringement defenses to the claims of the original patents-in-suit and has improperly kept and unreasonably delayed in keeping patent applications pending, not to claim additional inventions the inventors believed they had invented, but to glean information from Roxane to craft broader or different claims in an attempt to read on Roxane's sodium oxybate product and method of dosing and distributing same.

37. On information and belief, this serial and directed prosecution of patent applications has and does materially prejudice Roxane's development and market entry of its sodium oxybate product.

38. On information and belief, Jazz Pharmaceuticals has also used the additional new patents to try to serially consolidate new patent lawsuits with older patent lawsuits in order to delay resolution of these patent infringement litigations.

39. Roxane relied on Jazz Pharmaceuticals' list of five patents in the Orange Book when Roxane filed its ANDA in 2010. In particular, Roxane invested substantial time, money, and resources to develop its sodium oxybate product based on its conclusion that Jazz Pharmaceuticals' five patents listed in the Orange Book at that time were either invalid or not infringed.

40. On information and belief, Jazz Pharmaceuticals will continue to use Roxane's product information and specifications disclosed as part of this litigation to file additional patent applications claiming priority to the '431 or '730 patents and subsequently bring suit against Roxane on such patents.

41. Jazz Pharmaceuticals has five non-public continuation patent applications pending in the patent office, two from the '431 patent family and three from the '730 patent family.

42. On information and belief, as Jazz Pharmaceuticals continues to seek and obtain new patents, add patents to the Orange Book, bring patent infringement suits against Roxane, and then seek consolidation of all suits related to sodium oxybate, Roxane will suffer material prejudice by being forced to continually defend itself against patents that were not invented by the named inventors but are based on information gleaned by patent attorneys during a litigation, causing Roxane to face an "at-risk" launch of its sodium oxybate product due to delayed resolution of this litigation.

SIXTH AFFIRMATIVE DEFENSE
(Unclean Hands)

43. Roxane repeats, reasserts and incorporates by reference paragraphs 1-42 above, as if fully set forth herein.

44. On information and belief, the claims of the '650 patent are unenforceable due to Jazz Pharmaceuticals' unclean hands in prosecuting the application that matured into the '650 patent in the United States Patent Office, including but not limited to, Jazz Pharmaceuticals' prosecution of the '650 patent application with prior and concurrent access to Roxane's confidential business and product specification information and Jazz Pharmaceuticals' use of that information to craft the '650 patent claims.

45. On information and belief, Jazz Pharmaceuticals has continued to file and prosecute patent applications as continuations to the '431 and '730 patent families, including the '650 patent, with claims based on information Jazz Pharmaceuticals has gleaned from Roxane before and during litigation about Roxane's sodium oxybate product, the method of dosing and the distribution of same.

46. On information and belief, Jazz Pharmaceuticals has continued to file and prosecute patent applications as continuations to the '431 and '730 patent families, including the '650 patent, with no claims based on what the inventors thought they invented.

47. On information and belief, Jazz Pharmaceuticals' misconduct in the prosecution of the '650 patent is directly related to the issues in this litigation.

COUNTERCLAIMS

1. Counterclaimant Roxane Laboratories, Inc. ("Roxane") is a corporation organized under the laws of Nevada having a principal place of business at 1809 Wilson Road, Columbus OH 43228-8601.

2. Upon information and belief, Plaintiff and Counterclaim Defendant Jazz Pharmaceuticals Inc. ("Jazz Pharmaceuticals") is a corporation organized under the laws of Delaware having a principal place of business at 3180 Porter Drive, Palo Alto, California 94304.

3. As a consequence of Jazz Pharmaceuticals' Complaint against Roxane, there is now an existing, continuing actual controversy between Jazz Pharmaceuticals and Roxane regarding the alleged infringement, validity and enforceability of U.S. Patent No. 8,263,650 ("the '650 patent").

4. This Court has jurisdiction over the subject matter of these counterclaims pursuant to §§ 1331 and 1338(a) of Title 28 of the U.S. Code, as they involve substantial claims arising out of the United States Patent Act, 35 U.S.C. § 1, et. seq.

5. This Court may declare the rights and legal relations for the parties pursuant to §§ 2201 and 2202 of Title 28 of the U.S. Code and § 271(e)(5) of Title 35 of the U.S. Code because Roxane's Counterclaims present an actual controversy within the Court's jurisdiction that the patent asserted by Jazz Pharmaceuticals against Roxane are not infringed and/or are invalid.

6. Venue for these Counterclaims is proper within this District in which Jazz Pharmaceuticals' Complaint is pending.

COUNT 1
Declaratory Judgment of Noninfringement of the '650 Patent

7. The manufacture, use, sale, offer to sell or importation into the United States of Roxane's proposed sodium oxybate oral solution product that is the subject matter of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of the '650 patent either literally or under the doctrine of equivalents.

COUNT 2
Declaratory Judgment of Invalidity of the '650 Patent

8. Upon information and belief, the claims of the '650 patent are invalid for failure to comply with one or more of the provisions of Title 35 of the United States Code, including, but not limited to §§ 101, 102, 103 and/or 112.

COUNT 3
Declaratory Judgment of Unenforceability of the '650 Patent

9. Counterclaimant Roxane incorporates paragraphs 1-8 of its Counterclaim by reference, as though fully set forth herein.

10. The '650 patent and its claims are unenforceable due to inequitable conduct committed during the prosecution, as set forth more fully below.

11. Title 37 of the Code of Federal Regulations §1.56 and the Manual for Patent Examining Procedure §2000.01 et seq. impose a duty of candor and good faith on each individual associated with the filing and prosecution of a patent application before the United States Patent and Trademark Office ("USPTO"), which requires that he or she disclose to the USPTO all information that is material to the patentability of the application under examination.

Breach of this duty of candor, good faith and honesty with an intent to deceive the USPTO constitutes inequitable conduct so as to render at least the affected patent unenforceable.

12. Upon information and belief, the '650 patent is void, unenforceable and of no legal effect by reason of inequitable conduct on the part of the inventors thereof and/or those acting on their behalf before the USPTO. Jazz Pharmaceuticals, the inventors and/or those acting on their behalf committed acts of inequitable conduct by failing to disclose information material to the prosecution of the application. Specifically, Jazz Pharmaceuticals, the inventors, and/or those acting on their behalf withheld material invalidating prior art from the USPTO. Such acts were committed with an intent to deceive the USPTO.

13. The '650 patent is entitled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt For the Treatment of Narcolepsy" and issued from Application Serial No. 13/446,940, which Jazz filed with the USPTO on April 13, 2012.

14. Claim 1 of the '650 patent claims "[a] pharmaceutical composition, comprising an aqueous solution of about 500 mg/ml sodium gamma-hydroxybutyrate, wherein the composition has a pH of about 7.3 to about 8.5, wherein the composition is chemically stable and resistant to microbial growth, and wherein the composition is free of preservatives."

15. The '650 patent issued from an application which is a continuation of U.S. Application No. 12/913,644, which is a continuation of the application which issued as U.S. Patent No. 7,851,506 ("the '506 patent"), which is a divisional of the application which issued as U.S. Patent No. 7,262,219 ("the '219 patent"), which is a divisional of the application which issued as U.S. Patent No. 6,780,889 ("the '889 patent"), which is a divisional of the application which issued as U.S. Patent No. 6,472,431 ("the '431 patent").

16. The validity and enforceability of the claims of the '431, '889, '219 and '506 patents (collectively, "the '431 patent family") are already at issue in Civil Action No. 10-cv-6108 currently pending in this Court.

17. The '650 patent and the other individual patents of the '431 patent family each identifies the same individuals as inventors. The named inventors are as follows: Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad, and Dayton Reardan.

18. All of the named inventors of the '650 patent and the other patents in the '431 patent family signed a declaration under oath stating that:

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

19. The applications that matured into the '650, '431, '889, '219 and '506 patents were all prosecuted by attorneys and/or patent agents, including Ms. Monique M. Perdok Shonka from the law firm of Schwegman, Lundberg & Woessner, P.A.

20. Under 37 C.F.R. §1.56, patent attorneys prosecuting patent applications are individuals subject to the duty of candor and good faith in dealing with the USPTO, which includes a duty to disclose to the USPTO all information known to those individuals to be material to patentability.

21. Upon information and belief, during the prosecution of the '650 patent, Jazz Pharmaceuticals, the inventors and/or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, such as the attorneys and/or patent agents from the law firm of Schwegman, Lundberg & Woessner,

P.A., including Ms. Perdok Shonka, were each aware of his or her duty to disclose information material to patentability to the USPTO.

22. Upon information and belief, Jazz Pharmaceuticals, the inventors and/or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, failed to disclose Chem Abstract ES302338 ("CA 338"), a non-cumulative prior art reference material to the patentability of the claims of the '650 patent, to the USPTO during prosecution of that application.

23. CA 338 sets forth information contained in Spanish Patent No. ES 302338, entitled "Solutions of 4-hydroxybutyric acid salts for injection," issued on January 16, 1965, from application number ES 1964-30233864 filed on July 22, 1964.

24. CA 338 teaches the preparation of chemically stable, microbial growth resistant, preservative free, pH 7.2-7.7 solutions of the sodium salt of gamma-hydroxybutyrate by reacting pure sodium hydroxide (NaOH) with gamma-butyrolactone (GBL) so as not to prepare solutions that "have far too high a pH for injection." CA 338, therefore, would have been material to claim 1 in the application that matured into the '650 patent, alone or in combination with other references. Furthermore, CA 338 is not cumulative of any reference that was already in front of the USPTO.

25. On April 14, 2011, over a year before the application that matured into the '650 patent was filed, Roxane provided to Jazz Pharmaceuticals its Initial Invalidity Contentions regarding the '431 patent family in Civil Action No. 10-cv-6108, as required by the Local Patent Rules of this Court. Roxane contended in its Initial Invalidity Contentions that one or more of the claims of the '431 patent are invalid in light of CA 338 in combination with other references.

26. Roxane provided its Initial Invalidity Contentions with respect to the '431 patent, as well as the other patents-in-suit, to Jazz Pharmaceuticals on a non-confidential basis. Upon information and belief, these Initial Invalidity Contentions were provided by Jazz Pharmaceuticals, or those acting on its behalf, to attorneys and/or patent agents from the law firm of Schwegman, Lundberg & Woessner, P.A., including Ms. Perdok Shonka, who have subsequently filed copies of the Initial Invalidity Contentions during prosecution of related patent applications, such as U.S. Patent Application No. 13/453,915.

27. Upon information and belief, as of at least April 14, 2011, Jazz Pharmaceuticals, the inventors and/or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent were aware of CA 338.

28. Specifically, CA 338 was known to Ms. Perdok Shonka, who disclosed CA 338 to the USPTO in an Information Disclosure Statement during the prosecution of a co-pending, related Application Serial No. 13/446,892 ("the '892 application"), which also claims priority to the '431 patent and was co-pending at the same time as the application for the '650 patent. The '892 application, instead of claiming the pH of sodium oxybate liquid formulation, claims a method of orally dosing a liquid formulation of sodium oxybate with no mention of formulation specifics or pH.

29. Upon information and belief, Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, knew that CA 338 was material to the patentability of at least claim 1 of the '650 patent and not cumulative of any prior art that is already in front of the USPTO.

30. Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, did not disclose CA 338 to the USPTO during the pendency of the application that matured into the '650 patent.

31. Failure to disclose CA 338 to the USPTO was an omission by Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, in contravention of their duties to the USPTO during the prosecution of the '650 patent.

32. Upon information and belief, Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, had knowledge of, and intentionally withheld, CA 338 from the USPTO with intent to deceive the USPTO.

33. This omission was material to patentability because, among other things, CA 338 was relevant to the question of whether the claims of the '650 patent would have been novel or obvious to one of ordinary skill in the art and because there is a substantial likelihood that a reasonable examiner would have considered CA 338 important in deciding whether to allow at least claim 1 of the '650 patent because this reference either alone or in combination with other art, teaches or implies elements of, or renders obvious, at least claim 1 of the '650 patent.

34. CA 338 was not cumulative of any prior art that was already before the examiners who examined the '431 patent family or the application for the '650 patent.

35. Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent,

including on information and belief Ms. Perdok Shonka, believed the CA 338 reference was sufficiently relevant to this family of patent applications and not cumulative of any prior art already in front of the USPTO to cite CA 338 to the USPTO during the prosecution of the '892 application. CA 338 has less direct relevance to the '892 application claims, which relate to a dosing schedule, than to the '650 patent claims, which relate to liquid formulation pH.

36. Citation of CA 338 during the prosecution of the less relevant '892 application but not the more relevant '650 patent evidences an intent to deceive the USPTO into granting the '650 patent by Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including, on information and belief Ms. Perdok Shonka.

37. But for the material omission of Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, the USPTO would not have issued at least claim 1 of the '650 patent.

38. By failing to cite CA 338 during prosecution of the '650 patent, Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, materially misrepresented the patentability of at least claim 1 of the '650 patent.

39. On information and belief, this material misrepresentation was part of a deliberately planned and carefully executed scheme carried out by Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, to defraud the USPTO and the courts and effect issuance of at least claim 1 of the '650 patent.

40. This material omission of Jazz Pharmaceuticals, the inventors or those acting on their behalf associated with the preparation, filing and/or prosecution of the application that matured into the '650 patent, including Ms. Perdok Shonka, amounted to affirmative egregious misconduct in dealing with the USPTO.

41. For each of the aforesaid reasons, Roxane is entitled to a declaratory judgment that the '650 patent is unenforceable due to inequitable conduct.

ROXANE'S PRAYER FOR RELIEF

WHEREFORE, Roxane respectfully requests that the Court enter judgment against Jazz Pharmaceuticals as follows:

(A) Declaring that Roxane would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 8,263,650 either literally or under the doctrine of equivalents by submitting ANDA No. 202090;

(B) Declaring that Roxane's proposed sodium oxybate oral solution that is the subject of ANDA No. 202090 would not and will not directly, indirectly, contributorily and/or by inducement, infringe any validly construed claim of U.S. Patent No. 8,263,650 either literally or under the doctrine of equivalents;

(C) Declaring that U.S. Patent No. 8,263,650 is invalid for failure to comply with one or more provisions of 35 U.S.C. § 101, 102, 103, and/or 112;

(D) Declaring that U.S. Patent No. 8,263,650 is unenforceable;

(E) Granting an injunction permanently preventing Jazz Pharmaceuticals from asserting or enforcing U.S. Patent No. 8,263,650 against Roxane, its divisions, subsidiaries, licensees, customers or agents;

(F) Awarding Roxane its reasonable costs and attorneys' fees incurred in connection with this action pursuant to 35 U.S.C. § 285;

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

Dated:

Respectfully Submitted,

s/_____
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Attorneys for Defendant
Roxane Laboratories, Inc.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Dayton T. Reardan Ph.D et al.

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

Docket No.:	101.031US9	Serial No.:	13/592,202
Filed:	August 22, 2012	Due Date:	N/A
Examiner:	Lena Najarian	Group Art Unit:	3686
Customer No.:	21186	Confirmation No.:	5805

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

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

X Supplemental Information Disclosure Statement (2 pgs.), Form 1449 (1 pg.) Copies of Cited References (6).

If not provided for in a separate paper filed herewith, please consider this a PETITION FOR EXTENSION OF TIME for sufficient number of months to enter these papers and please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
Customer No.: 21186

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Dayton T. Reardan Ph.D et al.	Examiner:	Lena Najarian
Serial No.:	13/592,202	Group Art Unit:	3686
Filed:	August 22, 2012	Docket:	101.031US9
Customer No.:	21186	Confirmation No.:	5805
Title:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD		

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

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

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

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

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

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

Respectfully submitted,

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

Date May 28, 2013 By /David D'Zurilla/

David D'Zurilla
Reg. No. 36,776

DDZ:vam

Electronic Acknowledgement Receipt

EFS ID:	15885524
Application Number:	13592202
International Application Number:	
Confirmation Number:	5805
Title of Invention:	SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD
First Named Inventor/Applicant Name:	Dayton T. Reardan
Customer Number:	21186
Filer:	Eric B. Andersland/Valerie Murphy
Filer Authorized By:	Eric B. Andersland
Attorney Docket Number:	101.031US9
Receipt Date:	28-MAY-2013
Filing Date:	22-AUG-2012
Time Stamp:	17:13:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13592202_SIDS_5-28-13.pdf	257186 b77b1a7ac5534885889062121398 22c278692f8f	yes	4

	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Miscellaneous Incoming Letter		1	1	
	Transmittal Letter		2	3	
	Information Disclosure Statement (IDS) Form (SB08)		4	4	
Warnings:					
Information:					
2	Non Patent Literature	0001_101031u10_oarn_20130321.pdf	2727888 0dabb915180a89a16c6827d3c3975b8acc8a212e	no	23
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Information:					
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Information:					
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Information:					
6	Non Patent Literature	0005_roxanesproposedamendedanswer275patent_042613.pdf	148912 6f558e5a0b69b63835066ab59dbd77ab6307e4b6	no	15
Warnings:					
Information:					
7	Non Patent Literature	0006_roxanesproposedamendedanswer650patent_042613.pdf	185052 e4341951fea8092259f477778a575a6a33f7542e	no	23
Warnings:					
Information:					
		Total Files Size (in bytes):	5063807		

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.

Modified form PTO/SB/08A(04-07) OMB 651-0031
US Patent & Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)	*Complete if Known*	
	Application Number	13/592,202
	Filing Date	August 22, 2012
	First Named Inventor	Dayton T. Reardan Ph.D
	Group Art Unit	3686
	Examiner Name	Lena Najarian
Sheet 1 of 1	Attorney Docket No: 101.031US9	

US PATENT DOCUMENTS			
Examiner Initial *	**USP Document Number**	**Publication Date**	**Name of Patentee or Applicant of cited Document**
	US-20030074225	4/17/2003	Borsand, Gerlad, et al.

OTHER DOCUMENTS – NON PATENT LITERATURE DOCUMENTS		
Examiner Initial *	**Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.**	**T 1**
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	Application Number	13/592,202
	Filing Date	August 22, 2012
	First Named Inventor	Dayton T. Reardan Ph.D
	Group Art Unit	3626
	Examiner Name	Unknown
Sheet 1 of 5	Attorney Docket No: 101.031US9	

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

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	Group Art Unit	3626
	Examiner Name	Unknown
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	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint", (June 1, 2011), 12 pgs.	
	"Roxane Laboratories, Inc.'s Answer, Affirmative Defenses and Counterclaims to Plaintiff's Complaint", (November 9, 2012), 18 pgs.	

EXAMINER /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./

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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

21186 7590 06/05/2013

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

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

NOTIFICATION DATE	DELIVERY MODE
06/05/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@slwip.com
SLW@blackhillsip.com

Office Action Summary	Application No. 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 --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-22,27 and 28* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-22,27 and 28* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

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)).

* See the attached detailed Office action for a list of the certified copies not received.

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20121004; 20130214; 20130304; 20130311*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 23-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/15/13.

2. Applicant's election without traverse of Group I (claims 1-22) in the reply filed on 2/15/13 is acknowledged.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, 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. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 3-15, 19, 22, 27, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Talk About Sleep ("An Interview with Orphan Medical about Xyrem").

(A) Referring to claim 1, Moradi discloses a computer-implemented system for treatment of a 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 (para. 27 & 31 of Moradi);

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 (para. 27 & 43-45 of Moradi);

said patient fields, contained within the database schema, storing information sufficient to identify the patient for whom the company's prescription drug is prescribed (para. 27 & 43-45 of Moradi);

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 (para. 27 & 43-45 of Moradi);

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 (para. 31 of Moradi);

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 (para. 101 of Moradi).

Moradi does not disclose that the patient is narcoleptic.

Talk About Sleep teaches that the patient is narcoleptic (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned feature of Talk About Sleep within Moradi. The motivation for doing so would have been to provide medications to only those that need it (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

(B) Referring to claim 3, Moradi discloses wherein the data processor is configured to process a second database query that identifies a potential misuse, abuse or diversion by the patient (para. 43, 45, 6, and Fig. 3 of Moradi).

Moradi does not disclose that the patient is narcoleptic.

Talk About Sleep teaches that the patient is narcoleptic (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned feature of Talk About Sleep within Moradi. The motivation for doing so would have been to provide medications to only those that need it (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

(C) Referring to claim 4, Moradi disclsoes wherein the data processor selectively blocks shipment of the prescription drug to the patient based upon said identifying by the database query (para. 45-46 of Moradi).

(D) Referring to claim 5, Moradi discloses wherein the prescription drug is shipped to the patient if no potential misuse, abuse or diversion is found for the patient (para. 43-45 and para. 6 of Moradi).

Moradi does not disclose that the patient is narcoleptic.

Talk About Sleep teaches that the patient is narcoleptic (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned feature of Talk About Sleep within Moradi. The motivation for doing so would have been to provide medications to only those that need it (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

(E) Referring to claim 6, Moradi discloses wherein the single computer database is an exclusive database that receives data associated with all patients being prescribed the prescription drug that are associated with the company (para. 27 of Moradi).

(F) Referring to claim 7, Moradi discloses wherein the exclusive central pharmacy controls the single computer database (para. 24 & 35 of Moradi).

(G) Referring to claim 8, Moradi does not disclose wherein the prescription drug comprises gamma hydroxyl butyrate (GHB).

Talk About Sleep discloses wherein the prescription drug comprises gamma hydroxyl butyrate (GHB). (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned feature of Talk About Sleep within Moradi. The motivation for doing so would have been to treat narcoleptic patients (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

(H) Referring to claim 9, Moradi discloses wherein the single computer database comprises a relational database (para. 43 of Moradi).

(I) Referring to claim 10, Moradi discloses where the single computer database is distributed among multiple computers provided the database query that operates over all data relating to said prescription fields, prescriber fields, and patient fields for the prescription drug (para. 27, 31, 43-45 of Moradi).

(J) Referring to claim 11, Moradi discloses 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 (para. 27, 31, and 43-45 of Moradi).

(K) Referring to claim 12, Moradi discloses wherein the data processor is configured to process a second database query that identifies an expected date for a refill of the prescription drug (para. 25, 42, and 46 of Moradi).

(L) Referring to claim 13, Moradi discloses wherein the expected date is based on a prescription for the prescription drug and a date of a previous filling of the prescription (para. 25, 42, and 46 of Moradi).

(M) Referring to claim 14, Moradi discloses wherein the prescription identifies an amount of the prescription drug to be provided and a schedule for consumption of the prescription drug (para. 25, 42, and 46 of Moradi).

(N) Referring to claim 15, Moradi discloses 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 (para. 25 & 193 of Moradi).

(O) Referring to claim 19, Moradi does not expressly disclose wherein additional controls for distribution are selected in a negotiation with an approval body to garner the approval of distribution.

Talk About Sleep discloses wherein additional controls for distribution are selected in a negotiation with an approval body to garner the approval of distribution (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned feature of Talk About Sleep within Moradi. The motivation for doing so would have been to obtain permission to provide medications to those that need it (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

(P) Referring to claim 22, Moradi discloses wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent (para. 101 of Moradi).

(Q) Referring to claim 27, Moradi discloses 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 (para. 27 and 43-45 of Moradi).

(R) Referring to claim 28, Moradi discloses 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 (para. 27 and 43-45 of Moradi).

5. Claim 2 is rejected under 35 U.S.C. 103(a) as being 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 *Official Notice*.

(A) Referring to claim 2, Moradi discloses wherein the data processor is configured to process a second database query that identifies: whether the patient is a payer and a physician that is interrelated with the patient through the schema of the single computer database (para. 7 & 32 of Moradi);
said identifying by said second database query being an indicator of a potential misuse, abuse or diversion by the patient and being used to notify the physician that is interrelated with the patient through the schema of the single computer database (para. 27 and 43-45 of Moradi).

Moradi does not disclose a *narcoleptic* patient and a *cash* payer.

Talk About Sleep discloses a narcoleptic patient (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned feature of Talk About Sleep within Moradi. The motivation for doing so would have been to provide medications to only those that need it (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

The Examiner takes *Official Notice* that cash is a form of payment. At the time of the invention, it would have been obvious to a person of ordinary skill in the art to indicate the type of payment to be submitted in combination with Moradi and Talk About Sleep in order to provide a complete record of the transaction.

6. Claims 16-18, 20, and 21 are rejected under 35 U.S.C. 103(a) as being 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 Lilly et al. (US 2004/0176985 A1).

(A) Referring to claims 16 and 17, Moradi and Talk About Sleep do not expressly disclose 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 and wherein one or more controls for distribution of the prescription drug are selected based on the identified pattern.

Lilly discloses 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 and wherein one or more controls for distribution of the prescription drug are selected based on the identified pattern (para. 33, 69, 54, 57-58, 61, and 11 of Lilly).

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 Lilly within Moradi and Talk About Sleep. The motivation for doing so would have been to immediately detect problems related to abuse, fraud, and misuse of medications (para. 57 of Lilly).

(B) Referring to claims 18 & 21, Moradi does not expressly disclose wherein the one or more controls are submitted to an approval body for approval of distribution of the prescription drug and wherein the approval body is the Food and Drug Administration (FDA) or the Drug Enforcement Agency (DEA).

Talk About Sleep discloses disclose wherein the one or more controls are submitted to an approval body for approval of distribution of the prescription drug and wherein the approval body is the Food and Drug Administration (FDA) or the Drug Enforcement Agency (DEA). (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned feature of Talk About Sleep within Moradi. The motivation for doing so would have been to obtain permission from the government to provide medications to those that need it (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

(C) Referring to claim 20, Moradi and Talk About Sleep do not expressly disclose wherein the data processor is used to add further controls until approval is obtained.

Lilly discloses wherein the data processor is used to add further controls until approval is obtained (para. 43 & 54 of Lilly).

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 Lilly within Moradi and Talk About Sleep. The motivation for doing so would have been to

detect problems related to abuse, fraud, and misuse of medications (para. 57 of Lilly).

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LENA NAJARIAN whose telephone number is (571)272-7072. The examiner can normally be reached on Monday - Friday, 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jerry O'Connor can be reached on (571) 272-6787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LENA NAJARIAN/
Primary Examiner, Art Unit 3686
5/30/13

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S2	130	(database or data adj1 base) same prescription same patient same (prescriber or doctor or physician or practitioner) same (field)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/05/28 16:22
S3	20	(database or data adj1 base) same prescription same patient same (prescriber or doctor or physician or practitioner) same (field) and (authoriz$ or DEA adj2 number) and (track$ or reconcil$) same (inventory or supply)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/05/28 16:24

5/30/2013 1:54:30 PM
C:\Users\lnajarian2\Documents\EAST\Workspaces\13592202.wsp

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							
	1	÷	✓							
	2	÷	✓							
	3	÷	✓							
	4	÷	✓							
	5	÷	✓							
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	20	÷	✓							
	21	÷	✓							
	22	÷	✓							
	23	÷	N							
	24	÷	N							
	25	÷	N							
	26	÷	N							
	27		✓							
	28		✓							

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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

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, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402
UNITED STATES

TITLE

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

FILING FEE RECEIVED		
1910	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).

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

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	FILE WRAPPER LOCATION
13/592,202		3686	

OC000000082205769

Correspondence Address/Fee Address Change

The following fields have been set to Customer Number 107632 on 06/25/2013

- **Correspondence Address**
- **Maintenance Fee Address**

The address of record for Customer Number 107632 is:

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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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 07/09/2013

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

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

NOTIFICATION DATE	DELIVERY MODE
07/09/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

slw@blackhillsip.com
uspto@slwip.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/592,202	REARDAN ET AL.	
	Examiner	Art Unit	
	LENA NAJARIAN	3686	

All participants (applicant, applicant's representative, PTO personnel):

(1) *LENA NAJARIAN*.

(2) *Philip McGarrigle (Reg. No. 31,395)*.

(3) *John Biernicki (Reg. No. 40,511)*.

(4) *David D'Zurilla (Reg. No. 36,776)*.

Date of Interview: *02 July 2013*.

Type: ☐ Telephonic ☐ Video Conference
☒ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *all*.

Identification of prior art discussed: *Moradi*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Discussed possible amendments to the claims. The Examiner will reconsider the applied references in light of any amendments and/or remarks to be submitted in response to the non-final rejection.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/LENA NAJARIAN/ Primary Examiner, Art Unit 3686	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

lease find clo an or attached an ffice comm nication concerning this application or proceeding

he time period for reply, if any, is set in the attached communication.

Notice of the ffice communication was sent electronically on a e indicated. "Notification ate" to the following e-mail address es:

PAR1002
IPR of U.S. Patent No. 8,731,963
Page 2288 of 3920

	Application No	Applicant
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	LENA NA AR AN	36 8

ll participants applicant, applicant's representative, T pers nnel

(1) *LENA NA AR AN.* (3) *Ma arci ie Re No 31 3*

(2) *David D unlis Re No 36 776* (4)

Date of interview: *28 Ma 2 13*

Type: ☒ Telephonic ☐ ideo Conference
☐ ersonal copy iven to: ☐ applicant ☐ applicant's representative

hibit shown or demonstration conducted: ☐ Yes ☒ o
If Yes, brief description:

Issues Discussed ☐ 101 ☐ 12 ☐ 102 ☐ 103 ☐ thers

Claim(s) discussed: *1*

Identification of prior art discussed: *eresman and Lill*

ubstance of interview

Discussed A licant's ro osed amendments. The Examiner su ested includin an active ste of checkin for abuse, misuse, or diversion of both the atient and the rescribe . The Examiner ill reconsider the a lied references in li ht of an remarks and or amendments to be made in res onse to the non final re ection.

pp icant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (ee MPEP section 713.04). If a reply to the last O ice action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

E aminer recordation instructions: Examiners must summari e the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

ttachment

LENA NA ARIAN
Primary Examiner, A rt 3686

37 Code of Federal Regulations (CFR) 1.133 Interviews

PAR1002
IPR of U.S. Patent No. 8,731,963
Page 2290 of 3920

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Dayton T. Reardan Ph.D et al.	Examiner: Lena Najarian
Serial No.: 13/595,676	Group Art Unit: 3686
Filed: August 27, 2012	Docket No.: 101.031U10
Customer No.: 21186	Confirmation No.: 1006

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

AMENDMENT & RESPONSE UNDER 37 C.F.R. § 1.111

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

In response to the Office Action dated March 21, 2013, please amend the application as follows.

IN THE CLAIMS

Please amend the claims as follows:

1. (Currently Amended) A method of 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:

receiving, using a computer processor, into a single computer database of the company that obtained approval for distribution of the prescription drug, from any and all patients being prescribed the company's prescription drug, all prescriptions for the company's 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~~;

entering, using the computer processor, into the single computer database information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

entering, using the computer processor, into the single computer database information sufficient to identify [[a]] any and all physicians or other prescribers of the company's prescription drug and information to show that the physicians or other prescribers are [[is]] authorized to prescribe the company's prescription drug;

entering and maintaining, using the computer processor, in the single computer database information that indicates that the narcoleptic patient or prescriber has abused, misused, or diverted the company's prescription drug; and

checking for abuse**,** using the computer processor and the single computer database, ~~to authorize~~ and authorizing filling of the prescriptions 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 [[or]] prescriber, and [[or]] if there is a record of such incidents, the single computer database indicates that such incidents have been

investigated, and the single computer database indicates that such incidents do not involve abuse, misuse or diversion.

2. (Original) The method of claim 1, comprising delivering the prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the prescription drug.

3. (Currently Amended) The method of claim 1, wherein ~~an exclusive central~~ a pharmacy enters data into ~~controls~~ the single computer database.

4. (Original) The method of claim 1, comprising selectively blocking shipment of the prescription drug to the narcoleptic patient.

5. (Original) The method of claim 1, wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the prescription drug is blocked based upon such association.

6. (Original) The method of claim 1, wherein the prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

7. (Original) The method of claim 6, wherein said GHB drug product treats cataplexy in said narcoleptic patient.

8. (Currently Amended) A method of treatment of a narcoleptic patient with a prescription drug that has the 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:

receiving, using a computer processor, into a single computer database of the company that obtained approval for distribution of the prescription drug, from any and all patients being prescribed the company's prescription drug, all prescriptions for a prescription drug with the potential for abuse, misuse or diversion sold or distributed under a single trademark;

entering, using the computer processor, into the single computer database information sufficient to identify the narcoleptic patient for whom said prescription drug was prescribed;

entering, using the computer processor, into the single computer database information sufficient to identify [[the]] any and all physicians or other prescribers of said prescription drug and information to show that the any and all physicians or other prescribers were [[was]] authorized to prescribe said prescription drug;

entering and maintaining, using the computer processor, in the single database information which may suggest that the narcoleptic patient or prescriber has abused, misused, or diverted said prescription drug;

checking for abuse, using the computer processor and the single computer database, ~~to authorize~~ and authorizing filling of the prescriptions for said prescription drug only if there is no record of incidents that may suggest abuse, misuse, or diversion by the narcoleptic patient and [[or]] prescriber, and [[or]] if there is a record of such incidents, the single computer database indicates that such incidents have been investigated, and the single computer database indicates that such incidents do not involve abuse, misuse or diversion.

9. (Original) The method of claim 8, comprising delivering the prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the prescription drug.

10. (Currently Amended) The method of claim 8, wherein ~~an exclusive central~~ a pharmacy enters data into ~~controls~~ the single computer database.

11. (Original) The method of claim 8, comprising selectively blocking shipment of the prescription drug to the narcoleptic patient.

12. (Original) The method of claim 8, wherein an abuse pattern is associated with the patient, and shipment of the prescription drug is blocked based upon such association.

13. (Original) The method of claim 8, wherein the prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

14. (Original) The method of claim 13, wherein said GHB drug product treats cataplexy in said narcoleptic patient.

15. (Currently Amended) A method of treatment of a narcoleptic patient with a prescription drug that has the 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:

receiving, using a computer processor, into a single computer database of the company that obtained approval for distribution of the prescription drug, all prescriptions for the [[a]] prescription drug from any and all patients being prescribed the company's prescription drug, wherein the company's prescription drug [[that]] has been manufactured at a single manufacturing site, and wherein the company's prescription drug has [[with]] the potential for abuse, misuse or diversion;

entering, using the computer processor, into the single database information sufficient to identify the narcoleptic patient for whom the company's [[said]] prescription drug was prescribed,

entering, using the computer processor, into the single database information sufficient to identify the physician or other prescriber of the company's [[said]] prescription drug and information to show that the physician or other prescriber was authorized to prescribe the company's [[said]] prescription drug;

entering and maintaining, using the computer processor, in the single database information which may suggest that the narcoleptic patient or prescriber has abused, misused, or diverted the company's [[said]] prescription drug;

checking for abuse, using the computer processor and the single computer database, ~~to authorize~~ and authorizing filling of the prescription for the company's [[said]] prescription drug only if there is no record of incidents that may suggest abuse, misuse, or diversion by the narcoleptic patient and [[or]] prescriber and [[or]] if there is a record of such incidents, the single computer database indicates that any such incidents have been investigated and found not to involve abuse, misuse or diversion; and

providing the company's [[said]] prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the company's prescription drug;

wherein the company's prescription drug that has the potential for misuse, abuse or diversion is a gamma hydroxybutyrate (GHB) drug product; and

wherein said GHB drug product treats cataplexy in said narcoleptic patient.

16. (Currently Amended) The method of claim 15, wherein ~~an exclusive central~~ a pharmacy enters data into ~~controls~~ the single computer database.

17. (Original) The method of claim 15, comprising selectively blocking shipment of the prescription drug to the narcoleptic patient.

18. (Original) The method of claim 15, wherein an abuse pattern is associated with the patient, and shipment of the prescription drug is blocked based upon such association.

19. (Currently Amended) A method of treatment of a narcoleptic patient with a single prescription drug that has a potential for misuse, abuse or diversion, comprising:

receiving, using a computer processor, into a single computer database and storing in a computer memory all prescriptions for the single prescription drug received at a pharmacy and sold or distributed by a company that obtained approval for distribution of the prescription drug, the single prescription drug having ~~with~~ the potential for abuse, misuse or diversion, ~~wherein the prescription drug inventory is owned by a company and is managed thorough said single computer database~~ wherein the pharmacy is permitted to distribute the single prescription drug based on two or more of the following: processing of a prescription enrollment form for the single prescription drug; agreeing to document adverse events relating to the single prescription drug; providing educational materials relating to the single prescription drug; and verifying that the single prescription drug is medically necessary;

entering, using the computer processor, into the single computer database information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

entering, using the computer processor, into the single computer database 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, including verifying that the prescriber's drug enforcement agency (DEA) number and state license are current and that there are no pending disciplinary actions against the prescriber;

verifying two or more of the following using the computer processor prior to providing the single prescription drug to the narcoleptic patient: patient name; patient address; that the patient has received educational material regarding the single prescription drug; a quantity of the single prescription drug; and dosing directions for the single prescription drug;

entering and maintaining, using the computer processor, in the single computer database information that indicates that the narcoleptic patient or prescriber has abused, misused, or diverted the company's single prescription drug; and

checking for abuse, using the computer processor and the single computer database, ~~to authorize~~ and authorizing filling of the prescriptions for the company's single prescription drug only if there is no record of incidents that indicate abuse, misuse, or diversion by the narcoleptic patient and [[or]] prescriber, and [[or]] if there is a record of such incidents, the single computer database indicates that such incidents have been investigated, and the single computer database indicates that such incidents do not involve abuse, misuse or diversion.

20. (Original) The method of claim 19, comprising delivering the prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the prescription drug.

21. (Currently Amended) The method of claim 19, wherein ~~an exclusive central~~ a pharmacy enters data into ~~controls~~ the single computer database.

22. (Currently Amended) The method of claim 19, comprising selectively blocking shipment of the single prescription drug to the narcoleptic patient.

23. (Currently Amended) The method of claim 19, wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the single prescription drug is blocked based upon such association.

24. (Currently Amended) The method of claim 19, wherein the single prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

25. (Original) The method of claim 19, wherein said GHB drug product treats cataplexy in said narcoleptic patient.

26. (New) The method of claim 1, comprising identifying, using the computer processor, information relating to the prescriptions and the information relating to the narcoleptic patient,

and using the information for reconciling inventory for the company's prescription drug before shipments for a day or other time period are sent.

REMARKS

This communication responds to the Office Action dated March 21, 2013.

Claims 1, 3, 8, 10, 15, 16, 19, and 21-24 are currently amended; no claims are canceled; and claim 26 is added; as a result, claims 1-26 are now pending and subject to examination in this application.

Examiner Interview

Applicant expresses its gratitude to Examiner Najarian for the courtesies extended to its representatives David D'Zurilla and Philip McGarrigle during a telephonic interview on May 23, 2013.

During the interview, Examiner Najarian, Mr. D'Zurilla, and Mr. McGarrigle discussed claim amendments that were previously faxed to Examiner Najarian on May 21, 2013. These proposed claim amendments have been incorporated into this response.

Examiner Najarian requested that the claims further be amended such that in the authorizing feature, the authorization is based on both the patient *and* the prescriber, and the authorization further considers both incidents of abuse *and* no incidents of abuse. Applicants have amended the claims in this response per the Examiner's request.

New Claims

Claim 26 is new. Support for new claim 26 may be found in the specification, such as at page 9, lines 13-15. Applicants believe that no new matter has been introduced in claim 26. Additionally, Applicants respectfully submit that new claim 26 is patentably distinct over the references currently cited as a basis of rejection, because none of the references disclose, either alone or in combination, the feature of reconciling inventory for the prescription drug before shipments for a day or other time period are sent. Accordingly, Applicants respectfully request that the Examiner consider and allow newly added claim 26.

The Rejection of Claims Under § 101

Claims 1-25 are rejected under 35 U.S.C. 101 because the claimed invention is allegedly directed to non-statutory subject matter.

Applicants have amended independent claims 1, 8, 15, and 19 to recite that a computer processor is used to execute the operations of the claims. Support for this amendment can be found in Applicants' specification at page 5, line 22 – page 6, line 10, and in FIG. 1. Applicants respectfully submit that the amendments to claims 1, 8, 15, and 19 overcome the rejection of claims 1-25 under 35 U.S.C. 101, and respectfully request the withdrawal of the rejection of claims 1-25.

The Rejection of Claims Under § 112

Claims 3, 10, 16, and 21 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for a pre-AIA the applicant, regards as the invention.

Applicants have amended the claims to recite that a pharmacy enters data into the single computer database. Support for this amendment can be found in Applicants' specification at page 6, lines 26-31. Applicants respectfully submit that the amendments to claims 3, 10, 16, and 21 overcome the rejection of these claims under 35 U.S.C. 112, and respectfully request the withdrawal of the rejection of these claims.

The Rejection of Claims Under § 103

Claims 1-25 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Keresman, III et al (US 2001/0047281 A1) in view of Lilly et al. (US 2004/0176985 A 1), and further in view of Talk About Sleep ("An Interview with Orphan Medical about Xyrem").

Applicants have amended claim 1 to recite:

receiving, using a computer processor, into a single computer database of the company that obtained approval for distribution of the prescription drug, from any and all patients being prescribed the company's prescription drug, all prescriptions for the company's prescription drug with the potential for abuse, misuse or diversion

Applicants have amended independent claims 8 and 15 in a similar manner. Applicants respectfully submit that the features added to claims 1, 8, and 15 are not disclosed in Keresman, or in any of the other references of record. Applicants further respectfully submit that the

amendments to claims 1, 8, and 15 overcome the rejections of claims 1-18 under section 103, and respectfully request the withdrawal of the rejection of claims 1-18.

Keresman relates to a prescription drug fulfillment system wherein doctors, patients, and pharmacies register and thereafter have their identities authenticated. Specifically, the doctor submitting the prescription has his or her identity authenticated, and the patient identified on the prescription also has his or her identity authenticated. (Keresman, Abstract). These prescriptions are then forwarded to a registered pharmacy. (Keresman, paragraph [0015]). The patient can select a registered pharmacy of choice. (Keresman, paragraph [0029]). The authentication involves the use of a central database that includes accounts created by the registration process for each of the registered participants, that is, the doctors, patients, and pharmacies. (Keresman, paragraph [0015]).

Applicants respectfully submit that Keresman does not disclose the feature of "receiving . . . into a single computer database of the company that obtained approval for distribution of the prescription drug, from any and all patients being prescribed the company's prescription drug, all prescriptions for the company's prescription drug." There is no indication, teaching, or disclosure in Keresman that the central database of Keresman is associated with a company that obtained approval of the prescription drug. Indeed, the Keresman system only relates to doctors, patients, and pharmacies. There is no mention in Keresman of a company that obtained approval for distribution of the prescription drug, or of a database of such a company.

Since amended claims 1, 8, and 15 recite a feature that is not disclosed by Keresman or any of the other references of record, Applicants respectfully submit that the amendments to claims 1, 8, and 15 overcome the rejection of claims 1-18 under section 103, and respectfully request the withdrawal of the rejections of claims 1-18.

Applicants have amended independent claim 19 to recite several new features including:

> the pharmacy is permitted to distribute the single prescription drug based on two or more of the following: processing of a prescription enrollment form for the single prescription drug; agreeing to document adverse events relating to the single prescription drug; providing educational materials relating to the single prescription drug; and verifying that the single prescription drug is medically necessary;

Support for these features can be found in Applicants' specification at page 7, lines 22-25; page 5, lines 4-6; page 5, lines 7-10; and in FIG. 12.

verifying that the prescriber's drug enforcement agency (DEA) number and state license are current and that there are no pending disciplinary actions against the prescriber;

Support for this feature can be found in Applicants' specification at page 7, lines 26-30.

verifying two or more of the following using the computer processor prior to providing the single prescription drug: patient name; patient address; that the patient has received educational material regarding the single prescription drug; a quantity of the single prescription drug; and dosing directions for the single prescription drug;

Support for these features can be found in Applicants' specification at page 6, line 22 – page 7, line 1; page 6, lines 23-24; page 5, lines 10-11; page 6, lines 23-24; and page 6, lines 23-24.

Applicants respectfully submit that neither the Keresman reference, nor the Lilly nor the Talk About Sleep reference, discloses these features that have been added to claim 19. Applicants respectfully submit that the amendments to claim 19 overcome the rejection of claims 19-25 under section 103, and respectfully request the withdrawal of the rejection of claims 19-25.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone the undersigned 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 May 31, 2013

By / /

David D'Zurilla
Reg. No. 36,776

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	

AMENDMENT & RESPONSE UNDER 37 C.F.R. § 1.111

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

In response to the Office Action dated June 5, 2013, please amend the application as follows.

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:

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

~~said database query identifying information in the prescription fields and patient fields for reconciling~~ 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.

2. (Currently Amended) The system of claim 1, wherein the data processor is configured to process a second database query that identifies: ~~whether~~ 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

23 - 26. (Canceled).

27. (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. (New) 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.

30. (New) 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, from any and all patients being prescribed the company's prescription drug, 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. (New) 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. (New) 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. (New) 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. (New) 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.

REMARKS

This communication responds to the Office Action dated June 5, 2013.

Claims 1 and 2 are currently amended, claims 23-26 are canceled, and claims 29-34 are added; as a result, claims 1-22 and 27-34 are now pending and subject to examination in this application.

Interview Summary

Applicant expresses its gratitude to Examiner Najarian for the courtesies extended to its representatives Mr. Philip McGarrigle, Mr. John Biernicki, and Mr. David D'Zurilla during an in-person (Mr. McGarrigle) and telephonic (Mr. Biernicki, Mr. D'Zurilla) interview on July 2, 2013. The interview participants discussed the claims, and in particular claim 1, and the references cited by the Office Action of June 5, 2013. The participants further discussed some clarifying amendments to the claims. Applicant agreed to submit the clarifying amendments in a written response. No agreement on the claims was reached.

New Claims

Claims 29-34 are new. Support for the new claims may be found throughout Applicant's specification, including at page 2, lines 6-16, page 3, lines 4-8, page 10, lines 3-18, and page 12, lines 12-24. Applicant believes that no new matter has been introduced in the added claims. Additionally, Applicant respectfully submits that the new claims are patentably distinct over the references currently cited as a basis of rejection.

Applicant notes that new claim 29 incorporates features from claims 1, 4, and 22. Applicant respectfully submits that new claim 29 is patentably distinct over the cited references at least because of the following feature---"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."

Applicant further respectfully submits that new claim 30 is patentably distinct over the cited references at least because of the following features, in combination with the other claim limitations---"one or more computer memories for storing a central computer database of the company that obtained approval for distribution of the prescription drug" and "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." (Applicant notes that the last two limitations in claim 30 (as well as some language in dependent claims 31 and 32) as provided herein contain differences from the version presented during the interview).

Accordingly, Applicant respectfully requests that the Examiner consider and allow the newly added claims.

The Rejection of Claims Under § 103

Claims 1, 3-15, 19, 22, 27, and 28 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Talk About Sleep ("An Interview with Orphan Medical about Xyrem").

Claim 2 is rejected under 35 U.S.C. 103(a) as allegedly being 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 Official Notice.

Claims 16-18, 20, and 21 are rejected under 35 U.S.C. 103(a) as allegedly being 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 Lilly et al. (US 2004/0176985 A1).

1. The combination of Moradi and Xyrem Interview does not teach or suggest a database query that identifies 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.

The final limitation of claim 1 states:

> 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

The '202 application includes examples in the specification of inventory reconciliation, including at page 9, lines 13-15 where, "for the sensitive drug, Xyrem, all inventory is cycle counted and reconciled with the database system quantities before shipments for the day are sent. This provides a very precise control of the inventory." As this example shows, inventory reconciliation involves a physical check being made with respect to the physical inventory and then compared to a database system inventory value to determine whether the physical inventory matches the database inventory value. In this example, inventory reconciliation is independent of a specific medication order, and instead involves whether the aggregate amount of a drug in the physical inventory agrees with the aggregate amount in the database. If not, then a mismatch/discrepancy has been detected between the physical inventory and the database inventory amounts.

In rejecting claim 1, the Office Action cites to paragraph [0101] of Moradi as teaching or suggesting this limitation. Paragraph [0101] of Moradi states:

> [0101] In addition to not being "on-line," a pharmacy or other POD may not be able to deliver the medication at the required or requested delivery time. A pharmacy may also be out of inventory of the prescribed medication. The exemplary embodiment of the present invention handles this case by determining an alternative pharmacy or POD 106 to deliver the prescribed medicine and the scanned image of the prescription is rerouted to that pharmacy or POD 106.

This paragraph of Moradi merely checks whether a pharmacy has a sufficient amount of the medication to fulfill a specific prescription order. There is no disclosure of checking whether there is a mismatch between the aggregate amount of a drug in physical inventory with the aggregate amount in the database as required by the inventory reconciliation features of claim 1.

Because of the significant differences between the disclosure of paragraph [0101] of Moradi and the claimed inventory reconciliation features of claim 1 (in combination with the other limitations of claim 1), Applicant respectfully submits that claim 1 is allowable.

2. The combination of Moradi and Xyrem Interview does not teach or suggest the data processor selectively blocking shipment of the prescription drug to the patient based on said identifying by the database query, as recited in claim 4.

Claim 4 states:

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

Claim 4 must be read in context with claim 1, from which claim 4 indirectly depends. Claim 1 describes the database query referenced in claim 3 in the final limitation:

> 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

Thus, the shipment blocking in claim 4 is in response to the reconciling inventory query of claim 1.

Paragraphs [0045]-[0046] of Moradi are cited as teaching or suggesting the limitation of claim 4. These paragraphs describe automated prescription filling and preventing abusive double filling of prescriptions. There is no disclosure related to inventory reconciliation in these paragraphs and there is no disclosure of selectively blocking shipments based on identifying information in the prescription fields and patient fields for reconciling inventory of the prescription drug, as required by claim 4. Applicant therefore respectfully submits that claim 4 is allowable

3. The combination of Moradi and Xyrem Interview does not teach or suggest the current inventory being cycle counted and reconciled with database quantities before shipments for a day or other time period are sent, as recited in claim 22.

Claim 22 states:

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

The Office Action again cites to paragraph [0101] as teaching or suggesting this claim limitation. As described above, paragraph [0101] describes seeing if there is sufficient quantity of medication to fulfill a particular order. If not, the order is sent to another pharmacy. This is significantly different from determining whether there is a mismatch between the aggregate amount of a drug in physical inventory with the aggregate amount of the drug in the computer database. Thus, paragraph [0101] does not describe reconciling inventory at all. Further, paragraph [0101] does not describe cycle counting, an inventory auditing procedure where a subset of physical inventory is counted on a specific day. Applicant therefore respectfully submits that claim 22 is allowable

4. Applicant has amended claim 2 as follows.

> 2. The system of claim 1, wherein the data processor is configured to process a second database query that identifies: [[whether]] 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.

Claim 2 recites that the narcoleptic patient being determined to be a cash payer is used as an indicator of potential misuse, abuse, or diversion. As noted at page 1, lines 28-31 of Applicant's specification, an unscrupulous physician may write multiple prescriptions for a patient who uses cash to pay for the drugs, where those drugs can then be resold to drug dealers for profit. Screening for cash payers is described at page 10, lines 10-18.

While the Office Action correctly notes that cash is a form of payment, none of the cited references teach or suggest flagging a patient for potential misuse, abuse, or diversion based on that patient being a cash payer and subsequently following up with the prescribing physician, as recited in claim 2. Applicant therefore respectfully submits that claim 2 is allowable

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 July 25, 2013

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

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

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:				
Claims in Excess of 20	1202	2	80	160
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**340**

Electronic Acknowledgement Receipt	
EFS ID:	16414078
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:	25-JUL-2013
Filing Date:	22-AUG-2012
Time Stamp:	13:36:07
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$340
RAM confirmation Number	11460
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		101031us9_resp_072513.pdf	168654 bd31eaf8fba39288bd04c8895c9a7e87024af7ba	yes	19

Multipart Description/PDF files in .zip description

Document Description	Start	End
Miscellaneous Incoming Letter	1	1
Transmittal Letter	2	3
Information Disclosure Statement (IDS) Form (SB08)	4	4
Amendment/Req. Reconsideration-After Non-Final Reject	5	5
Claims	6	12
Applicant Arguments/Remarks Made in an Amendment	13	19

Warnings:					
Information:					
2	Non Patent Literature	101031U10_AARN_05-31-13.pdf	116068 67b6be7585f00ef230d848550508a27cf550fd85	no	14
Warnings:					
Information:					
3	Non Patent Literature	13595676-EXIR-Examiner_Interview_Summary-20130530.pdf	540348 be4ade2e4a8eeb5576fa7ce59373300400c69831	no	3
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	32198 c7ef68c5bbc1bdd349e320c1eec4d7670391ed87	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	857268		

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

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		

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

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

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

Pursuant to 37 C.F.R. § 1.97(c)(2), Applicants hereby authorize the Commissioner to charge the fee of $180.00 as set forth in 37 C.F.R. § 1.17(p), to Deposit Account No. 19-0743. Please charge any additional fees or deficiencies, or credit any overpayment to Deposit Account No. 19-0743.

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 July 25, 2013 By /David D'Zurilla/

David D'Zurilla
Reg. No. 36,776

DDZ:jdgw

Electronic Acknowledgement Receipt	
EFS ID:	16414078
Application Number:	13592202
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Filer:	Gregory M. Stark/John Gustav-Wrathall
Filer Authorized By:	Gregory M. Stark
Attorney Docket Number:	101.031US9
Receipt Date:	25-JUL-2013
Filing Date:	22-AUG-2012
Time Stamp:	13:36:07
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$340
RAM confirmation Number	11460
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		101031us9_resp_072513.pdf	168654 bd31eaf8fba39288bd04c8895c9a7e87024af7ba	yes	19

Multipart Description/PDF files in .zip description

Document Description	Start	End
Miscellaneous Incoming Letter	1	1
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Information Disclosure Statement (IDS) Form (SB08)	4	4
Amendment/Req. Reconsideration-After Non-Final Reject	5	5
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Warnings:					
Information:					
2	Non Patent Literature	101031U10_AARN_05-31-13.pdf	116068 67b6be7585f00ef230d848550508a27cf550fd85	no	14
Warnings:					
Information:					
3	Non Patent Literature	13595676-EXIR-Examiner_Interview_Summary-20130530.pdf	540348 be4ade2e4a8eeb5576fa7ce59373300400c69831	no	3
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	32198 c7ef68c5bbc1bdd349e320c1eec4d7670391ed87	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	857268		

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

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New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Dayton T. Reardan Ph.D et al.

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

Docket No.:	101.031US9	Serial No.:	13/592,202
Filed:	August 22, 2012	Due Date:	September 5, 2013
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 Amendment and Response under 37 C.F.R. § 1.111 (15 pgs.)
X Authorization to charge Deposit Account 19-0743 in the amount of $160.00 to cover the fee for additional claims.
X Supplemental Information Disclosure Statement (2 pgs.), Form 1449 (1 pg.) Copies of Cited References (2).
X Authorization to charge Deposit Account 19-0743 in the amount of $180.00 to cover the fee for consideration of Information Disclosure Statement under 37 C.F.R. § 1.97(c).

The fee for additional claims has been calculated as follows:

CLAIMS AS AMENDED						
	Claims Remaining After Amendment		**Highest Number Previously Paid For**	**Present Extra**	**Rate**	**Fee**
TOTAL CLAIMS	**30**	**-**	**28**	**2**	**x 80.00 =**	**160.00**
INDEPENDENT CLAIMS	**3**	**-**	**3**	**0**	**x 420.00 =**	**0.00**
[] MULTIPLE DEPENDENT CLAIMS PRESENTED						**0.00**
TOTAL						**160.00**

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.

/David D'Zurilla/

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
Customer No.: 107632

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

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**

FOREIGN PATENT DOCUMENTS				
Examiner Initial *	**Foreign Document Number**	**Publication Date**	**Name of Patentee or Applicant of cited Document**	**T 1**

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 , Response filed 05-31-13 to Non Final Office Action mailed 03-21-13", 14 pgs	
	"Application Serial No. 13/595,676, Examiner Interview Summary mailed 05-30-13", 3 pgs	

EXAMINER **DATE CONSIDERED**

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

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	07/25/2013	(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))	* 30	Minus	** 26	= 4	X $80 =	320
	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	**320**

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
/Theresa Dawkins/

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 07/29/2013

TDAWKINS SALE #00000001 Mailroom Dt: 07/25/2013 190743 13592202
01 FC : 1202 320.00 DA

Electronic Acknowledgement Receipt

EFS ID:	16934976
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:	Eric B. Andersland/Valerie Murphy
Filer Authorized By:	Eric B. Andersland
Attorney Docket Number:	101.031US9
Receipt Date:	24-SEP-2013
Filing Date:	22-AUG-2012
Time Stamp:	11:06:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13592202_SIDS_9-24-13.pdf	274013 3d90a5d92dc23971afe91f666b793e5a1ebf1fd6	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Miscellaneous Incoming Letter	1	1
	Transmittal Letter	2	3
	Information Disclosure Statement (IDS) Form (SB08)	4	4

Warnings:					
Information:					
2	Non Patent Literature	0001_101031u10_noar_091713.pdf	977730 f7f88ec94245a20ee05c76679c31c166f42a67bd	no	6
Warnings:					
Information:					
3	Non Patent Literature	0002_jazz_v__amneal__civil_cover_sheet_9_12_13.pdf	159861 36c8b5be8084e3796663288417ef57bc93d151ff	no	1
Warnings:					
Information:					
4	Non Patent Literature	0003_jazz_v__amneal__complaint_9_12_13.pdf	10155272 94688d863514ac4d88337fab1dd9abf1389e62b6	no	76
Warnings:					
Information:					
5	Non Patent Literature	0004_jazz_v__amneal__7_1_statement_9_12_13.pdf	57839 9dc0c4f3848a6023a2c5276f03105ab32561c3fd	no	2
Warnings:					
Information:					
6	Non Patent Literature	0005_jazz_v__amneal__ecf_filing_firmation_9_12_13.pdf	70260 2766edd00df58f5cce5311467402cc91215a9dee	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	11694975		

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.

Modified form PTO/SB/08A(04-07) OMB 651-0031
US Patent & Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)	*Complete if Known*	
	Application Number	13/592,202
	Filing Date	August 22, 2012
	First Named Inventor	Dayton T. Reardan Ph.D
	Group Art Unit	3686
	Examiner Name	Lena Najarian
Sheet 1 of 1	Attorney Docket No: 101.031US9	

OTHER DOCUMENTS – NON PATENT LITERATURE DOCUMENTS		
Examiner Initial *	**Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.**	**T 1**
	"Application Serial No. 13/595,676, Notice of Allowance mailed 09-17-13", 8 pgs	
	"Civil Cover Sheet", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey), (9/12/13), 2 pgs	
	"Complaint for Patent Infringement with Exhibit A", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey), (9/12/2013), 76 pgs	
	"Fed. R. Civ. P. Rule 7.1 Disclosure Statement", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey), (9/12/13), 2 pgs	
	"Notice of Electronic Filing: Civil Inital Pleadings (Attorney/Credit Card) USE CASE 33-1)", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey [LIVE]), (9/12/13), 1 pg	

EXAMINER **DATE CONSIDERED**

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Dayton T. Reardan Ph.D et al.	Examiner:	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		

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R §1.97(e)(2)

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

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

The attached documents were discovered as a result of an office action in a related U.S. patent application. Enclosed for the Examiner's information is a copy of the cited document and the Office Action.

Pursuant to 37 C.F.R. § 1.97(c)(1) and 37 C.F.R. § 1.97(e)(2), Applicants state that no item of information contained in the Supplemental Information Disclosure Statement was cited in any communication from a foreign patent office in a counterpart foreign application and that no item of information contained in the Supplemental Information Disclosure Statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

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 September 18, 2013 By / /

David D'Zurilla
Reg. No. 36,776

DDZ:vam

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Dayton T. Reardan Ph.D et al.

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

Docket No.:	101.031US9	Serial No.:	13/592,202
Filed:	August 22, 2012	Due Date:	N/A
Examiner:	Lena Najarian	Group Art Unit:	3686
Customer No.:	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 (5).

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

Civil Initial Pleadings (Attorney/Credit Card) USE CASE 33-1

2:33-av-00001 PLAINTIFF v. DEFENDANT

U.S. District Court

District of New Jersey [LIVE]

Notice of Electronic Filing

The following transaction was entered by LIZZA, CHARLES on 9/12/2013 at 5:32 PM EDT and filed on 9/12/2013

Case Name: PLAINTIFF v. DEFENDANT
Case Number: 2:33-av-00001
Filer:
Document Number: 19160

Docket Text:
COMPLAINT - Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC (Filing and Admin fee $ 400 receipt number 0312-5226999.). (Attachments: # (1) Corporate Disclosure (Re Complaint only), # (2) Civil Cover Sheet) (LIZZA, CHARLES)

2:33-av-00001 Notice has been electronically mailed to:

2:33-av-00001 Notice will not be electronically mailed to::

PLAINTIFF

The following document(s) are associated with this transaction:

Document description: Main Document
Original filename:n/a
Electronic document Stamp:
[STAMP dcecfStamp_ID=1046708974 [Date=9/12/2013] [FileNumber=6998431-0] [34c2a6d996fcc751df079585189199e6b3a108eb8279eb83a2a2b8dae8ae99e0379 658d80d5201e8d389a785b025c1300f65ba90c1715bc7b8160b09a2f76298]]
Document description: Corporate Disclosure (Re Complaint only)
Original filename:n/a
Electronic document Stamp:
[STAMP dcecfStamp_ID=1046708974 [Date=9/12/2013] [FileNumber=6998431-1] [7dfc58afdd0299ad0a26c2b06961f019e4994955c83ca44ec3805ae25fde6f4d5f4 0070fe9eb1978257ed4a25fbbdcc78aa7ce2bccab50cb3cfb534eb6a6eb95]]
Document description: Civil Cover Sheet
Original filename:n/a
Electronic document Stamp:
[STAMP dcecfStamp_ID=1046708974 [Date=9/12/2013] [FileNumber=6998431-2] [af72f6339159e49eb625c44ef311a543dadc908993b0ae6bb7ce3043c6a8bfdd640 5e8e14468e396e002436ddd83fd720a6e5484435a82ef25de812962199930]]

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clizza@saul.com

Attorneys for Plaintiff
Jazz Pharmaceuticals, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

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

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

Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. §100, *et seq.*, arising from Amneal's filing of an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market a generic version of Jazz Pharmaceuticals' XYREM® drug product prior to the expiration of United States Patent Nos. 8,457,988 (the "'988 patent") and 8,461,203 (the "'203 patent") (collectively, "the patents-in-suit") owned by Jazz Pharmaceuticals.

The Parties

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

3. On information and belief, defendant Amneal is a corporation organized under the laws of the State of Delaware, having a principal place of business 440 U.S. Highway 22 East, Suite 104, Bridgewater, New Jersey 08807.

Jurisdiction and Venue

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

5. This Court has personal jurisdiction over Amneal by virtue of, *inter alia,* its systematic and continuous contacts with the State of New Jersey. On information and belief, Amneal has purposefully availed itself of this forum by, among other things, operating its headquarters in the State of New Jersey, making, shipping, using, offering to sell or selling, or causing others to use, offer to sell, or sell, pharmaceutical products in the State of New Jersey and deriving revenue from such activities. Amneal currently is litigating, and has litigated in the past, patent cases in this District without contesting personal jurisdiction. In at least some of those actions, Amneal has asserted counterclaims. Further, on information and belief, Amneal has customers in the State of New Jersey.

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

The Patents-In-Suit

7. On June 4, 2013, the United States Patent and Trademark Office ("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 A.

8. 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 B.

The XYREM® Drug Product

9. 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*, methods of making 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.

10. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the '988 patent is 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

11. Pursuant to Section 505 of the FFDCA, Amneal filed ANDA No. 203631 ("Amneal's ANDA") seeking approval to engage in the commercial use, manufacture, sale, offer for sale or importation of 500 mg/mL sodium oxybate oral solution ("Amneal's Proposed Product"), before the patents-in-suit expire.

12. In connection with the filing of its ANDA as described in the preceding paragraph, Amneal has provided written certifications to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Amneal's Paragraph IV Certifications"), alleging that the claims of the '988 patent and other Orange-Book-listed patents owned by Jazz Pharmaceuticals are invalid, unenforceable, and/or will not be infringed by the activities described in Amneal's ANDA.

13. No earlier than August 2, 2013, Jazz Pharmaceuticals received written notice of Amneal's Paragraph IV Certification ("Amneal's Notice Letter") pursuant to 21 U.S.C. § 355(j)(2)(B) with respect to the '988 patent. Amneal's Notice Letter alleged that the claims of the '988 patent are invalid, unenforceable, and/or will not be infringed by the activities described in Amneal's ANDA. Amneal's Notice Letter also informed Jazz Pharmaceuticals that Amneal seeks approval to market Amneal's Proposed Product before the patents-in-suit expire.

Count I: Infringement of the '988 Patent

14. Plaintiff repeats and realleges the allegations of paragraphs 1-13 as though fully set forth herein.

15. Amneal's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '988 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

16. There is a justiciable controversy between the parties hereto as to the infringement of the '988 patent.

17. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe the '988 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States.

18. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of the '988 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '988 patent and knowledge that its acts are encouraging infringement.

19. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe the '988 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes the '988 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

20. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Amneal's infringement of the '988 patent is not enjoined.

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

22. 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 '203 Patent

23. Plaintiff repeats and realleges the allegations of paragraphs 1-22 as though fully set forth herein.

24. Amneal, through its submission of its Paragraph IV Certifications 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. Amneal's actions with respect to its ANDA show that there is a

substantial controversy between the parties of sufficient immediacy and reality to warrant the issuance of a declaratory judgment.

25. Amneal's submission of its ANDA to obtain approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '203 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

26. There is a justiciable controversy between the parties hereto as to the infringement of the '203 patent.

27. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe the '203 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States.

28. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of the '203 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '203 patent and knowledge that its acts are encouraging infringement.

29. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe the '203 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes the '203 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

30. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Amneal's infringement of the '203 patent is not enjoined.

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

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

PRAYER FOR RELIEF

WHEREFORE, Plaintiff Jazz Pharmaceuticals respectfully requests the following relief:

(A) A Judgment be entered that Amneal has infringed the patents-in-suit by submitting ANDA No. 203631;

(B) A Judgment be entered that Amneal has infringed, and that Amneal's making, using, selling, offering to sell, or importing Amneal's Proposed Product will infringe one or more claims of the patents-in-suit;

(C) An Order that the effective date of FDA approval of ANDA No. 203631 be a date which is not earlier than the later of the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

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

(E) A permanent injunction be issued, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Amneal, its officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any methods as claimed in the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit,

until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(F) A Declaration that the commercial manufacture, use, importation into the United States, sale, or offer for sale of Amneal's Proposed Product will directly infringe, induce and/or contribute to infringement of the patents-in-suit;

(G) To the extent that Amneal has committed any acts with respect to the compositions and methods claimed in the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), that Plaintiff Jazz Pharmaceuticals be awarded damages for such acts;

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

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

(J) Costs and expenses in this action; and

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

Dated: September 12, 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)(SCM), *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, Civil Action No. 11-660 (ES)(SCM), *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, Civil Action No. 11-2523 (ES)(SCM), *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, Civil Action No. 12-6761 (ES)(SCM), *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, Civil Action No. 12-7459 (ES)(SCM), and *Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC*, Civil Action No. 13-391 (ES)(SCM) are related to the matter in controversy because the matter in controversy involves the same plaintiff, the same patents, and defendants seeking FDA approval to market a generic version of the same pharmaceutical product.

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: September 12, 2013

By: s/ Charles M. Lizza
Charles M. Lizza
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EXHIBIT A

US008457988B1

(12) **United States Patent**
Reardan et al.

(10) **Patent No.: US 8,457,988 B1**
(45) **Date of Patent: *Jun. 4, 2013**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

(75) Inventors: **Dayton T. Reardan**, Shorewood, MN (US); **Patti A. Engel**, Eagan, MN (US); **Bob Gagne**, St. Paul, MN (US)

(73) Assignee: **Jazz Pharmaceuticals, Inc.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/595,757**

(22) Filed: **Aug. 27, 2012**

Related U.S. Application Data

(60) Division of application No. 13/013,680, filed on Jan. 25, 2011, now abandoned, which is a continuation of application No. 12/704,097, filed on Feb. 11, 2010, now Pat. No. 7,895,059, which is a continuation of application No. 10/322,348, filed on Dec. 17, 2002, now Pat. No. 7,668,730.

(51) **Int. Cl.**
G06Q 10/00 (2012.01)

(52) **U.S. Cl.**
USPC **705/2**; 705/3; 600/300

(58) **Field of Classification Search**
USPC 705/2, 3; 600/300
See application file for complete search history.

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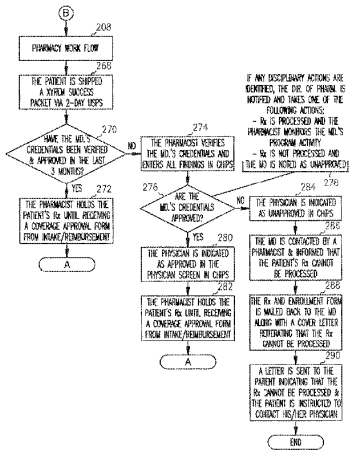
Primary Examiner — Lena Najarian
(74) *Attorney, Agent, or Firm* — Schwegman Lundberg & Woessner, P.A.

(57) **ABSTRACT**

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

15 Claims, 16 Drawing Sheets



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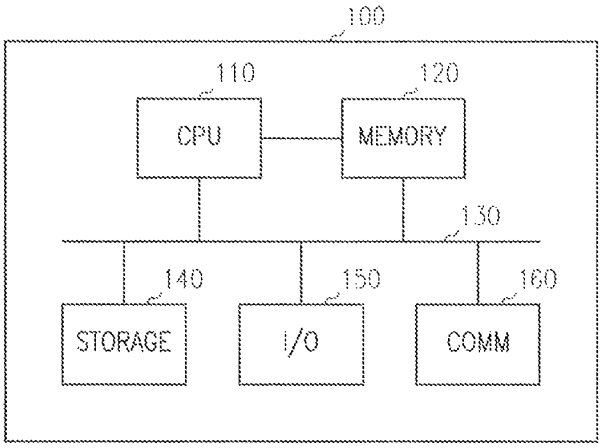

FIG. 1

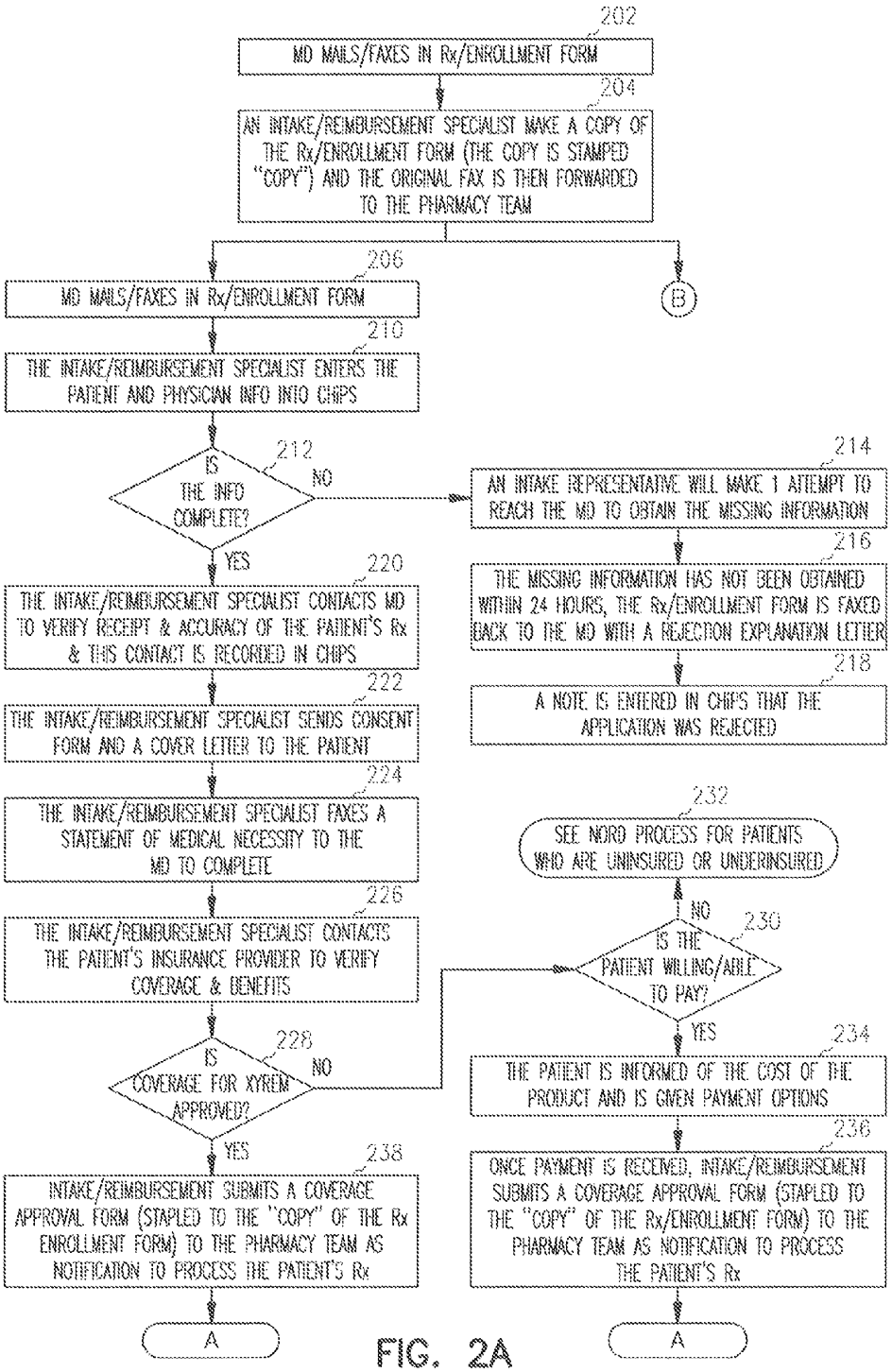
202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE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

FIG. 2A

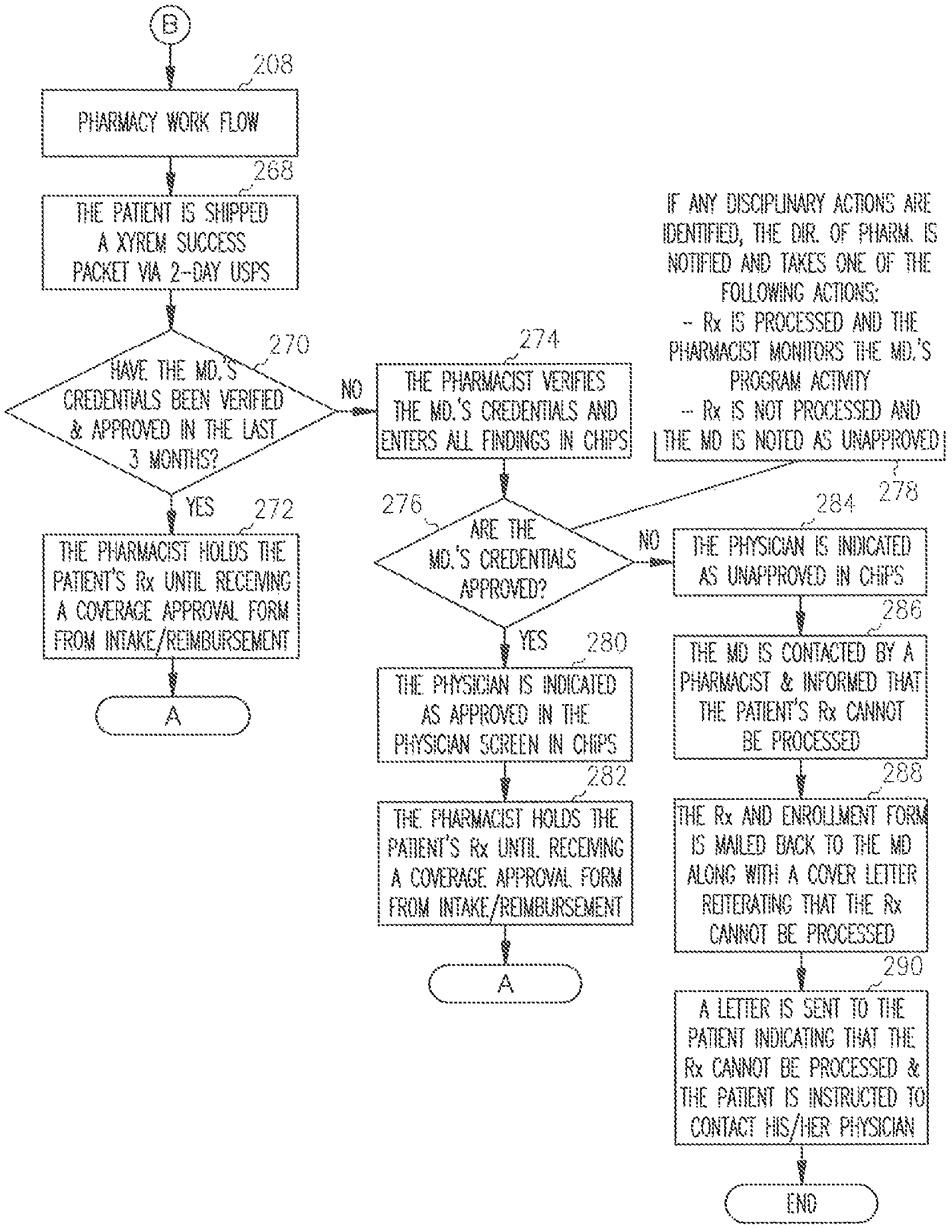
B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST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

FIG. 2B

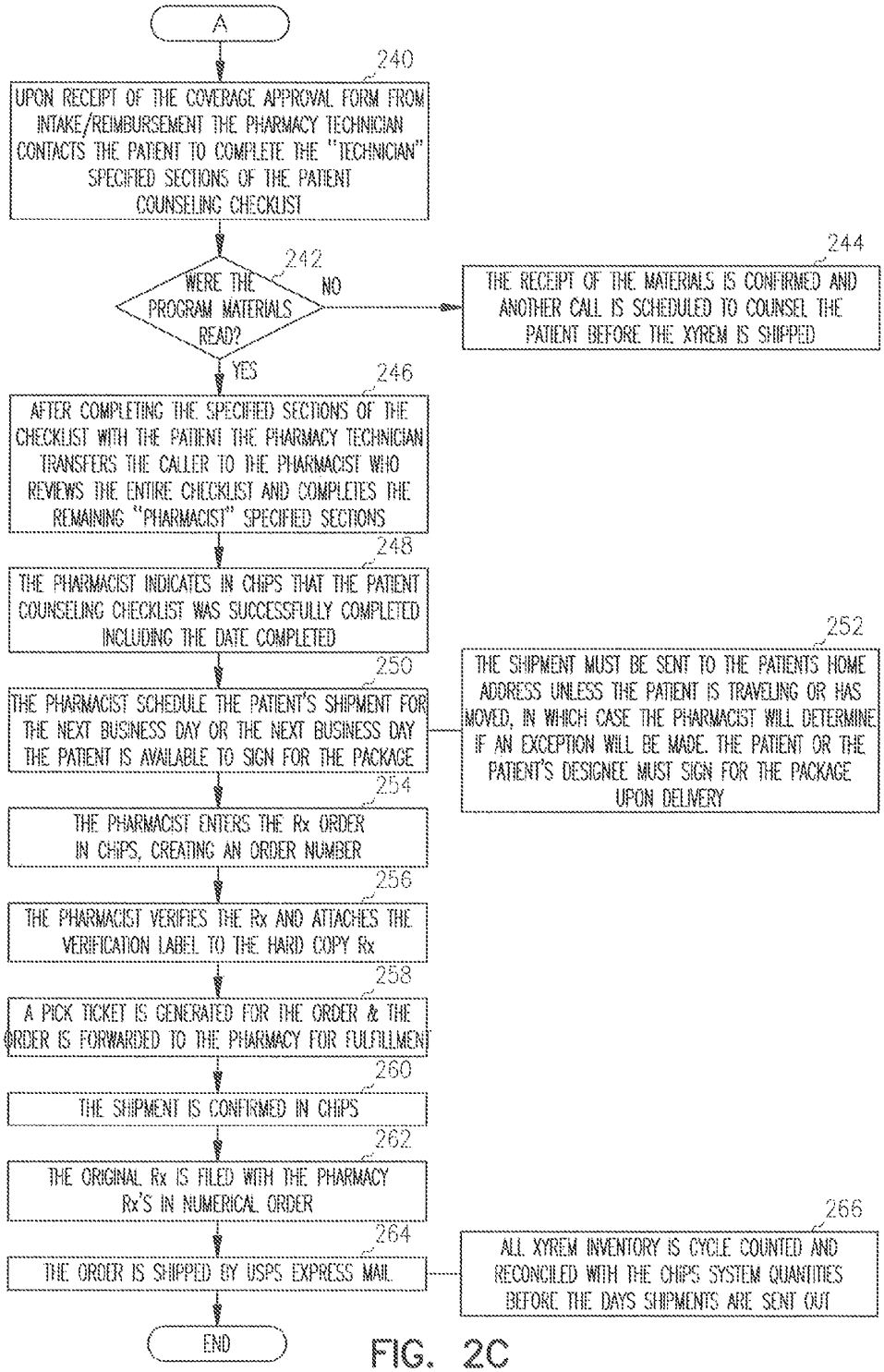
A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER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

FIG. 2C

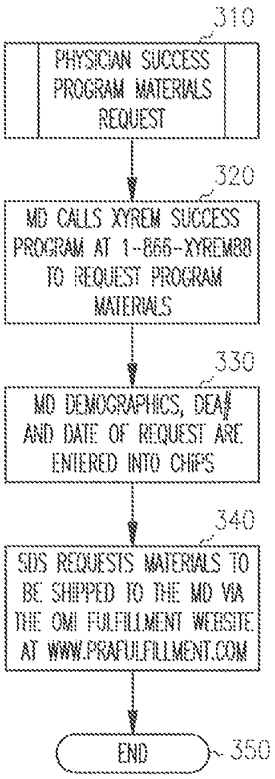
310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM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

FIG. 3

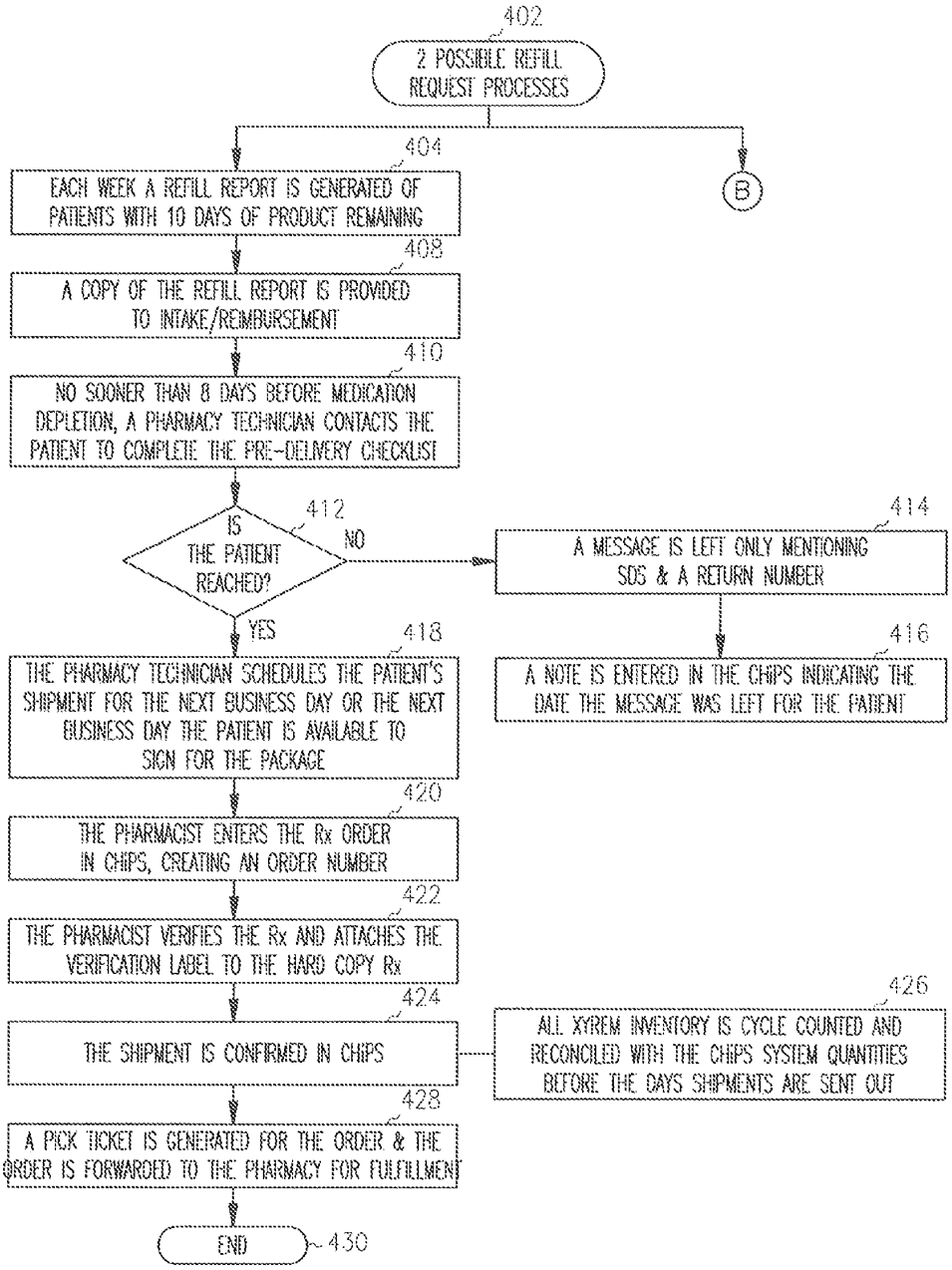
402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE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

FIG. 4A

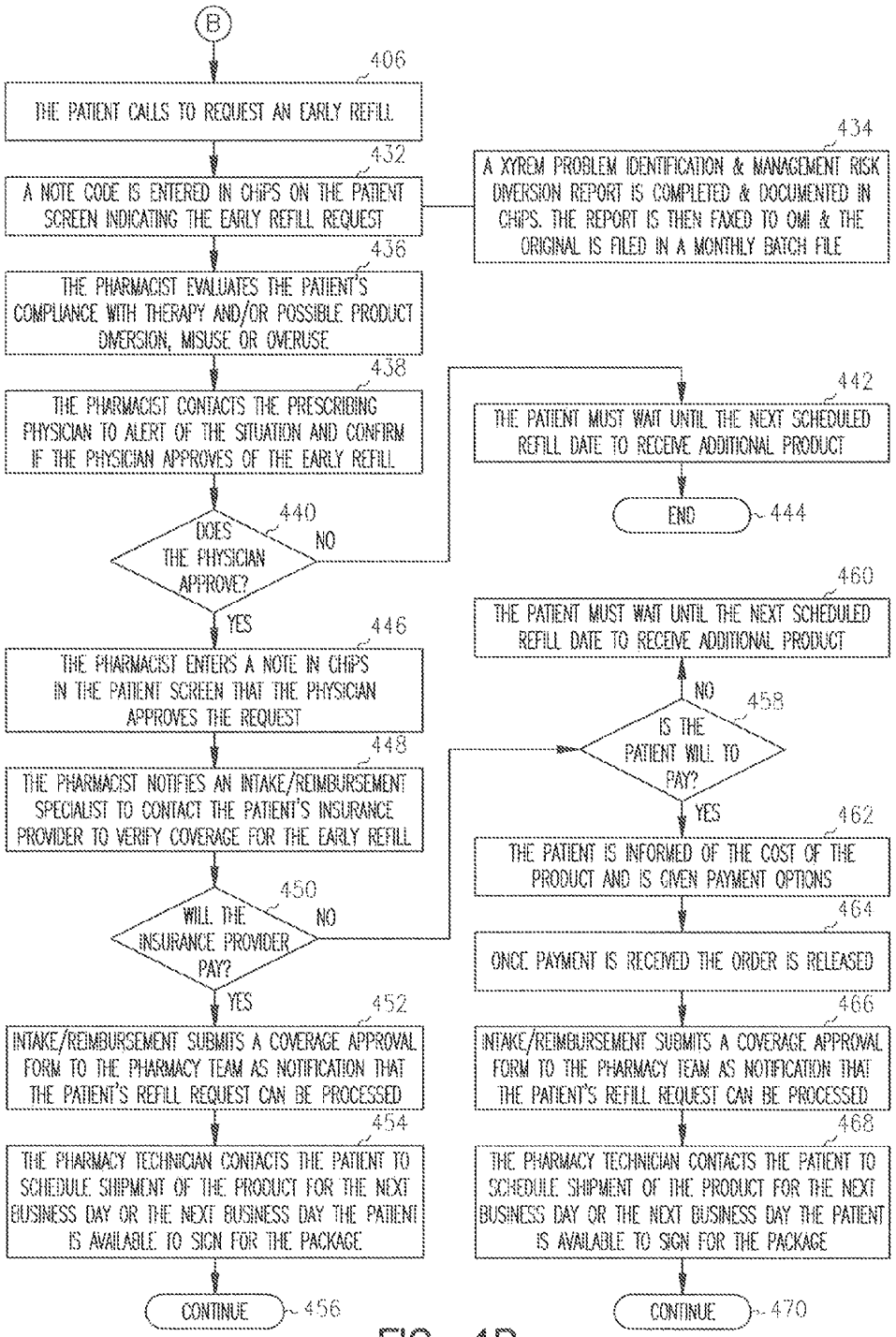
B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYROM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS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

FIG. 4B

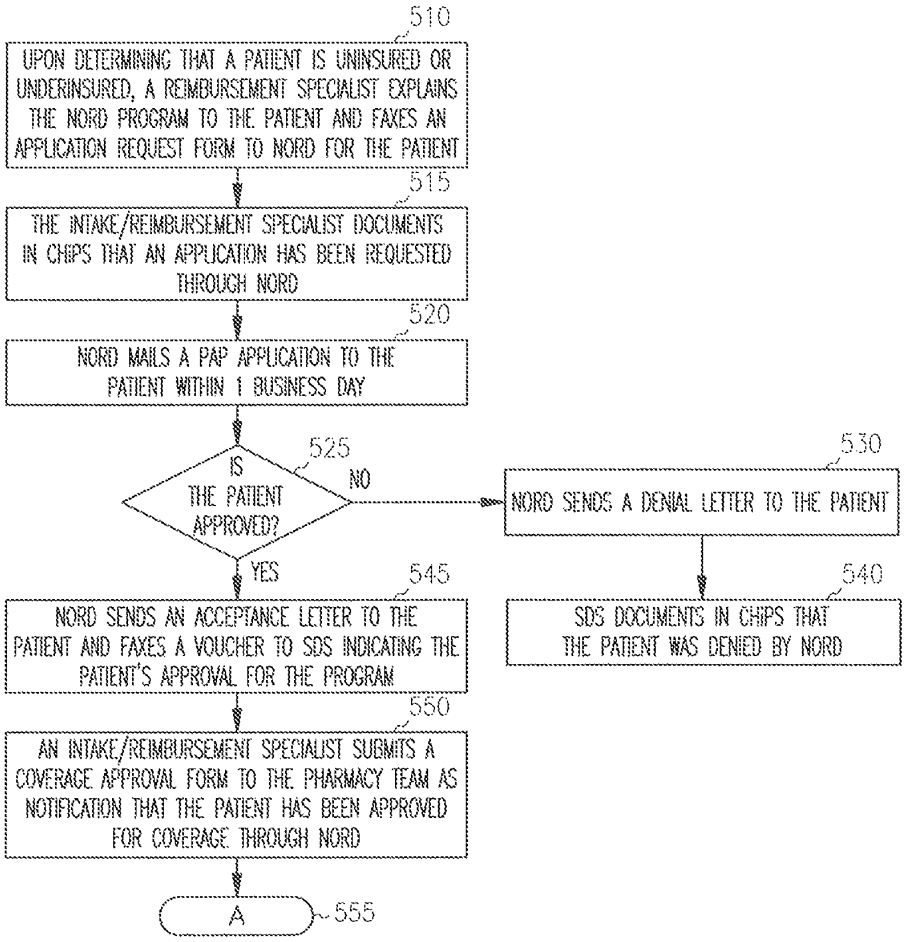
510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHIPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH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

FIG. 5

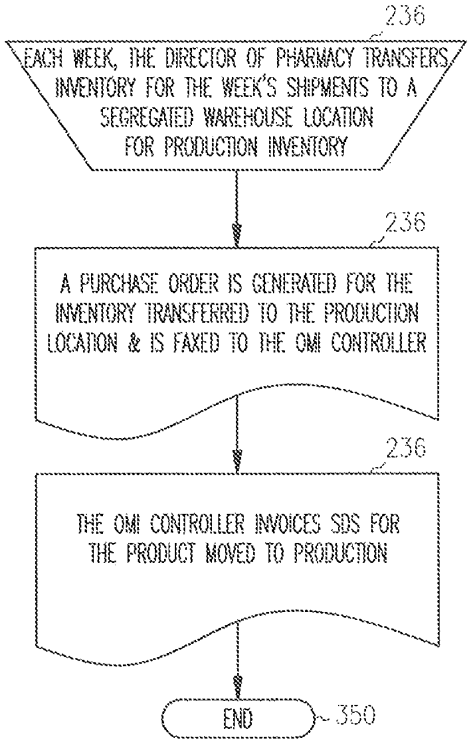

FIG. 6

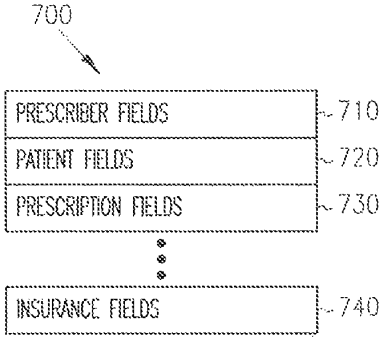

FIG. 7

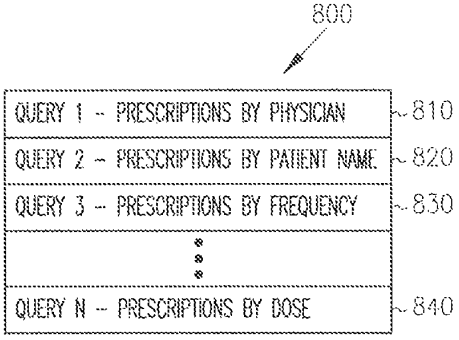

FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

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

PRESCRIPTION FORM

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

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

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

PATIENT INFORMATION

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

PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

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

FIG. 9

PATIENT ASSISTANCE APPLICATION REQUEST FORM

DATE:

TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS

FAX #: 203-798-2291

PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:

PATIENT NAME .....

ADDRESS .....

.....

.....

TELEPHONE: ( ) .....

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

_____ BOTTLES (THREE MONTHS SUPPLY)

BACKGROUND INFORMATION:

.....

.....

.....

.....

.....

.....

FIG. 10

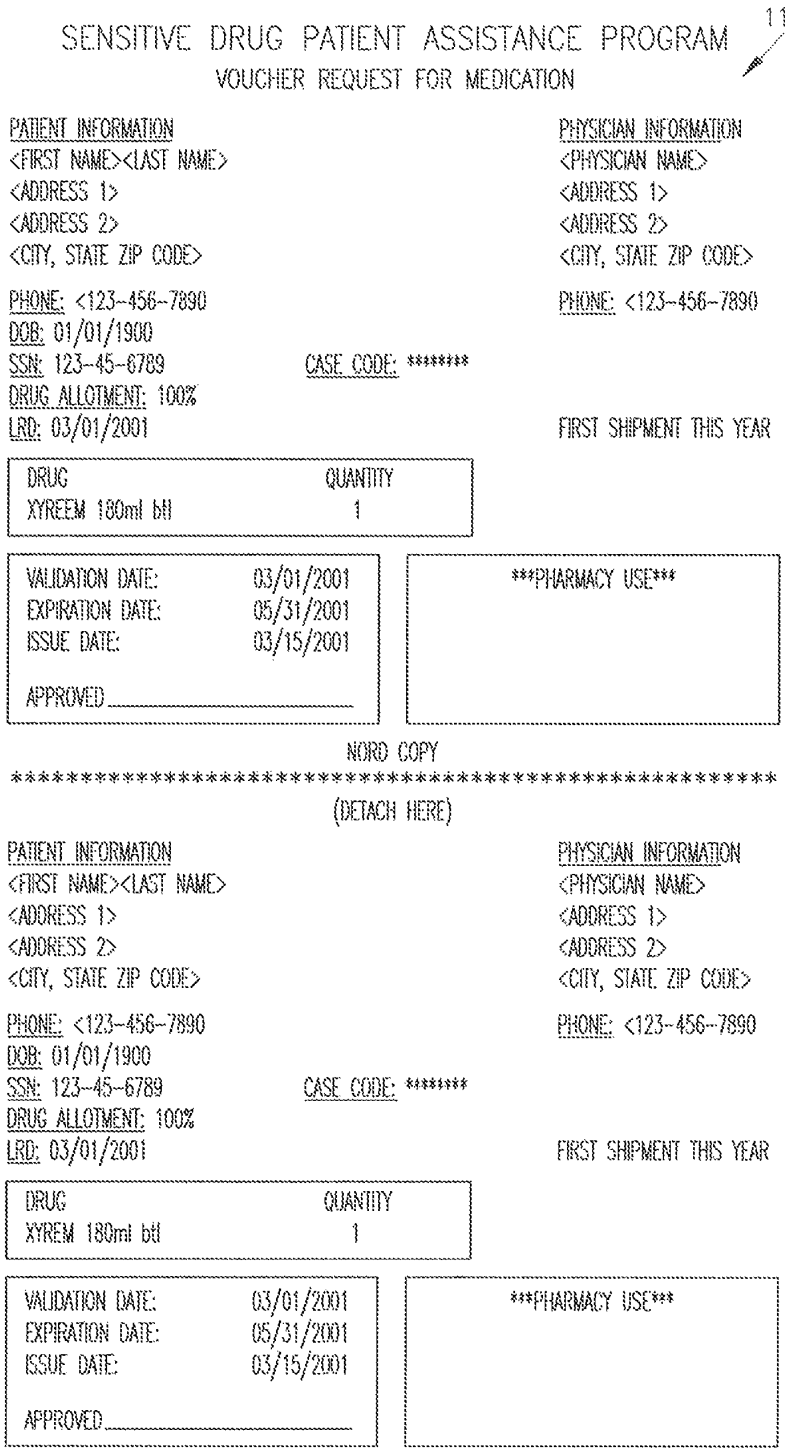
SENSITIVE DRUG PATIENT ASSISTANCE PROGRAM
1100
VOUCHER REQUEST FOR MEDICATION
PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>
PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
CASE CODE: ********
DRUG ALLOTMENT: 100%
LRD: 03/01/2001
PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>
PHONE: <123-456-7890
FIRST SHIPMENT THIS YEAR
DRUG
QUANTITY
XYREEM 180ml btl
1
VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001
APPROVED
PHARMACY USE
NORD COPY
****
(DETACH HERE)
PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>
PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
CASE CODE: ********
DRUG ALLOTMENT: 100%
LRD: 03/01/2001
PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>
PHONE: <123-456-7890
FIRST SHIPMENT THIS YEAR
DRUG
QUANTITY
XYREM 180ml btl
1
VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001
APPROVED
PHARMACY USE

FIG. 11

1200

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE
OF MEDICAL NEED

PATIENT INFORMATION

DATE: .....

NAME: .....
LAST FIRST M

DATE OF BIRTH: .....

DRUG BEING PRESCRIBED: XYREM

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

ICD-9: .....

PHYSICIAN INFORMATION

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

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

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

FIG. 12

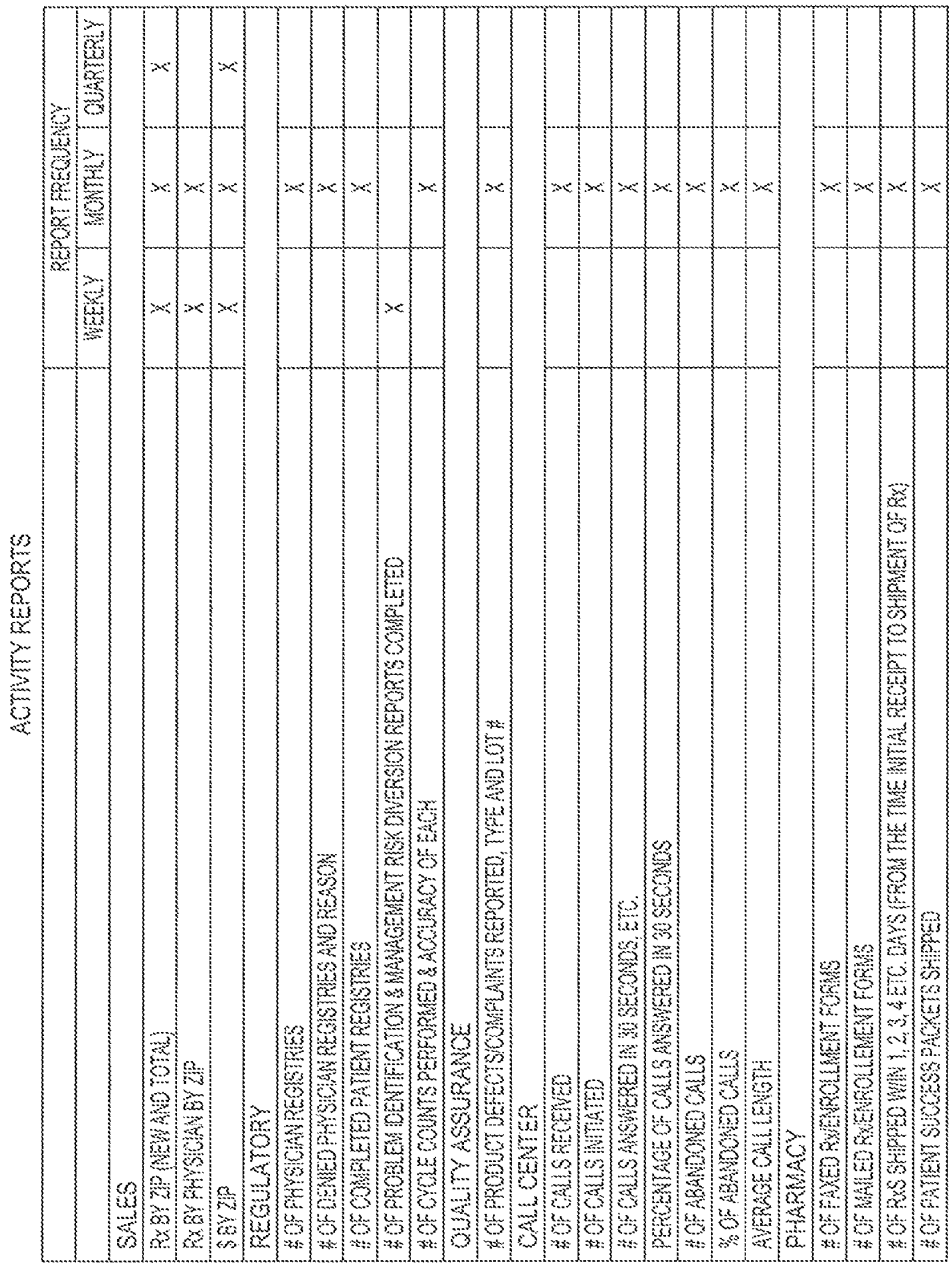
ACTIVITY REPORTS
REPORT FREQUENCY
WEEKLY
MONTHLY
QUARTERLY
SALES
Rx BY ZIP (NEW AND TOTAL)
Rx BY PHYSICIAN BY ZIP
$ BY ZIP
REGULATORY
OF PHYSICIAN REGISTRIES
OF DENIED PHYSICIAN REGISTRIES AND REASON
OF COMPLETED PATIENT REGISTRIES
OF PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORTS COMPLETED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

FIG. 13A

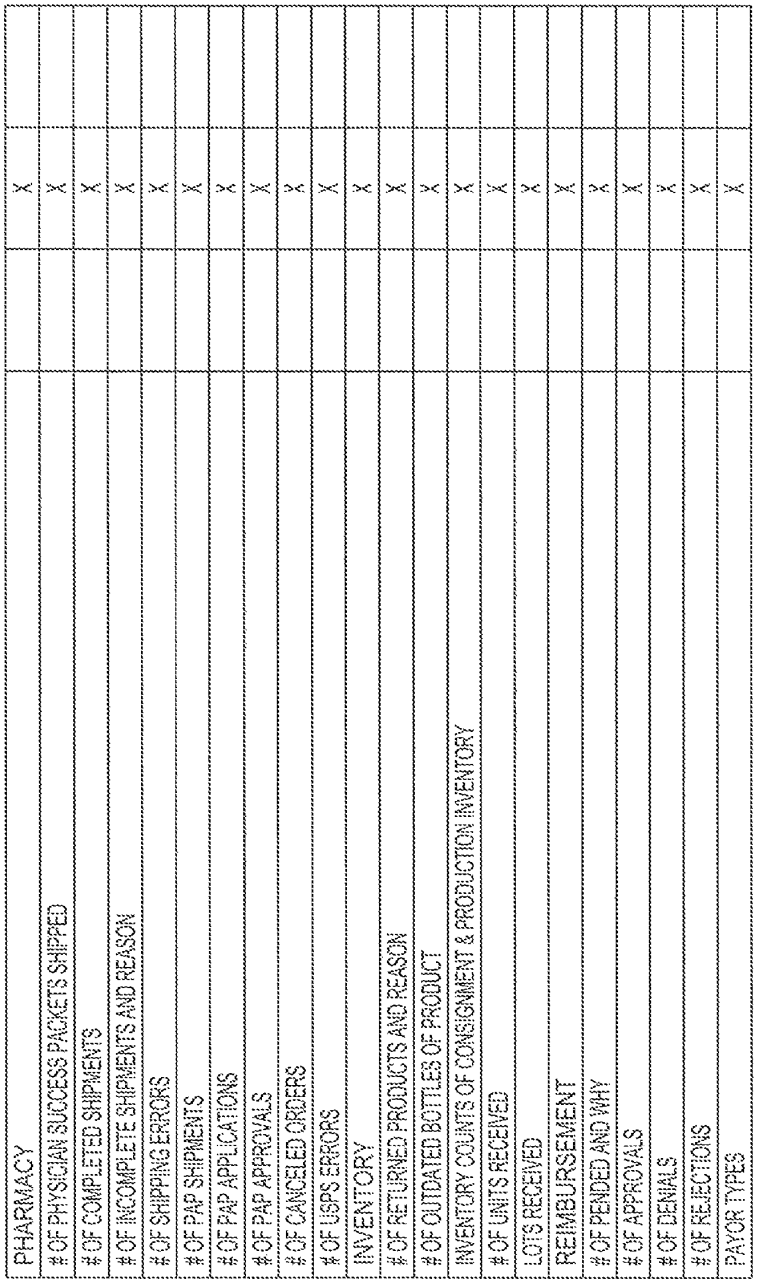
ACTIVITY REPORTS
PHARMACY
OF PHYSICIAN SUCCESS PACKETS SHIPPED
OF COMPLETED SHIPMENTS
OF INCOMPLETE SHIPMENTS AND REASON
OF SHIPPING ERRORS
OF PAP SHIPMENTS
OF PAP APPLICATIONS
OF PAP APPROVALS
OF CANCELED ORDERS
OF USPS ERRORS
INVENTORY
OF RETURNED PRODUCTS AND REASON
OF OUTDATED BOTTLES OF PRODUCT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

FIG. 13B

ACTIVITY REPORTS

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

FIG. 13C

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

RELATED APPLICATION

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

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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

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

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

SUMMARY OF THE INVENTION

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

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

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

Prescription refills are permitted in the number specified in the original prescription. In addition, if a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned. A lost, stolen, destroyed or spilled prescription/supply is documented and replaced to the extent necessary to honor the prescription, and will also cause a review or full investigation.

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

FIG. **7** is a block diagram of database fields.

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

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

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

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

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

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

DETAILED DESCRIPTION OF THE INVENTION

In the following description, reference is made to the accompanying drawings that form a part hereof, and in which is shown by way of illustration specific embodiments in

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

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

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

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

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

FIG. **1** is a simplified block diagram of a computer system **100**, such as a personal computer for implementing at least a portion of the methods described herein. A central processing unit (CPU) **110** executes computer programs stored on a memory **120**. Memory **120** in one embodiment comprises one or more levels of cache as desired to speed execution of the program and access to data on which the programs operate. The CPU is directly coupled to memory **120** in one embodiment. Both CPU **110** and memory **120** are coupled to a bus **130**. A storage **140**, I/O **150** and communications **160** are also coupled to the bus **130**. Storage **140** is usually a long term storage device, such as a disk drive, tape drive, DVD, CD or other type of storage device. In one embodiment, storage **140** is used to house a database for use with the present invention. I/O **150** comprises keyboards, sound devices, displays and other mechanisms by which a user interacts with the computer system **100**. Communications **160** comprises a network, phone connection, local area network, wide area network or other mechanism for communicating with external devices. Such external devices comprise servers, other peer computers and other devices. In one embodiment, such external device comprises a database server that is used in place of the database on storage **140**. Other computer system architectures capable of executing software and interacting with a database and users may also be used. Appropriate security measures such as encryption are used to ensure confidentiality. Further, data integrity and backup measures are also used to prevent data loss.

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

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

There are two workflows involved at the pharmacy team, intake reimbursement **206** and pharmacy workflow **208**, which may proceed in parallel or serially. The intake work flow **206** starts with an intake reimbursement specialist entering the patient and physician information into an application/database referred to as CHIPS, which is used to maintain a record of a client home infusion program (CHIP) for Xyrem®. A check is made to ensure the information is complete at **212**. If not, at **214**, an intake representative attempts to reach the MD or prescriber to obtain the missing information. If the missing information has not been obtained within a predetermined period of time, such as 24 hours at **216**, the Rx/Enrollment form is sent back to the MD with a rejection explanation. A note is entered in CHIPS that the application was rejected.

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

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

at **228**, the intake reimbursement specialist also submits the coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. Processing of the prescription is described below.

Upon receipt and initial processing of the prescription enrollment form and sending an original to the pharmacy work flow block **208**, the patient is shipped a Xyrem® success packet via mail. In one embodiment, the Xyrem® success packet contains educational material for a patient that advises of the proper use, care and handling of the drug and consequences of diversion at **268**. The medical doctor's credentials are checked to determine if the physician has a current DEA license to prescribe controlled substances and if he or she has had any actions related to misuse/misprescribing of controlled drugs against him or her, within a predetermined time, such as three months at **270**. If they have, a pharmacist holds the prescription until receiving a coverage approval form from the intake reimbursement specialist at **272**.

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

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

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

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

At **250**, the pharmacist schedules the patient's shipment for the next business day or the next business day that the patient or designee is able to sign for the package. Further, as indicated at **252**, the shipment must be sent to the patient's home address unless the patient is traveling or has moved. In that event, the pharmacist may determine that an exception may be made. The patient or the patient's designee who is at least 18 years old, must sign for the package upon delivery.

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

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

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

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

In the first path, a copy of the report is provided to an intake reimbursement specialist at **408**. No sooner than 8 days before the medication depletion, a pharmacy technician contacts the patient at **410** to complete the pre-delivery checklist. At **412**, if the patient is not reached, a message is left mentioning the depletion, and a return number at **414**. A note is also entered into the database indicating the date the message was left at **416**.

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

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

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

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

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

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

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

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

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

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

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

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

FIG. **11** is a copy of one example application **1100** for financial assistance as requested by form **1000**. The form requires both patient and physician information. Social security number information is also requested. The form provides information for approving the financial assistance and for tracking assistance provided.

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

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

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

The invention claimed is:

1. A 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.

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 hydroxy 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, 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, 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.

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.

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.

* * * * *

EXHIBIT B

US008461203B2

(12) **United States Patent**
Cook et al.

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(45) **Date of Patent: *Jun. 11, 2013**

(54) **MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(60) Continuation of application No. 12/913,644, filed on Oct. 27, 2010, which is a continuation of application No. 11/777,877, filed on Jul. 13, 2007, now Pat. No. 7,851,506, which is a division of application No. 10/841,709, filed on May 7, 2004, now Pat. No. 7,262,219, which is a division of application No. 10/194,021, filed on Jul. 11, 2002, now Pat. No. 6,780,889, which is a division of application No. 09/470,570, filed on Dec. 22, 1999, now Pat. No. 6,472,431.

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(58) **Field of Classification Search**
USPC 514/557, 473, 529, 553
See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are formulations of gamma-hydroxybutyrate in an aqueous medium that are resistant to microbial growth. Also disclosed are formulations of gamma-hydroxybutyrate that are also resistant to the conversion into GBL. Disclosed are methods to treat sleep disorders, including narcolepsy, with these stable formulations of GHB. The present invention also provides methods to treat alcohol and opiate withdrawal, reduced levels of growth hormone, increased intracranial pressure, and physical pain in a patient.

16 Claims, 2 Drawing Sheets

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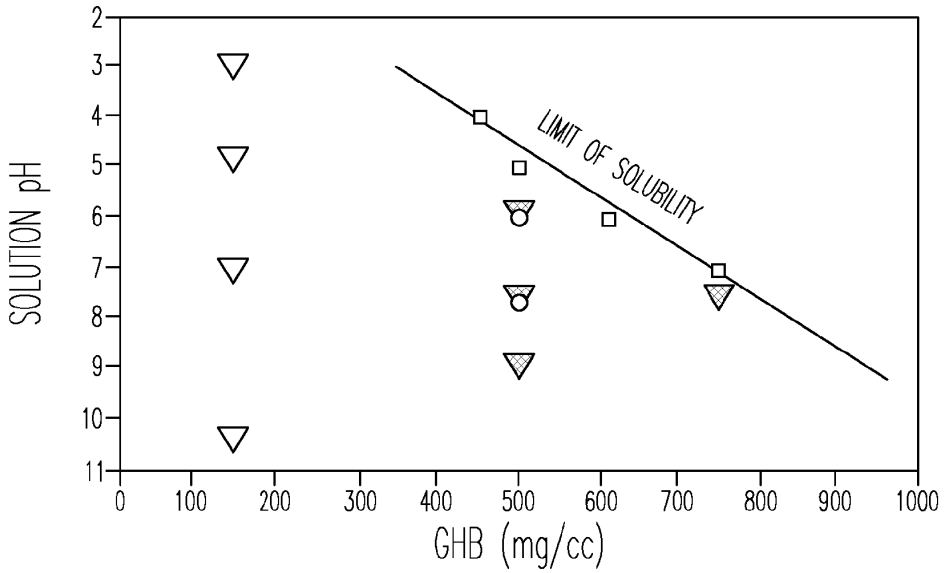

□ DATA POINTS INDICATING LIMIT OF SOLUBILITY OF GHB AS A FUNCTION OF CONCENTRATION AND pH, SEE TABLE 1.

▽ SOLUTIONS SUSCEPTIBLE TO MICROBIAL GROWTH, DESIGNATED "FAIL". (ALL SOLUTIONS DEMONSTRATED ACTIVITY AGAINST PSEUDOMONAS AERUGINOSA. SOME REDUCTION OF ASPERGILLUS NIGER MOLD OCCURRED IN 7 DAYS OF CONTACT TIME.)

▽ SOLUTIONS RESISTANT TO MICROBIAL GROWTH, DESIGNATED "PASS". RATE OF REDUTION OF MICROORGANISM COUNTS WAS SLIGHTLY HIGHER AT pH 7.5 AND 6.0 THAN pH 9.0. THE RATE OF REDUCTION OF FORMULATIONS AT 750mg/cc GHB WERE SLIGHTLY LOWER THAN FORMULATIONS AT 500 mg/cc GHB.)

○ SOLUTIONS RESISTANT TO MICROBIAL GROWTH, DESIGNATED "PASS". RESULTS WERE SIMILAR FOR MALIC ACID AND HCl. TASTE VARIATIONS HAS IMPLICATIONS FOR DEVELOPMENT OF FLAVOR SYSTEMS.

▽ ▽ INDICATES pH ADJUSTMENT WITH HCl.

○ INDICATES pH ADJUSTMENT WITH MALIC ACID.

NOTE: SOLUTIONS WITH pH AT 9.0 ARE NOT PALATABLE OR SAFE FOR ORAL CONSUMPTION.

Fig. 1

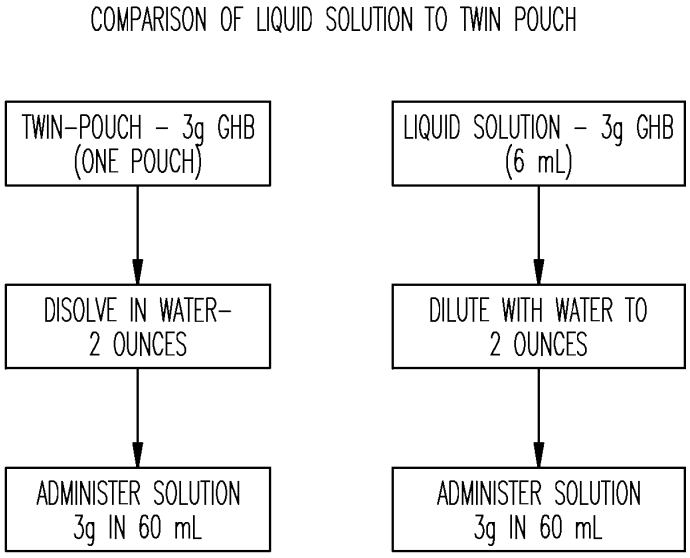
COMPARISON OF LIQUID SOLUTION TO TWIN POUCH
TWIN-POUCH – 3g GHB (ONE POUCH)
DISOLVE IN WATER– 2 OUNCES
ADMINISTER SOLUTION 3g IN 60 mL
LIQUID SOLUTION – 3g GHB (6 mL)
DILUTE WITH WATER TO 2 OUNCES
ADMINISTER SOLUTION 3g IN 60 mL

Fig.2

MICROBIOLOGICALLY SOUND AND STABLE SOLUTIONS OF GAMMA-HYDROXYBUTYRATE SALT FOR THE TREATMENT OF NARCOLEPSY

RELATED APPLICATIONS

This patent application is a continuation of U.S. application Ser. No. 12/913,644, filed on Oct. 27, 2010, which is a continuation of U.S. application Ser. No. 11/777,877 filed on Jul. 13, 2007 and issued on Dec. 14, 2010 as U.S. Pat. No. 7,851,506, which is a divisional of U.S. application Ser. No. 10/841,709, filed on May 7, 2004 and issued on Aug. 28, 2007 as U.S. Pat. No. 7,262,219, which is a divisional of U.S. application Ser. No. 10/194,021, filed Jul. 11, 2002 and issued on Aug. 24, 2004 as U.S. Pat. No. 6,780,889, which is a divisional of U.S. application Ser. No. 09/470,570, filed Dec. 22, 1999 and issued on Oct. 29, 2002 as U.S. Pat. No. 6,472,431, which claims priority from U.S. Provisional Patent Application Ser. No. 60/113,745, filed Dec. 23, 1998. These applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention relates generally to the fields of pharmaceutical compositions to be used in treatments, such as. sleeping disorders, such as, e.g., narcolepsy (particularly cataplexy), drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or for an increased level of intracranial pressure or the like. The present 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, e.g.

II. Description of Related Art

GHB is an endogenous compound with hypnotic properties that is found in many human body tissues. GHB is present, for example, in the mammalian brain and other tissues. In brain the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter (Snead and Morley, 1981). The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB is converted to succinate and then metabolized via the Krebs cycle. Clinical trials have shown that GHB increases delta sleep and improves the continuity of sleep (Ladinsky et al., 1983; Anden and Stock, 1973; Stock et al., 1973; Laborit, 1973; Lapierre et al., 1988; Lapierre et al., 1990; Yamda et al., 1967; Grove-White and Kelman, 1971; Scharf, 1985).

GHB has typically been administered in clinical trials as an oral solution (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993). GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e. daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency (Mamelak et al, 1973; Yamada et al., 1967; Bedard et al., 1989), reduces sleep apnea (Series et al, 1992; Scrima et al., 1987), and improves general anesthesia (Hasenbos and Gielen, 1985).

GHB has several clinical applications other than narcolepsy and sleep disorders. GHB has been reported to reduce alcohol craving, the number of daily drinks consumed, and the symptoms of alcohol withdrawal in patients (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992). GHB has been used to decrease the symptoms of opiate withdrawal, including both heroin and methadone withdrawal (Gallimberti et al., 1994; Gallimberti et al., 1993). It has analgesic effects that make it suitable as a pain reliever (U.S. Pat. No. 4,393,236). Intravenous administration of GHB has been reported to reduce intracranial pressure in patients (Strong, A. 1984). Also, administration of GHB was reported to increase growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970).

A good safety profile for GHB consumption, when used long term for treatment of narcolepsy has been reported. Patients have been safely treated for many years with GHB without development of tolerance (Scharf, 1985). Clinical laboratory tests carried out periodically on many patients have not indicated organ or other toxicities (Lammers, 1993; Scrima, 1990; Scharf, 1985; Mamelack, 1977; Mamelak, 1979; Gallimberti, 1989; Gallimberti, 1992; Gessa, 1992). The side effects of GHB treatment have been minimal in incidence and degree of severity, though they include sleepwalking, enuresis, headache, nausea and dizziness (Broughton and Mamelak, 1979; Mamelak et al., 1981; Mamelak et al., 1977; Scrima et al., 1989; Scrima et al., 1990; Scharf et al., 1985).

The pharmacokinetics of GHB have been investigated in alcohol dependent patients (Ferrara et al., 1992) and in normal healthy males (Palatini et al., 1993) after oral administration. GHB possesses a rapid onset and short pharmacological effect (Ferrara et al., 1992; Palatine et al., 1993; Lee, C., 1977; van der Bogert; Gallimberti, 1989; Gallimberti, 1992; Lettieri and Fung, 1978; Arena and Fung, 1980; Roth and Giarman, 1966; Vickers, 1969; Lee, 1977). In alcohol dependent patients, GHB absorption into and elimination from the systemic circulation were fast processes. Virtually no unchanged drug could be recovered in the urine. There were preliminary indications that the pharmacokinetics of GHB might be non-linear or dose-dependent (Ferrara et al., 1992). In the healthy volunteers study, the pharmacokinetics of three rising GHB doses (12.5, 25, and 50 mg/kg) were investigated. These findings indicate that both the oral absorption and elimination processes of GHB were capacity-limited though the degree of dose dependency was moderate (Palatini et al., 1993).

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). 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.

SUMMARY OF THE INVENTION

The present invention overcomes deficiencies in the prior art by providing compositions of GHB in an aqueous medium

that are resistant to microbial growth. These compositions are also resistant to the uncontrolled degradation of GHB into GBL or other substances. The compositions of the present invention are stable compositions of GHB that improve shelf-life, and provide a titratable formulation of GHB for easy dose measurement. In addition, the concentrated solutions embodied in this invention reduce shipping and storage requirements and allow patients to carry more drugs for their convenience. The present invention provides methods to treat a number of conditions treatable by GHB, referred to herein as "therapeutic categories." Therapeutic categories for the present invention include, but are not limited to, sleeping disorders, drug abuse, alcohol and opiate withdrawal, a reduced level of growth hormone, anxiety, analgesia, effects in certain neurological disorders, such as Parkinson's Disease, depression, certain endocrine disturbances and tissue protection following hypoxia/anoxia such as in stroke or myocardial infarction, or an increased level of intracranial pressure or other conditions treatable with GHB.

The invention first provides a pharmaceutical composition of GHB rendered chemically stable and/or resistant to microbial growth in an aqueous medium. Preferred GHB salts of the present invention include sodium, ammonium and calcium. As used herein in certain embodiments, "stable" may mean resistant to degradation of GHB into its known or unknown decomposition elements. The level of GBL that is acceptable can be up to 0.1% of the formulation as per the ICH guidelines for shelf-life determination. As used herein in certain embodiments, "resistant to microbial growth" or "resistant to microbial challenge" means that the formulations meet the criteria set by the Food and Drug Administration and the U.S. Pharmacopoeia for products made with aqueous bases or vehicles, which for bacteria means not less than a 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days, and for yeast and molds, no increase from the initial calculated count at 14 and 28 days. As used herein in certain embodiments, an "aqueous medium" may mean a liquid comprising more than about 50% water. In certain preferred embodiments, an "aqueous medium" may be a solution, suspension, gel or emulsion of GHB, with a solution of GHB being most preferred. Preferred gels are thixotropic gels. Compositions that are resistant to microbial growth are created by dissolving or mixing GHB in an aqueous medium to a concentration or content of greater than of about 150 mg/ml GHB to the maximal solubility of GHB. The solubility of GHB is up to about 750 mg/ml at room temperature (20° C. to about 25° C.), however, heating the aqueous medium during preparation up to 100° C. will increase GHB solubility to at least about 1000 mg/ml. A preferred concentration or content of GHB is about 500 mg/ml.

The amount of GHB that may be mixed or dissolved into an aqueous medium and still be resistant to microbial growth depends upon the pH of the aqueous medium. In certain embodiments the presence of a preservative may allow the amount of GHB contained in the compositions of the present invention to be increased and still maintain resistance to chemical degradation and/or microbial growth. In one embodiment of the present invention, the pH of the aqueous medium of the pharmaceutical composition is about 3 to about 10.

In a preferred embodiment, the pH of said aqueous medium is about 6 to about 7.5. The pH may be from about 3.0 to about 10.3, namely of about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0, about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, about 10.0, about 10.1, about 10.2, or about 10.3, and all pH values between each of the listed pH values, of the aqueous media. This will produce a GHB composition that is resistant to microbial growth as defined by the test described herein. As used herein, the term "about" generally means within about 10-20%.

These pH values will produce compositions resistant to microbial growth in an aqueous medium if the amount of GHB added, admixed, or dissolved is from above about 150 mg/ml to about 450 mg/ml, namely, above about 150 mg/ml, about 160 mg/ml, about 170 mg/ml, about 180 mg/ml, about 190 mg/ml, about 200 mg/ml, about 210 mg/ml, about 220 mg/ml, about 230 mg/ml, about 240 mg/ml, about 250 mg/ml, about 260 mg/ml, about 270 mg/ml, about 280 mg/ml, about 290 mg/ml, about 300 mg/ml, about 310 mg/ml, about 320 mg/ml, about 330 mg/ml, about 340 mg/ml, about 350 mg/ml, about 360 mg/ml, about 370 mg/ml, about 380 mg/ml, about 390 mg/ml, about 400 mg/ml, about 410 mg/ml, about 420 mg/ml, about 430 mg/ml, about 440 mg/ml, to about 450 mg/ml, and all amounts of GHB between the values listed.

At the medium to high end of the concentration or content of GHB that may be dissolved or mixed in the aqueous medium, the maximal pH that may be used is reduced at room temperature. This is shown in FIG. **1**, a graphical presentation of acceptable formulation ranges. At a concentration or content of about 450 mg/ml GHB, the pH may be of about 3.9 to about 10.3. At a concentration or content of about 500 mg/ml GHB, the pH may be of about 4.75 to about 10.3. At a concentration or content of about 600 mg/ml GHB, the pH may be of about 6.1 to about 10.3. At a concentration or content of about 750 mg/ml GHB, the pH may be of about 7.0 to about 10.3. Of course, all pH and concentration or content values in between each of the listed pH and concentration or content values are encompassed by the invention.

Certain embodiments may be selected as sub-ranges from these values of GHB content and aqueous medium pH. For example, a specific embodiment may be selected as a content of about 170 mg/ml to about 440 mg/ml GHB in an aqueous medium, at a pH range of about pH 5.5 to about pH 8.7. Another example of how a range may be selected in an embodiment would be the selection of a content of about 155 mg/ml of GHB, which is a value between the above listed values, to a content of about 350 mg/ml of GHB, and the selection of a pH range of the aqueous medium, such as a pH range of about 8.87, which is a value between the listed pH values, to a pH of about 8.93, which is another value between the listed values of pH. A third example of ranges that may be selected for a specific embodiment would be selection of a single content or concentration of GHB, such as about 200 mg/ml of GHB, and the selection of a pH range, such as a pH of about 3.5 to about 8.2. A fourth example of ranges that may be selected for a specific embodiment would be selection of a content or concentration of GHB over a range, such as about 300 mg/ml to about 400 mg/ml, and the selection of a single pH value for the aqueous medium, such as a pH of about 3. Another example of a range selected for an embodiment may be the selection of a single content or concentration of GHB, such as 400 mg/ml GHB, and a single pH value of the aqueous medium, such as pH 7.7.

Other examples of how a range of an embodiment of GHB content or concentration may be selected include a range of GHB content or concentration from about 200 mg/ml to about 460 mg/ml GHB, encompassing the ranges for GHB described herein, and a range of pH for the aqueous medium may be from about pH 4.3 to about pH 7, encompassing ranges for GHB in an aqueous medium at room temperature described herein. Another example would be the selection of a range of GHB content or concentration from about 153 mg/ml to about 750 mg/ml, and a pH range of about 7 to about 9, encompassing ranges between the listed values of GHB content and pH described herein. An example may be the selection as a GHB concentration or content of about 170 mg/ml to about 640 mg/ml in an aqueous medium, at a pH range of about pH 6.5 to about pH 7.7. Another example of how a range may be selected in an embodiment would be a content or concentration of about 185 mg/ml of GHB, which is a value between the listed values, to a content or concentration of about 750 mg/ml of GHB, at a pH range of about 7.87, which is a value between the listed pH values, to a pH of about 8.91, which is another value between the listed values of pH. An additional example of ranges that may be selected for a specific embodiment would be a content or concentration of about 200 mg/ml of GHB at a pH of about 7 to about 8.2. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 750 mg/ml to about 400 mg/ml at a pH of about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 300 mg/ml to about 750 mg/ml at a pH of about 8.5 to about 7. Another example of ranges that may be selected for a specific embodiment would be a content or concentration of about 400 mg/ml to about 600 mg/ml at a pH of about 9 to about 5.8. And so forth. Thus, all ranges of pH and GHB concentration or content that can be selected from the values herein and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

The chemical stability of GHB is affected by pH, with compositions of GHB in an aqueous medium with a pH below about 6 being less effective in maintaining the chemical stability of GHB. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, all concentrations or content of GHB in an aqueous medium, as described herein, and as would be understood by those of ordinary skill in the art, may be selected to produce compositions of the present invention.

Additionally, the ranges described above are for a composition at room temperature, which is defined herein as from about 20° C. to about 25° C., namely, about 20° C. about 21° C., about 22° C., about 23° C., about 24° C., to about 25° C. Within the values and ranges of pH described above, the ranges of concentration or content of GHB may increase at temperatures greater than room temperature. Thus, the maximal content or concentration of GHB in an aqueous medium at a temperature of from about 26° C. about 100° C., namely about 26° C., about 27° C., about 28° C., about 29° C., about 30° C., about 31° C., about 32° C., about 33° C., about 34° C., about 35° C., about 36° C., about 37° C., about 38° C., about 39° C., about 40° C., about 41° C., about 42° C., about 43° C., about 44° C., about 45° C., about 46° C., about 47° C., about 48° C., about 49° C., about 50° C., about 51° C., about 52° C., about 53° C., about 54° C., about 55° C., about 56° C., about 57° C., about 58° C., about 59° C., about 60° C., about 61° C., about 62° C., about 63° C., about 64° C., about 65° C., about 66° C., about 67° C., about 68° C., about 69° C., about 70° C., about 71° C., about 72° C., about 73° C., about 74° C., about 75° C., about 76° C., about 77° C., about 78° C., about 79° C., about 80° C., about 81° C., about 82° C., about 83° C., about 84° C., about 85° C., about 86° C., about 87° C., about 88° C., about 89° C., about 90° C., about 91° C., about 92° C., about 93° C., about 94° C., about 95° C., about 96° C., about 97° C., about 98° C., about 99° C., to about 100° C. may be from about 750 to about 1 g/ml, namely to about 751 mg/ml, about 760 mg/ml, about 770 mg/ml, about 780 mg/ml, about 790 mg/ml, about 800 mg/ml, about 810 mg/ml, about 820 mg/ml, about 830 mg/ml, about 840 mg/ml, about 850 mg/ml, about 860 mg/ml, about 870 mg/ml, about 880 mg/ml, about 890 mg/ml, about 900 mg/ml, about 910 mg/ml, about 920 mg/ml, about 930 mg/ml, about 940 mg/ml, about 950 mg/ml, about 960 mg/ml, about 970 mg/ml, about 980 mg/ml, about 990 mg/ml, to about 1000 mg/ml. At temperatures below room temperature, the solubility of GHB may decrease, and compositions at lower temperature and solubility of GHB at the pH values and ranges described herein are also encompassed by the invention. Additionally, differences of atmospheric pressure may also increase or decrease the solubility of GHB within the ranges described, and embodiments of the invention with an increased or decreased content of GHB due to changes in pressure are also encompassed by the invention. Of course, it is understood that the present invention encompasses embodiments of GHB concentration or content in an aqueous medium at higher or lower temperature within the values described herein, such as about 980 mg/ml to about 200 mg/ml at 95° C. GHB at a pH of about 9 to about 7.5. Or about 150 mg/ml GHB at about 17° C. at about pH 6 to about pH 7. And so forth. Thus, all ranges of pH and GHB content that can be selected at various temperatures and pressures from the values above, and as would be understood by those of ordinary skill in the art, are encompassed by the present invention.

In certain other embodiments of the present invention, the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids, bases, or combinations thereof. In certain embodiments, the acid may be an organic acid, preferably a carboxylic acid or alphahydroxy carboxylic acid. In certain other embodiments, the acid is selected from the group including, but not limited to, acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like. In a preferred embodiment, the acid is malic or hydrochloric acid. In certain other embodiments, the pH adjusting agent may be a base selected from the group including, but not limited to, acetanilide, ammonia, apomorphine, atropine, benzocaine, caffeine, calcium hydroxide, cocaine, codeine, ephedrine, morphine, papaverine, physostigmine, pilocarpine, potassium bicarbonate, potassium hydroxide, procaine, quinine, reserpine, sodium bicarbonate, sodium dihydrogen phosphate, sodium citrate, sodium taitrate, sodium carbonate, sodium hydroxide, theobromine, thiourea or urea. 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.

In certain embodiments, the composition may contain one or more salts. A "salt" is understood herein to mean certain embodiments to mean a compound formed by the interaction of an acid and a base, the hydrogen atoms of the acid being replaced by the positive ion of the base. Various salts, including salts of GHB, are also encompassed by ***the invention, particularly as pH adjusting or buffering agents. Pharmaceutically acceptable salts, include inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as malic, acetic, oxalic, tartaric, mandelic, and the like. Salts formed can also be derived from inorganic bases such as, for example, sodium, potassium, silicates, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropyamine, trimethylamine, histidine, procaine and the like. Alkali metal salts such as lithium, potassium, sodium, and the like may be used, preferably with an acid to form a pH adjusting agent. Other salts may comprise ammonium, calcium, magnesium and the like. In one embodiment, a salt of GHB comprising an alkali metal may be combined with an acid to create a composition that achieves the desired pH when admixed with an aqueous medium. In another embodiment, a weak base may be combined with GHB to create a composition that achieves the desired pH when admixed with an aqueous solution. Of course, other salts can be formed from compounds disclosed herein, or as would be known to one of ordinary skill in the art, and all such salts are encompassed by the invention.

In certain embodiments, excipients may be added to the invention. An "excipient" as used herein shall mean certain embodiments which are more or less inert substances added as diluents or vehicles or to give form or consistency when the remedy is in a solid form, though they may be contained in liquid form preparations, e.g. syrups, aromatic powders, honey, and various elixirs. Excipients may also enhance resistance to microbial growth, and thus act as a preservative. Such excipients include, but are not limited to, xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, cellulose derivatives, magnesium carbonate and the like.

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, propyl gallate BP, sorbic acid, chlorobutanol, dihydroacetic acid, monothioglycerol, potassium benzoate, propylparaben, benzoic acid, benzalkonium chloride, alcohol, benzoic acid, benzalkonium chloride, benzethonium chloride, benzyl alcohol, butylparaben, cetylpyridinium chloride, ethylenediamine, ethylparaben, ethyl vanillin, glycerin, hypophosphorus acid, methylparaben, phenol, phenylethyl alcohol, phenylmercuric nitrate, propylparaben, sassafras oil, sodium benzoate, sodium propionate, thimerosal and potassium sorbate. Preferred preservatives may be selected from the group comprising, but not limited to, xylitol, sodium benzoate, methylparaben, propylparaben and potassium sorbate. Xylitol is particularly preferred in certain compositions of the invention, because it acts as an preservative and a sweetener, is a caries preventative, is less laxative than other sweeteners, and is recommended for diabetics.

In certain embodiments, the pharmaceutical composition may also contain an antioxidant. An "antioxidant" is understood herein to mean certain embodiments which are substances that inhibits oxidation. Such antioxidants include, but are not limited to, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, potassium metabisulfite, sodium metabisulfite, anoxomer and maleic acid BP.

In certain embodiments, the pharmaceutical composition may also contain a flavoring agent. A "flavoring agent" is understood herein to mean certain embodiments which are substances that alters the flavor of the composition during oral consumption. A type of "flavoring agent" would be a sweetener. Preferred sweeteners or flavoring agents would be microbially non-metabolizable. Especially preferred sweeteners or flavoring agents would be carbohydrates such as xylitol and sorbitol. Such flavoring agents include, but are not limited to, acacia syrup, anethole, anise oil, aromatic elixir, benzaldehyde, benzaldehyde elixir-compound, caraway, caraway oil, cardamom oil, cardamom seed, cardamom spirit, cardamom tincture-compound, cherry juice, cherry syrup, cinnamon, cinnamon oil, cinnamon water, citric acid, citric acid syrup, clove oil, coca, coca syrup. coriander oil, dextrose, eriodictyon, eriodictyon fluidextract, eriodictyon syrup aromatic, ethyl acetate, ethyl, vanillin, fennel oil, ginger, ginger fluidextract, ginger oleoresin, glucose, glycerin, glycyrrhiza, glycyrrhiza elixir, glycyrrhiza extract, glycyrrhiza extract-pure, glycyrrhiza fluidextract, glycyrrhiza syrup, honey, non-alcoholic elixir, lavender oil, citrus extract or oil, lemon oil, lemon tincture, mannitol, methyl salicylate, nutmeg oil, orange-bitter-elixir, orange-bitter-oil, orange flower oil, orange flower water, orange oil, orange peel-bitter, orange-peel-sweet-tincture, orange spirit-compound, compound, orange syrup, peppermint, peppermint oil, peppermint spirit, peppermint water, phenylethyl alcohol, raspberry juice, raspberry syrup, rosemary oil, rose oil, rose water, saccharin, saccharin calcium, saccharin sodium, sarsaparilla syrup, sorbitol solution, spearmint, spearmint oil, sucrose, syrup, thyme oil, tolu balsam, tolu balsam syrup, vanilla, vanilla tincture, vanillin or wild cherry syrup.

Salts, excipients, pH adjusting agents such as acids, bases and buffering agents, flavoring agents, and other agents that may be combined with the compositions of the present invention, or may be used to prepare the compositions of the present invention, are well known in the art, (see for example, "Remington's Pharmaceutical Sciences" 8th and 15th Editions, and Nema et al., 1997, incorporated herein in their entirety), and are encompassed by the invention.

In certain other embodiments, the pharmaceutical composition comprises GHB, a pH adjusting or buffering agent, and an aqueous medium, wherein the components are admixed (sequentially or simultaneously) to prepare said pharmaceutical composition. The pH adjusting or buffering agent and aqueous medium may be any described herein.

The invention also provides a method of preparing a chemically stable and microbial growth-resistant pharmaceutical composition for the treatment of a condition responsive to GHB, comprising admixing GHB and a pH-adjusting or buffering agent in an aqueous medium. In certain embodiments, the method of preparing the pharmaceutical composition further comprises admixing a preservative with the pharmaceutical composition. Other components, such as flavoring agents, salts, and the like, may be added to the composition. The pH adjusting or buffering agent, aqueous medium, preservative, flavoring agents, salts, or other ingredient may be any described herein.

In certain other embodiments, the method of preparing the pharmaceutical composition comprises admixing GHB, a pH adjusting or buffering agent, and an aqueous medium soon before administration to a patient suspected of having a condition responsive to GHB.

The invention also provides a method of treating any therapeutic category of disorder responsive to GHB, comprising

administering to a patient suspected of having such a condition a therapeutic amount of a pharmaceutical composition comprising chemically stable GHB (e.g. 1-10 gms.) in an aqueous medium resistant to microbial growth. In certain embodiments, the method of treating a condition responsive to GHB comprises a patient taking a first dosage of from about 0.1 g to about 10 g, namely about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1-9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, about 7.8, about 7.9, about 8.0, about 8.1, about 8.2, about 8.3, about 8.4, about 8.5, about 8.6, about 8.7, about 8.8, about 8.9, about 9.0 about 9.1, about 9.2, about 9.3, about 9.4, about 9.5, about 9.6, about 9.7, about 9.8, about 9.9, to about 10 grams of GHB, or as needed by the patient as would be recognized by one of skill in the art. Of course, it will be understood that all values in between those listed, such as 9.45 grams, 6.32 grams, etc. may be administered, and those values are encompassed well. In preferred embodiments, the first dose is administered within an hour of sleep. In preferred embodiments, a second dose of GHB within the values described above may be administered. This second dose is administered preferably within about 2.0 to about 5.0 hrs, namely about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, to about 5.0 hours after the first dose, though it may be administered at a time outside of the preferred range.

In certain embodiments, a second pharmaceutical may be administered with the composition of GHB. Such a second pharmaceutical may be e.g., a stimulant administered within the same 24 hour period as the first dose of GHB. The stimulant may be, e.g., but not limited to, methylphenidate or pemoline to counter the residual effects of GHB treatment during periods of wakefulness. In certain embodiments, the method of treating a sleep disorder may include the discontinuation of other second pharmaceuticals used to control a sleep disorder. Such second pharmaceuticals may include, but are not limited to, a tricyclic antidepressant.

In certain embodiments, the invention provides a method of treating any appropriate therapeutic category of disorder, by administration of GHB compositions of the present invention as described above for the treatment of sleep disorders. When GHB is used in methods of treating any therapeutic category of disorder, the GHB composition of the present invention may be mixed with the aqueous medium, and optionally pH adjusting or buffering agent or other additives, by the patient or administrator soon before consumption. The patient may prepare the composition within a few minutes to hours before administration. Alternatively, one or more of the components may be premixed for ready use. The components of the GHB composition of the present invention, GHB, an aqueous medium, pH adjusting or buffering agent, excipients, preservatives, flavoring agents, and/or other components or additives may be stored in a container means suitable to aid preservation. Preferably, the container means is in the form of a set. A "set" as used herein certain embodiments is one or more components of the composition packaged in a container or other suitable storage means.

The present invention also provides a set for the treatment of a condition responsive to GHB comprising, in suitable storage means, GHB and a pH adjusting or buffering agent. In certain embodiments, the GHB and the pH-adjusting or buffering agent are separately packaged. In certain other embodiments the GHB and the pH adjusting or buffering agent may be mixed. The set may contain an aqueous medium. In certain other embodiments, at least one component selected from the group including, but not limited to, GHB, the pH-adjusting or buffering agent and/or an aqueous medium is separately packaged. In certain other embodiments, at least two of the components selected from the group comprising GHB, a pH adjusting or buffering agent and an aqueous medium are mixed together. In some embodiments, the set further contains a preservative. Such a set may have one, two, or more components from the group comprising GHB, a pH-adjusting or buffering agent, an aqueous medium or a preservative packaged separately. Such a set may have two or more components mixed together. Thus, both liquid and dry formulations of GHB and other components may be packaged in a set for mixing before administration, or one or more components may be premixed and packaged together with other components, or all the components may be premixed and packaged in a set.

It is understood that the compositions of the present invention, including those in a set, may be dispersed in a pharmaceutically acceptable carrier solution as described below. Such a solution would be sterile or aseptic and may include water, co-solvent vehicle buffers, isotonic agents, pharmaceutical aids or other ingredients known to those of skill in the art that would cause no allergic or other harmful reaction when administered to an animal or human subject. Therefore, the present invention may also be described as a pharmaceutical composition of GHB with increased stability in a pharmaceutically acceptable carrier solution.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also as used herein, the term "a" "an" or "the" is understood to include the meaning "one or more". Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. **1**. The Range of Gamma-Hydroxybutyrate's Resistance to Microbial Growth and Chemical Stability in Aqueous Solution. The ordinate is the pH of solutions of GHB. The axis is the concentration (mg/ml) of GHB in aqueous solution. The region below the diagonal line [/] is the range of GHB solubility at room temperature. Greater solubility can be achieved, up to 1 g/ml, by heating the solution up to 100° C.

FIG. **2** illustrates the concentration and volume of GHB solution that a patient administers (see also Table 4).

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

I. Formulations of Gamma-Hydroxybutyrate

A. Microbial Growth and Gamma-Butyrolactone Formation

The present invention arises from the discovery of chemically stable and microorganism resistant formulations of GHB in an aqueous medium, preferably a solution, and the efficacy of these formulations in the treatment of therapeutic categories of disorders, such as narcolepsy and other sleep disorders. Specifically, GHB is prepared at a concentration greater than about 150 mg/ml in an aqueous medium, up to the limits of GHB's solubility or retention in an aqueous medium, to produce the compositions of the present invention.

The maximum solubility of GHB is affected by the pH of the aqueous medium. At about pH 4, the maximum amount of sodium-GHB that can be dissolved is about 450 mg/ml. The value of pH that is conducive to GHB solubility increases, as is shown at FIG. **1**, so that the minimal pH that will dissolve 750 mg/ml GHB was found to be about pH 6.8. This is shown in Table 1.

TABLE 1

	Limits of Sodium Oxybate Solubility		
ID A	Sodium Oxybate Maximum Solubility	pH of Solution	Temperature
B	450 mg/cc	pH 4 (HCl)	25°
C	500 mg/cc	pH 5 (HCl)	25°
D	600 mg/cc	pH 6 (HCl)	25°
E	750 mg/cc	pH 6.8 (HCl)	25°
F	750 mg/cc+	pH 10.3	25°
G	1000 mg/cc	pH unadjusted	65° Soluble, 25° Gel

The pH of the aqueous medium also affects the resistance of the composition to microbial growth at about 500 mg/ml GHB. GHB at this concentration in an aqueous medium that is between about pH 5 and pH 9 is resistant to microbial growth, with compositions at about pH 6 to about pH 7.5 being particularly resistant to microbial growth. However, at concentrations of GHB greater than about 750 mg/ml above about pH 7.5, the resistance to microbial growth is reduced. This is shown at Table 2.

TABLE 2

	Microbial Challenge Data Summary		
ID H	Sodium Oxybate Concentration	pH of Solution	Microbial Challenge Result
I	750 mg/cc	7.5 (HCl)	pass
J	500 mg/cc	6.0 (HCl)	pass
K	500 mg/cc + Excipients (Xylitol)	6.0 (Malic Acid)	pass
L	500 mg/cc	9.0 (HCl)	pass (borderline *aspergillus*)
M	150 mg/cc (BDL 1995)	5.0 (HCl)	fail (*aspergillus* only)
N	150 mg/cc (BDL 1995)	7.0 (HCl)	fail (*aspergillus* & *staph*)
O	150 mg/cc (BDL 1995)	3.0 (HCl)	fail (*aspergillus* only)
P	150 mg/cc (BDL 1995)	10.3 (unadjusted)	fail (*aspergillus* & *staph*)
Q	500 mg/cc	6.0 (Malic Acid)	discontinued
R	500 mg/cc	7.5 (Malic Acid)	pass

TABLE 2-continued

	Microbial Challenge Data Summary		
ID H	Sodium Oxybate Concentration	pH of Solution	Microbial Challenge Result
S	500 mg/cc (May 1998)	9.0 (Malic Acid)	discontinued
T	500 mg/cc (May 1998)	7.5 (HCl)	pass*
U	Others: 200 mg/cc-800 mg/cc	5.0-9.0	pending

*pass is generally defined as:
For Category 1C Products
Bacteria: Not less than 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days' count at 28 days.
Yeast and Molds: No increase from the initial calculated count at 14 and 28 days.

The data from Table 1 and Table 2 are graphically shown in FIG. **1**. The concentration of GHB in the composition, when evaluated in relationship to the pH, affects the resistance of the GHB composition to microbial challenge. Compositions of GHB at or below 150 mg/ml are poorly resistant to microbial challenge from a pH range of about pH 3 to about pH 9. However, concentrations of GHB of greater than about 150 mg/ml, up to about 1000 mg/ml of GHB, are believed to be suitably resistant to microbial contamination at these pH ranges.

The chemical stability of GHB is affected by pH. Accordingly, the method for preparing GHB, as described herein, particularly as disclosed in the specific examples, varies with pH. GBL begins to form if the pH is about 6 or less. Compositions with a pH of greater than about 6.0 are preferred to produce chemically stable formulations of 15 GHB. Thus, a preferred range to produce chemically stable GHB would be from about pH 6 to about pH 9. However, any pH or range of pH values where a clinically acceptable amount of GBL is produced is also contemplated as being preferred, and is encompassed by the present invention. The range of GBL could be regulatorily broadened with availability of sufficient toxicological data.

In certain embodiments of the invention, a pH-adjusting agent may be added to the composition. The choice of a pH adjusting agent may affect the resistance to microbial challenge and/or the stability of GHB, as measured by the reduction in assayable GHB. Compositions of GHB, pH adjusted with malic acid are resistant to both microbial growth and chemical degradation of GHB, and are preferred. Other pH adjusting or buffering agents may be selected. Agents that adjust pH that are selected on this basis will undergo a taste testing study. However, any pH adjusting agent disclosed herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the invention. Of course, any salt, flavoring agent, excipient, or other pharmaceutically acceptable addition described herein or as would be known to one of ordinary skill in the art is contemplated as being useful in the invention.

Any of the above formulations may be prepared and/or packaged as a powdered or dry form for mixing with an aqueous medium before oral administration, or they may be prepared in an aqueous medium and packaged. After mixing with an aqueous medium, preferably to prepare a solution, these formulations are resistant to both microbial growth and chemical conversion of GHB to GBL, thereby increasing the shelf-life of therapeutic formulations of GHB in an aqueous medium. These formulations-then provide an easily titratable liquid medium for measuring the dosage of GHB to be administered to a patient. Additional embodiments of the composition and methods of preparation are described below and in the examples.

B. Pharmaceutical Compositions

1. Pharmaceutically Acceptable Carriers

Aqueous compositions of the present invention comprise an effective amount of GHB dissolved or dispersed in a pharmaceutically acceptable carrier and/or an aqueous medium. The phrases "pharmaceutically or pharmacologically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is not appropriate. Supplementary compatible active ingredients can be incorporated into the compositions. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by the Food and Drug Administration (FDA).

The GHB may be lyophilized for more ready formulation into a desired vehicle where appropriate. The active compounds may be formulated for parenteral administration, e.g., formulated for injection via intravenous, intraarterial, intramuscular, sub-cutaneous, intralesional, intraperitoneal or other parenteral routes. The preparation of an aqueous composition that contains a GHB agent as an active component or ingredient will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for using to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including, e.g., aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

Solutions of the active compounds as free acid or pharmacologically acceptable salts can be prepared in water suitably mixed with hydroxypropylcellulose and/or a pharmaceutically acceptable surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof as well as in oils. Under ordinary conditions of storage and use, these preparation may best contain a preservative to further prevent the growth of microorganisms.

A GHB composition of the present invention can be formulated into a composition in a neutral or salt form. Such salts can be formed from any of the acids and bases described herein particularly depending on the particular GHB or GHB salt used, or as would be known to one of ordinary skill in the art.

The carrier can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, or the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a substance, such as lecithin (e.g. a coating), by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by any of the preservatives described herein, or as would be known to one of ordinary skill in the art, including various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The preparation of more, or highly, concentrated solutions for direct injection is also contemplated, where the use of DMSO as solvent (although DMSO may not now be a permitted human drug) is envisioned to result in extremely rapid penetration, delivering high concentrations of the active agents to a small area.

Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above, but drug release capsules and the like can also be employed.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences"15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The active GHB may be formulated within a therapeutic mixture to comprise about 100 to about 10,000 milligrams per dose. Multiple doses can also be administered.

In addition to the compounds formulated for parenteral administration, such as intravenous or intramuscular injection, other pharmaceutically acceptable forms include, e.g., tablets or other solids; liposomal formulations; time release capsules; and any other form currently used, including cremes, which then may be admixed with an aqueous medium for oral administration.

One may also use nasal solutions or sprays, aerosols or inhalants in the present invention. Nasal solutions are usually aqueous solutions designed to be administered to the nasal passages in drops or sprays. Nasal solutions are prepared so that they are similar in many respects to nasal secretions, so that normal ciliary action is maintained. Thus, the aqueous nasal solutions usually are isotonic and slightly buffered to maintain a pH of 5.5 to 6.5, though other pH ranges disclosed

herein the specific examples, such as pH 3 to about pH 9, or pH 6 to about 7.5, are contemplated. In addition, preservatives, similar to those used in ophthalmic preparations, and appropriate drug stabilizers, if required, may be included in the formulation. Various commercial nasal preparations are known and include, for example, antibiotics and antihistamines and are used for asthma prophylaxis.

The preferred oral formulations may include such normally employed excipients, as, for example, pharmaceutical grades of xylitol, mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate and the like. These compositions can take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders to be admixed with an aqueous medium. In certain defined embodiments, oral pharmaceutical compositions will comprise an inert diluent or assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsule, or they may be compressed into tablets, or the GHB may be packaged separately from or in combination with the excipients, salts, flavorings or any other components described herein, to be admixed with an aqueous medium for oral or injectable formulations, or they may be incorporated directly with the food (i.e. a beverage) of the diet.

For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of tablets, buccal tablets or tabs, troches, capsules, elixirs, suspensions, syrups, wafers, and the like, to be admixed with an aqueous medium. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 75% of the weight of the unit, or preferably between 25-60%. The amount of active compounds in such therapeutically useful compositions is such that a suitable dosage will be obtained.

The tablets, troches, pills, capsules and the like may also contain the following: a binder, natural as gum tragacanth, acacia, cornstarch, or gelatin or synthetic as polyvinyl acetate; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a natural or synthetic flavoring agent. When the dosage unit form is a capsule for admixing with a specific volume of an aqueous medium, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with sugar, natural or synthetic polymers, or both. A syrup or elixir may contain the active compounds, sucrose as a sweetening agent, a preservative, a dye and/or a flavoring.

Additionally, any excipient, salt, acid, pH-mediating, adjusting or buffering compound or agent, flavoring, solution, solvent, dispersion, glycerol, glycol, oil, antibacterial and antifungal agents, antibiotics and antihistamines, binders, disintegrating agents, lubricants, sweetening agents, or any other additive or ingredient from those enumerated above or in the examples, or in any pharmaceutically acceptable composition or carrier described herein, or as would be known by one of skill in the art, is contemplated for use in aqueous mediums or solid forms of the GHB compositions of the invention. One or more of these compositions may be packaged with GHB or packaged separately from GHB prior to consumption. If packaged separately, useful compositions of GHB may be obtained by mixing GHB with the other components with an aqueous medium prior to consumption. Such components may be packaged in a set, described below.

2. Sets

Therapeutic sets of the present invention are sets comprising GHB. Such sets will generally contain, in suitable container, a pharmaceutically acceptable formulation of GHB. The set may have a single container, or it may have distinct container for each component, or distinct container for various combinations of components.

When the components of the set are provided in one or more liquid formulations, the liquid formulation is an aqueous medium, with a sterile aqueous solution being particularly preferred. The GHB compositions may also be formulated into a syringeable composition. In which case, the container means may itself be a syringe, pipette, vial, ampule or other such like apparatus, from which the formulation may be applied to an infected area of the body, injected into an animal, or even applied to and mixed with the other components of the set.

However, the components of the set may be provided as dried powder(s). When reagents or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent. It is envisioned that the solvent may also be provided in another container means.

The container means will generally include at least one vial, test tube, flask, bottle, pouch syringe or other container means, into which the GHB formulation or components thereof are placed, preferably, suitably allocated. The sets may also comprise a second container means for containing a sterile, pharmaceutically acceptable buffer or other diluent.

The sets of the present invention will also typically include a means for containing the vials in close confinement for commercial sale, such as, e.g., injection or blow-molded plastic containers into which the desired vials are retained.

Irrespective of the number or type of containers, the sets of the invention may also comprise, or be packaged with, an instrument for assisting with the injection/administration or placement of the GHB composition within the body of an animal. Such an instrument may be a drinking cup, syringe, pipette, or any such medically approved delivery vehicle.

II. Methods of Treatment with the GHB Compositions

Because GHB has been shown to be effective in treating narcolepsy and sleep disorders (Lee, 1977; Mamelak, 1977; Hoes, 1980; Scharf, 1985; Scrima, 1990; Gallimberti, 1992; Series, 1992; Lammers, 1993), reducing alcohol craving and alcohol withdrawal symptoms, (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992), reducing opiate withdrawal symptoms (Gallimberti et al, 1994; Gallimberti et al., 1993), reducing pain (U.S. Pat. No. 4,393,236), reducing intracranial pressure in patients (Strong, A. 1984), and increasing growth hormone levels in patients (Gerra et al, 1994; Oyama et al., 1970), the formulations of the present invention are also contemplated to be useful in the treatment of any of these disorders or conditions in patients. GHB has also been used alone as a narcotic in patients with a terminal carcinomatous state. GHB has been used with other analgesics, neuroleptics, or with a subliminal barbiturate dose for use as an anesthesia. GHB has been used in closed craniocerebral trauma and as a soporific (U.S. Pat. No. 5,380,937). The inventors contemplate the use of the GHB compositions of the present invention as a narcotic, hypnotic, or as a soporific. The inventors also contemplate the use of the GHB compositions of the present invention in combination with analgesics, neuroleptics or barbiturates for use as an anesthesia. The GHB compositions of the present invention may be prepared and administered by any of the means described herein, particularly those described in the section "Pharma-

ceutical Compositions" and the examples, or by any means as would be known to those of skill in the art.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

Preferred Embodiments

XYREM™ Clinical Trials

The inventors developed a liquid formulation composed of GHB, xylitol, and preservative in water (XYREM®). Subsequent instability of the preservative in this formulation and a desire to initiate clinical trials in a timely manner led to a change in the formulation to a foil pouch. One clinical trial utilized a twin-pouch dosage form, with one side (pouch 1) of the foil packet containing GHB and the other side (pouch 2) containing the flavoring agents (Xylitol, [NF]; Malic Acid, NF.

Patients were instructed to open the twin-pouch with a scissors, empty the contents into a dosing cup, add 2 ounces of water, snaphthe lid on the dosing cup, shake to dissolve, and drink the entire contents of the cup. Clinical trials conducted by the inventors have been performed using the twin-pouch dosage form.

However, the inventors have continued development of a liquid solution and have now overcome inherent problems with particular formulations and/or preservatives. The inventors have converted patients currently enrolled in a GHB open-label trial to a liquid solution composed of GHB, malic acid, and water—that is diluted with water immediately prior to oral administration.

The need for a liquid solution dosage form is further evidenced by the range of doses being used in a subsequent GHB open-label trial. Three sizes of pouches were prepared for the GHB open-label trial: 1.5 grams, 3.0 grams. and 4.5 grams. The initial dose for all patients in the GHB open-label trial was 6 grams of GHB nightly in divided doses. Dosage adjustments were permitted in the first two weeks of the trial as indicated for intolerance or lack of efficacy. The investigator was permitted to decrease the dose of GHB to 3 grams or 4.5 grams, or increase the dose to 7.5 grams or 9 grams nightly. After two weeks, further dosage adjustments were made if clinically indicated.

Thirty-five patients had their dose increased, and 16 patients had their dose decreased. Patients in the lowest dose group were disproportionately female and weighed 15 kg less than patients in the other two groups. Current dosing levels are noted below:

TABLE 3

Dosing Levels in the GHB Open-Label Trial

	Total	1.5 gram	3.0 gram	4.5 gram	6.0 gram	7.5 gram	9.0 gram
Number of Patients	95	0	4	10	39	12	30
PerCent of Patients	100%	0%	4%	10%	41%	13%	32%

To achieve these individualized doses, it has been necessary to provide a combination of different dose strengths. This complexity would be very difficult to achieve with a marketed product. In addition, a month's supply of twin-pouches is quite bulky. A liquid formulation allows for ease in dosing adjustment with one dosage form. In addition "child-resistant" packaging has been developed with the liquid formulation.

A number of patients have also complained about the flavor with the twin-pouches. As follow-up the inventors sent questionnaires to participants in the inventors' clinical trial, and performed taste testing in normal volunteers. The questionnaire responses, taste testing results, and the clinical experience in narcolepsy patients of the study administrator have all confirmed that unflavored solutions were acceptable.

The concentration and volume of the GHB solution that the patient administers will be the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. This is illustrated in FIG. **2** and Table 4:

TABLE 4

Comparison of Liquid Solution to Twin-Pouch

	Twin-Pouch	Liquid Solution
Amount of GHB	3 grams (1 pouch)	3 grams (6 mL)
Inactive Components	malic acid xylitol lemon/lime flavor orange flavor	malic acid
Final Concentration	50 mg/mL	50 mg/mL*
Final Volume	60 mL	60 mL

*Final concentration outside the range of the most stable formulation. This formulation strength may be only stable at short periods of time such as 48 hours. The twin pouch version could be solubilized at a a concentration within the preferred range of pH and GHB concentration for longer term storage.
Apart from the elimination of the sweetener (xylitol) and flavoring, the two formulations result in identical solutions.

Conclusions

The concentration and volume of the GHB solution that the patient administers is the same irrespective of whether it is dissolved from the pouch or diluted from the liquid. Either method may be used to produce acceptably stable solutions of GHB.

EXAMPLE 2

Preferred Embodiments

Self Preserving Formulations of Gamma-Hydroxybutyrate

Summary of Formulation Studies—Liquid XYREM™

I. Maximum Solubility Range

As seen in FIG. **1** and Table 1, the solubility of GHB varies with pH levels at room temperature (25° C.). Additional amounts of GHB can be solubilized in a gel if heat is applied, in which case a 1000 mg/ml concentration can be achieved. The inventors to contemplate that though the concentrations or contents of GHB shown in FIG. **1** and Table 1 are preferred for use, due to the ease of preparing and consuming unheated

preparations, higher concentrations of GHB in aqueous medium may also be made, up to 1000 mg/ml.

II. Microbial Testing

The inventors used a three factor analysis involving pH, concentrations of GHB and the pH adjuster used. As seen in FIG. **1**, and Table 2, unacceptably low resistance to microbial challenge was seen at 150 mg/ml GHB at pH 3, 5, 7, and 9.0, using HCl as the pH adjusting agent. 150 mg/ml GHB at pH 10.3 without a pH adjusting agent also proved unacceptably resistant to microbial challenge. Borderline acceptable microbial preservativeness was seen in a solution pH adjusted with HCl at 500 mg/ml GHB at pH 9. At a concentration of 500 mg/ml at pH 6.0 or 7.5, adjusted with either malic acid or HCl, and 500 mg/ml at pH 9.0 adjusted with HCl, the formulation is very effective in a microbial challenge test. The inventors contemplate that a concentration of greater than about 150 mg/ml of GHB, up to the maximal solubility in aqueous solution of GHB, will be suitably resistant to microbial challenge from about pH 3 to pH 10.3. Preferably, the aqueous medium will contain a pH-adjusting or buffering agent.

III. Gamma-Butyrolactone Degradation Range

GBL begins to form if the pH is about 6 or less with the formulation tested thus far.

A. Liquid Formulation Development

The objective of these experiments was to develop a commercial formulation for sodium gamma hydroxybutyric acid. The initial formulation for sodium gamma hydroxybutyric acid (GHB) was intended to be an aqueous liquid formulation containing 150 mg/ml GHB, preservatives and flavoring agents. To develop this formulation, studies were conducted to establish the: solubility of the drug in water and as a function of pH, type and concentrations of suitable preservatives, type and concentrations of flavor ingredients, and stability of the formulations.

1. Solubility

The feasibility of preparing formulations containing 150 mg/mL of GHB at pH 3, 5 and 7 was established. Solutions containing 150 mg/mL GHB were prepared. The initial pH was greater than pH 7.5 and the final pH was adjusted to 3, 5 or 7 with hydrochloric acid. The solutions were observed for precipitation and assayed by HPLC for GHB content. The results showed that no precipitation was observed and the drug concentration was found to be 150 mg/mL by HPLC. This information was used as the basis for additional formulation development studies.

2. Preservatives

Preservative effectiveness studies were conducted to identify a suitable preservative for the GHB liquid formulation. The following formulations shown in Table 5 were prepared and tested using *Staphylococcus aureus* (ATCC #6538), *Pseudomonas aeruginosa* (ATCC #9027) and *Aspergillus niger* (ATCC #16404).

TABLE 5

Liquid Formulations Used in Preservative Effectiveness Testing

Formulation	pH	Sodium Benzoate	Methylparaben Propylparaben	Potassium Sorbate	Control
1	3	X			
2	5	X			
3	7	X			
4	3		X		
5	5		X		
6	7		X		
7	3			X	
8	5			X	
9	7			X	
10	3				X
11	5				X
12	7				X
13	no pH adjustment				X

The preservative used in each formulation is marked with an X. The results showed that formulations #3, 4, 6 and 9 reduced all three challenge microorganisms by >99.99% in 48 h of contact time. Formulations #1, 5 and 7 reduced all three challenge microorganism by >99.99% in 7 days of contact time. Formulations #2, 8, 10, 11, 12 and 13 did not reduce *Aspergillus niger* mold to >99.99%, although some reduction occurred in 7 days of contact time. Controls #10, 11, 12 and 13 demonstrated activity against *Pseudomonas aeruginosa.*

3. Stability

Based on the results of the preservative effectiveness testing, five formulations were selected for stability testing. Table 6 shows the composition of the formulations.

TABLE 6

Liquid Formulations Used in Informal Stability Program

Chemical	1	2	3	4	5
Potassium Sorbate	0.4 gm	0.4 gm			
Sodium Benzoate			1.0 gm		
Methylparaben				0.36 gm	0.36 gm
Propylparaben				0.04 gm	0.04 gm
GHB	30 gm	30 gm	30 gm	30 gm	30 gm
Xylitol	40 gm	40 gm	40 gm	40 gm	40 gm
Water q.s.	200 mL	200 mL	200 mL	200 mL	200 mL
Initial pH	8.68	8.68	9.30	7.75	7.75
Formulation Adjusted pH	3.01	5.00	3.00	2.98	4.98

The formulations were packaged in 125 mL, amber PET bottles with safety lined child-resistant caps and stored upright and inverted at 60° C., 40° C./75% relative humidity (RH) and 25° C./60% relative humidity. Samples were removed from the stability chambers after 1, 2 and 3 months and assayed by high performance liquid chromatography (HPLC) for GHB content. Appearance and pH were also monitored.

Table 7 shows the results for the 3 month time point. Samples stored at 60° C. changed color but samples at all other conditions remained unchanged in color.

The pH of all formulations migrated upward over the three month stability period at 60° C. The percent increase in pH from initial to 3 months, was greater for the formulations which were initially adjusted to lower values.

For example, the migration of pH in formulations 1, 3 and 4 (adjusted down to pH 3) were 21-30 percent across all conditions in three months. The migration of pH in formulations 2 and 5 (adjusted down to pH 5) were 4.2-12 percent across all conditions in 3 months. Maintenance of pH becomes important for long term storage since preservatives are known to degrade in formulations having pH levels above approximately pH 6.

Additionally, development of flavor systems to mask the negative taste of preservatives is difficult.

TABLE 7

Results of Liquid Formulation Informal Stability Study at Three Months

Formulation # (See Table 6)	Attribute	25° C./60% RH Upright	25° C./60% RH Inverted	40° C./75% RH Upright	40° C./75% RH Inverted	60° C. Upright
1	% t = 0	100.7	101.6	101.2	NA	NA
Potassium	pH	3.63	3.64	3.84	3.82	3.91
Sorbate (pH3) at 3 months storage	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light yellow
2	% t = 0*	102.1	105.0	104.0	102.0	99.6
Potassium	pH	5.21	5.28	5.55	5.56	5.61
Sorbate (pH5)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light brown
3	% t = 0	102.4	104.1	99.1	102.6	97.0
Sodium	pH	3.60	3.74	3.78	3.75	3.79
Benzoate (pH3)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, colorless
4	% t = 0	101.5	102.7	100.6	101.2	93.7
4 Methyl &	pH	3.63	3.71	3.81	3.80	3.83
Propyl Parabens (pH3)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, colorless
5	% t = 0	103.1	105.8	101.9	103.1	95.6
4 methyl &	pH	5.22	5.55	5.55	5.56	5.60
Propyl Parabens (pH5)	Appearance	clear, colorless	clear, colorless	clear, colorless	clear, colorless	clear, light yellow

*% GHB at t = 0 percent of label claim

**initial time (t = 0)

4. Liquid Formulation Organoleptic Testing

Based on the above stability data and preservative effectiveness testing, a pH 5 formulation containing potassium sorbate was selected as the primary base formulation for flavor system development and organoleptic testing. A pH 3 formulation containing potassium sarbate was selected as the back-up formulation.

B. Dry Powder Formulation Development

Developing a flavor system for the primary and back-up liquid formulations proved to be difficult and a decision was made to develop a dry powder formulation for reconstitution with water before consumption. This approach removed the need for a preservative system, the requirement to adjust pH to levels below pH 6, and allowed the development of a suitable flavor system.

1. Dry Powder Formulation Organoleptic Testing

To develop a flavor system for the powder formulation, several parameters were evaluated. The flavor attributes of a GHB solution was characterized by a professional sensory panel. A mimic base containing similar sensory properties as a GHB solution for flavor system was developed. Generally Recognized As Safe (GRAS) excipients for flavor system development were selected. Different excipients (flavorings, sweeteners, acidulants and flow agents) in the mimic base were screened. Three flavor systems for the focus group test were selected. A preferred flavor system was optimized based on comments obtained from the focus group testing. This final formulation with GHB was optimized.

Based on the above activities, the following formulations in Table 8 were selected for stability studies:

TABLE 8

Composition of Prototype Dry Powder Formulation

Ingredient	Composition (grams)	Purpose
GHB	3	Active
Xylitol	5.5	non-cariogenic sweetener
Malic acid	0.2	Acidulant

TABLE 8-continued

Composition of Prototype Dry Powder Formulation

Ingredient	Composition (grams)	Purpose
Flavor 1	0.2	Flavor ingredient
Flavor 2	0.04	Flavor ingredient
Silicon Dioxide (Cab-O-Sil ®)	0.03	Flow enhancer

2. Dry Powder Formulation Stability

A study was initiated to evaluate the stability of the above prototype formulation in two types of foil packages (high and moderate moisture resistant) as well as the stability of GHB alone in one type of foil package (high moisture resistant). Table 9 shows the Lots that were placed on stability. The foil packages were a high moisture resistant pouch and a moderate moisture resistant pouch. The study protocol, Table 10, required the samples to be stored at 40±2° C./75±5% relative humidity for six months, and 25±2° C./60±5% relative humidity for 12 months. Table 11 shows the tests, methods, number of packets/test and specifications for the study.

TABLE 9

Dry Powder Informal Stability Study Package Composition

Lot Number	Manufacture Date	Package Configuration	Special Comments
SPO #8018 A	Oct. 06, 1995	Foil Packet	Moderate moisture resistant pouch.
SPO #8018 B	Oct. 06, 1995	Foil Packet	Highest moisture protection pouch.
SPO #8018 C	Oct. 06, 1995	Foil Packet	Drug substance only. Highest moisture protection pouch.

TABLE 10

Dry Powder Informal Stability Study Protocol

	Stability Time in Months						
Storage Conditions	0	1	2	3	6	9	12
40 ± 2° C./75% ± 5% RH		X	X	X	X		
25 ± 2° C./60% ± 5% RH	X	X	C	C	R	R	R

X = Samples to be tested
C = Contingency Samples
R = Reduced testing; assay and H_2O only
RH = Relative Humidity

TABLE 11

Dry Powder Informal Stability Tests and Specifications

Test	Method	Packets/Test	Specification Limits
Appearance Dry Material	Visual	Use HPLC	White to off-white free flowing powder
Appearance Reconstituted Material	Visual	Use HPLC	Cloudy, off-white solution with visible particulates
Rate of Dissolution	Visual	Use HPLC	Material should dissolve completely in five min with mixing
Odor	Olfactory	Use HPLC	Characteristic Lemon/Lime odor
Assay: GHB	HPLC	3	90.0%-110.0%
Assay: Malic Acid	HPLC	Use HPLC	90.0%-110.0%
Impurities/ Degradants	HPLC	Use HPLC	Not more than 1% for any individual impurity/degradant and Not more than 3% total impurity/degradants
Vacuum Leak test	Visual	3	No Appearance of Leaking
pH	USP <791>	Use HPLC	For Information
Moisture	Karl Fisher	3	Report Value - to be determined

After two months at 40±2° C./75±5% relative humidity, the potency (% label claim) of Lots SPO SO ISA and SPO 80188 was less than 94.0%, the lower limit of the specification, whereas Lot SPO 8018C showed no loss in potency. Lots 8018A and 8018B showed approximately 96% potencies after 2 months at 25° C.±2° C./65%±5% relative humidity. Lot SPO 8018C again showed no loss in potency at this lower storage condition.

3. Appearance

After 2 months at 40±2° C./75±5% relative humidity, Lots SPO 8018A and SPO 8018B showed significant melting, whereas Lot 8018C showed no melting. Lots SPO 8018A and SPO 8018B also showed partial melting after 2 months at 25° C.±2° C./65%±5% relative humidity. Lot SPO 8018C again showed no evidence of melting at this lower storage condition.

Based on the physical changes in state observed during the stability studies, it was apparent that a solid state interaction between GHB and the excipient blend had occurred. Since xylitol made up the majority of the excipient blend, it was assumed that xylitol was the primary source of the drug-excipient interaction. An alternative hypothesis was also proposed, based on the possibility that the package was mediating the interaction between GHB and xylitol. Three studies were initiated to test these hypotheses.

4. Stability of GHB Solids in a Set Container-System

In the first study, the samples that were stored at 25±2° C./60±5% relative humidity were transferred to glass vials and then stored at 40±2° CI7±5% relative humidity. In the second study, mixtures of GHB and xylitol were gently rubbed between sheets of different types of foil packaging. The mixtures were observed for changes in physical appearance. In the third study, different mixtures of GHB and xylitol were prepared. Differential Scanning calorimetry (DSC) thermograms were then done to look for changes in the thermograms. The results of these studies are summarized below.

Transfer to Glass: Samples of Lot 8018A and Lot 8018C that were previously stored at 25±2° C./60±5% relative humidity were transferred to amber screw cap vials and stored at 40±2° C./75±5% relative humidity. Analyses similar to those shown in Table 6 were done. After 1 month, the potency of Lot 8018A was 94.6% whereas the potency of Lot 8018C (GHB only) was 100%. In addition, Lot 8018A also showed evidence of melting. The results supported the hypothesis that GHB and xylitol were interacting in the solid state and the interaction appeared to be independent of packaging.

Foil Study: Mixtures of GHB and xylitol were placed between folded sheets of several different foil packaging materials. Slight adhesion of the mixed granules with the foil lining was observed for all of the foils examined. No direct evidence of melting was observed, however, even when excessive force was applied to the outer foil surfaces. This data suggests that the packaging material was not responsible for the solid state interaction observed during the stability studies.

DSC thermographs were obtained for samples of GHB/xylitol containing GHB:xylitol mixtures of 33:66, 45:55 and 55 percent 45 respectively. The scans were conducted at a scan rate of 10° C./min. The thermograms showed that the sample containing GHB:xylitol 33:66 showed a broad endothermic transition starting at 35° C.-40° C. Samples with higher ratios of GHB:xylitol also showed broad endothermic transitions that started at temperatures of 45° C.-50° C. The changes seen in the thermograms supported the hypothesis that a solid state interaction may be occurring between GHB and. xylitol that resulted in low potencies for formulations containing mixtures of these two agents.

As a result of the changes seen in the DSC thermograms for different mixtures of GHB:xylitol, a study was initiated to investigate the stability of a formulation containing GHB:xylitol excipient blend 55:45. A formulation containing GHB:xylitol excipient blend 33:66 was used as a control sample. The formulations were packaged in glass vials and stored at 50° C., 40±2° C./75±5% relative humidity and 25±2° C./60±5% relative humidity. The appearance and potency of the formulations were monitored through analyses of. stability samples. The stability study also showed potency losses after 1 month at 40° C.±2° C./75±5% relative humidity with both the 50/50 GHB:xylitol ratio as well as the original 33/66 ratio formulation. Partial evidence of melting was also observed in both formulations.

Studies with mixtures of GHB:xylitol excipient blend indicated that the mixture was incompatible in the solid state. However, when prepared as an aqueous solution, these mixtures were chemically compatible. Using this information, a decision was made to package the GHB formulation in dual pouches; one pouch containing GHB alone and the other containing a mixture of xylitol and the other flavor ingredients. The formulation wiH contain equal amounts of GHB and the excipient blend. This product will be prepared, packaged, and may be checked for stability.

EXAMPLE 3

The Pharmacokinetics of Gamma-Hydroxybutyrate

I. Study Objectives

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; patients generally ingested the first dose of this medication prior to bedtime and the second dose from 2.5 to 4.0 h later) to narcoleptic patients who are maintained on a chronic regimen of GHB.

II. Study Design

This pharmacokinetic study was conducted as an open-label, single-center investigation in 6 narcoleptic patients. The study design is summarized as follows:

TABLE 12

Screening/Washout⇒	Treatment/Blood Sampling⇒	Follow-up
(1 or more days to dosing; washout, at least 8 h	(Two 3 g GHB oral doses, 4 h apart; 21 blood samples)	(Within 48 h after last blood sample)

Narcoleptic patients, 18 years of age or older, who volunteered for this study were screened at least one day prior to the treatment phase. Each patient was determined to be in stable health and evaluated for the presence of narcolepsy, defined for the purposes of this example as one or more years of medical history of narcolepsy as evidenced by a recent nocturnal polysomnogram (PSG) and a valid score from a Muhiple Sleep Latency Test (MSLT).

Patients maintained on GHB were allowed to participate. These patients had been weaned from antidepressants, hypnotics, sedatives, antihistamines, clonidine, and anticonvulsants though a stable regimen of methylphenidate (immediate release or sustained release) was allowed. Each patient passed a pre-study physical examination (which included hematology, blood chemistry, urinalysis, and vital signs measurements) prior to the commencement of the treatment phase.

Before oral administration of the first GHB dose, an indwelling catheter was placed in an arm vein and a baseline blood sample was collected. Each patient then ingested a 3 g dose of GHB before bedtime. Another 3 g GHB dose was administered 4 h after the first dose. Twenty-one sequential blood samples were collected over 12 h (starting at 10 min after the first dose and ending at 8 h after the second dose). Upon completion of the treatment phase, a follow-up physical examination which included the measurement of vital signs was performed on each patient within 48 h after the last blood sample. A detailed description of the trial methodology is presented in Section IV.

III. Inclusion Criteria

Patients were included in the study if they: had signed an informed consent prior to beginning protocol required procedures; had not participated in such a study at an earlier date; were willing and able to complete the entire study as described in the protocol; were 18 years of age or older at study entry; had not taken any investigational therapy other than GHB within the 30-day period prior to screening for this study; had an established diagnosis of narcolepsy for at least one year with documentation from a qualified laboratory by a nocturnal polysomnogram (PSG) and a Multiple Sleep Latency Test (MSLT) which demonstrated mean sleep latency to be less than 5 min and REM onset in at least 2 of 5 naps; had not been diagnosed with uncontrolled sleep apnea syndrome, defined as a sleep Apnea Index of 5 or an Apnea Hypopnea Index (AHI) greater than 10 per hour or any other cause of daytime sleepiness; and were free of any medication for their narcolepsy (including hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants) other than GHB and methylphenidate (IR or SR). Patients admitted to this study if they were not experiencing unstable cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, metabolic, neurological, pulmonary, and/or renal disease which would place them at risk during the study or compromise the protocol objective; did not have neurological or psychiatric disorders (including transient ischemic attacks, epilepsy, or multiple sclerosis) which, in the investigator's opinion, would preclude the patients' participation and completion of this study; did not have a current or recent (within one year) history of alcohol or drug abuse; did not have a serum creatinine greater than 2.0 mg/dL, abnormal liver function tests (SGOT or SGPT more than twice the upper limit of normal or serum bilirubin more than 1.5 times normal). Female patients were entered into the study if they were either post-menopausal (i.e. no menstrual period for a minimum of 6 months), surgically sterilized or provided evidence of effective birth control. Females of childbearing potential must agree to continue to use an IUD, diaphragm, or take their oral contraceptives for the duration of the study. Female patients of childbearing potential must have a negative pregnancy lest upon entry into the study.

IV. Trial Methodology

A time and events schedule is presented in Table 12.

A. Screening Period/Washout

Six narcoleptic patients who were chronically being treated with GHB were recruited to participate in this pharmacokinetic study. The screening period was at least one day prior to the treatment phase. During the screening period each patient completed the following procedures for the assessment of their physical condition: medical history evaluation; physical examination evaluation; clinical laboratory evaluation; inclusion criteria review. Each patient's GHB and methylphenidate regimen also were recorded on an appropriate case report form (CRF). The investigator also ensured that there was at least an 8-hour washout period for GHB prior to the treatment.

B. Treatment Period/Blood Samples Collection

All patients were hospitalized from approximately four hours prior to first GHB dosing (around 6 p.m.) until the end of the treatment period (around 10 a.m. the next morning). Patients ate their dinner at the clinical research unit soon after arrival and fasted until breakfast next morning. At least three hours elapsed between the completion of dinner and the administration of the first GHB dose. An indwelling catheter was placed in an arm vein of each patient for blood sampling at approximately 30 min and 1 h before the first GHB dose and a baseline blood sample (5 mL) was collected.

The first GHB dose (3 g) was administered at around 10 p.m. Dosing of individual patients were staggered. The second GHB dose was administered at 4 h after the first GHB dose (i.e. immediately after the 4 h blood sample). The exact dosing times in each patient were recorded on appropriate CRF pages. Blood samples (5 mL each) were collected through the indwelling catheter into heparinized tubes at 0.2, 0.4, 0.6, 0.8, 1, 1.5, 2, 3, 4, 4.2, 4.4, 4.6, 4, 8, 5, 5.5, 5, 7, 8, 10, and 12 h after the first GHB dose. Blood samples were processed according to the procedures described herein. Patients were monitored for adverse experiences throughout the study according to the specific procedures.

C. Follow-Up

Follow-up occurred within 48 h after the last blood sample had been collected. An abbreviated physical examination which included vital signs measurement was performed. Adverse experiences and concomitant medication use, if any, were assessed. Any ongoing adverse experiences and clinically important findings in a patient were followed to the investigator's and/or sponsor's satisfaction before the patient was discharged from the study.

D. Methods of Assessment

1. Medical History

The medical history was recorded during the screening period. The history included gender, age, race, height, prior reaction to drugs, use of alcohol and tobacco, history and treatment, if any, of cardiovascular pulmonary, gastrointestinal, hepatic, renal, immunologic, neurological, or psychiatric diseases and confirmation of inclusion criteria.

2. Physical Examination

Physical Examination included body system review as well as measurement of body weight and vital signs and a neurological examination.

3. Vital Signs

Vital signs measurements included recording of blood pressure, heart rate, respiration, and body temperature.

4. Clinical Laboratory

All clinical laboratory tests were performed at a local laboratory. The laboratory tests and analysis were required of each patient included: hematology, including hemoglobin, hematocrit, red blood cell count, white blood cell count and differential; fasting blood chemistries included blood urea nitrogen (BUN), uric acid, glucose, creatinine, calcium, phosphorus, total protein, albumin, sodium. potassium, SCOT (AST), SGPT (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), and total bilirubin; midstream catch urinalysis included specific gravity, pH, protein, occult blood, ketones and glucose by dipstick determination as well as a microscopic examination of urine sediment for RBC, WBC, epithelial cells or casts or crystals; and a urine pregnancy test. if applicable. Any laboratory parameter that was out of range and considered clinically significant excluded the patient from participation in this study. The investigator would provide an explanation of all observations that were significantly outside the reference range.

5. Concomitant Medication

The continued use of a fixed dose of methylphenidate immediate release or sustained release (IR or SR) is acceptable. The methylphenidate regimen was recorded on the appropriate case report form.

6. Adverse Experiences

An adverse experience are any undesirable event experienced by a patient or volunteer whether or not considered drug-related by the investigator. An undesirable event can be, but is not limited to, subjective symptoms experienced by a patient or, objective findings such as significant clinical laboratory abnormalities. Adverse experience is considered synonymous with the term "adverse event".

The investigators report in detail all adverse experiences and symptoms that occurred during or following the course of trial drug administration for up to 2 days. Included in the description was the nature of the sign or symptom; the date of onset; date or resolution (duration); the severity; the relationship to trial treatment or other therapy; the action taken, if any; and the outcome.

A serious adverse experience is defined as one that is fatal, life threatening, permanently disabling, or which results in or prolongs hospitalization. In addition, overdose, congenital anomaly and occurrences of malignancy are always considered to be serious adverse experiences. An unexpected adverse experience is one not previously reported.

Any serious or unexpected adverse experience (including death) due to any cause which occurs during the course of this investigation, whether or not it is related to the investigational drug, was reported within 24 h by telephone or facsimile. Appropriate authorities were to be informed if the serious or unexpected adverse experience, in the opinion of inventors, was likely to affect the safety of other patients or volunteers or the conduct of the trial.

7. Clinical Supplies-Study Medication

Formulation: Unit 3 g GHB doses (Lot PK1) were obtained from Orphan Medical. Each unit dose comprised twin foil pouches: one pouch containing GHB and the other containing a flavor excipient blend. (Table 8 formulation)

Labeling: The clinical supplies for individual patients were packaged in separate containers. Each container included two unit doses, i.e. two twin-pouches. Clinical supplies for eight patients (including those for two replacement patients) were delivered to the investigator. Foil twin-pouches were identified with a two-part label.

Dose Administration: The investigator or designee prepared the oral solution for dosing within 30 min prior to the first oral administration to individual patients. The contents of one twin-pouch was emptied into a dosing cup to which, two ounces of water were added. After replacing the lid of the dosing cup, it 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 ingesting in its entirety at 4 h after the first GHB dose.

Investigational Drug Accountability: At the conclusion of the study, all clinical supplies were accounted for on the drug accountability form and unused drug supplies were returned for proper disposition.

8. Determination of Plasma GHB Concentrations

Plasma samples were analyzed for GHB by the Department of Bioanalytical Chemistry (Covance (previously known as Hazelton Coming), Madison, Wis.) A gas chromatographic method with mass selective detection (GC-MSD) was used in the analysis.

9. Data Management and Analysis

Data Base: An EXCEL data base (spreadsheet) was constructed from data recorded on Case Report Forms (CRF) and plasma GHB concentration data sets received from Covance (Corning Hazleton). Each entry in the EXCEL spreadsheet was checked against the CRFs and any data entry error found was corrected.

Pharmacokinetic Analysis: Pharmacokinetic parameters were determined for individual sets of plasma GHB concentration vs. time data using the non-compartmental routine in WinNonlin Version 1.1. The peak GHB concentrations (C_{max}) and the times of their respectively occurrences (t_{max}) were observed values. Terminal half-life ($T_{1/2}$) was obtained by log-linear regression analysis of the terminal phase of concentration vs. time curves. The area under the curve (AUC_{inf}) and the area under the first moment curve ($AUMC_{inf}$) were calculated by the linear trapezoidal rule up to the last determined concentration and included extrapolated areas to time infinity. Apparent oral clearance (CL/F) was calculated as Dose/AUC_{inf}. Volume of distribution (V_z/F) was determined by taking the ratio between CL/F and λ_z (elimination rate constant). Mean residence time (MRT) was estimated from the ratio between $AUMC_{inf}$ and AUC_{inf}.

Safety Analyses: Results of physical examinations, vital signs, clinical laboratory data were summarized in tabular form and presented by patient number. Adverse events also were tabulated in a similar fashion.

10. Results

Patient and Study Accountability: Six narcoleptic patients were enrolled and all six completed the study in its entirety.

Protocol Compliance: There were no inclusion criteria violations. All patients admitted into the study met the study

entrance requirements and completed the screening phase at least one day before the treatment phase.

All six patients took non-study medications in addition to methylphenidate and GHB doses because none of their concomitant medications (Synthroid, Premarin, Lovastatin, Fluvastatin, furosemide, potassium, hydrochlorothiazide, lansoprazole, and verapamil) were on the exclusion list (which included hypnotics, sedatives, antidepressants, antihistamines, clonidine, and anticonvulsants). Adverse experience probes, vital sign measurements, and essentially all pharmacokinetic blood samples were performed at protocol specified times; the few deviations in blood sampling times should not have any impact on the outcome of the study since actual blood sampling times were used in the pharmacokinetic analysis.

The diagnosis of narcolepsy for at least one year in each patient was verified by a nocturnal polysomnogram (NSG) and a Multiple Sleep Latency Test (MSLT) conducted at a qualified laboratory. Five patients have been maintained on GHB nightly for over 10 years and one patient has been receiving GHB nightly for two years. One patient (Subject 101) also had multiple sclerosis; however, the attending physician, judged that it would not interfere with the objective of this study. A few of the screening clinical laboratory results marginally fell outside the reference range but none was considered by the attending physician to be clinically significant.

Exposure to Study Drug: All patients ingested the two GHB doses as scheduled (immediately prior to bedtime). The GHB doses per kg body weight ranged from 26.4 to 52.4 mg/kg.

Plasma GHB Concentration Profiles: It was noted that, in certain cases, (Patients #103, and #106), plasma GHB concentrations did not decline from the first C_{max} to zero concentration at h 4. Upon achievement of the second C_{max} the semi-logarithmic plots of concentration versus time data in Patients #102, #103, and #105 exhibited a convex decline profile. Such a decline pattern suggested non-linear pharmacokinetics. The highest plasma GHB concentration observed in the study was 125.0 μg/mL which occurred in Subject 101 after the second 3 g GHB dose.

Pharmacokinetic Parameter Estimates: The mean (±SD) showed that maximum GHB concentrations (C_{max}) were 62.8±27.4 μg/mL and 91.2±25.6 μg/mL for the first and second GHB doses, respectively. The corresponding mean observed times to maximum concentrations were 40±6 and 36±7 min after the first and second GHB doses, respectively. The mean AUC_{inf} was 17732±4603 μg/mL·h. The mean CL/F was 4.2±mL/min/kg and the mean V_z/F was 307±96 mL/kg. The mean MRT_{inf} was 249±56 min. The mean GHB $T_{1/2}$, estimated by linear regression of log [C] vs. time data of the terminal phase of the second GHB dose was 53±19 min.

Adverse Experiences: No adverse experiences were reported in the study.

Follow-up Safety Assessments: Inspection of screen and follow-up physical examination results per individual patient did not identify any changes attributable to GHB.

11. Discussion

To the inventors' knowledge, the level of GHB in human systemic circulation has not been reported in the literature. Hence, baseline (0 h) plasma samples were analyzed for GHB concentrations. The GC-MSD method used in the present study had a limit of quantification (LOQ) of 7.02 μg/mL and analysis of the baseline plasma samples showed the endogenous levels of GHB are below this sensitivity limit. This finding was confirmed by adding known amounts of GHB (5, 10, and 25 μg per mL of plasma) to blank human plasma samples and subjected these samples to GC-MSD analysis. This method of standard addition allowed an estimation of the endogenous GHB level in human plasma which was found to average about 2.02 μg/mL, (i.e. approximately ⅔ of the Limit Of Quantitation (LOQ) for a validated assay. Hence, the endogenous GHB level was not subtracted from exogenous GHB concentrations prior to pharmacokinetic analysis.

Values of mean t_{max} (~40 min after dosing) and $t_{1/2}$ (~35 min) suggest that the GHB solution administered to narcoleptic patients in this study was readily absorbed and rapidly eliminated. In 3 out of 6 patients the drug was essentially gone from the systemic circulation by h 4 after the first GHB dose whereas in the remaining three patients residual GHB levels of ~15 μg/mL was still detected at h 4.

The convex nature of the decline of plasma GHB concentrations in three patients after achievement of the second c_{max} indicated that elimination of GHB from the systemic circulation in these three patients is capacity limited. Nevertheless, it should be noted that plasma GHB concentrations were no longer detectable by h 6 after the second GHB dose (10 h after the first GHB dose). The mean apparent oral clearance found in this study was 4.2±1.0 mL/min/kg and appeared to be comparable to the apparent oral clearance of 5.3±2.2 mL/min/kg reported in the literature for a group of alcohol dependent patients who were administered a dose of 50 mg/kg (Ferrara, 1992). While it appeared that the GHB dose (ranging from 26.4 to 52.4 mg/kg with a mean of 36.5 mg/kg) in the present study was lower than the comparison GHB dose (50 mg/kg) administered to the alcohol dependent patients (Ferrara, 1992), it should be noted that each patient in the present study was administered two consecutive GHB doses at four-hour interval and residual GHB levels were detected in three out of six patients immediately prior to the second GHB dose. The GHB pharmacokinetic non-linearity in alcohol dependent patients easily can be observed from the apparent oral clearance which increased to 8.1±4.8 mL/min/kg when the GHB dose is reduced to 25 mg/kg dose (Ferrara, 1992). In the present study, the non-linearity was less obvious because each narcoleptic patient received two consecutive fixed 3 g doses regardless of body weight.

The mean elimination half-life of GHB in the six narcoleptic patients was determined to be 53±19 min, longer than that in alcohol dependent patients after a 50 mg/kg GHB dose (Ferrara, 1992). The lengthening of GHB elimination half-life observed in this study partially was caused by the wider spacing in sampling time points. However, capacity limited elimination of this drug in some of the narcoleptic patients also could have contributed to this prolongation.

GHB appears to have a shortcoming in that its elimination from the body is capacity limited in some patients when the drug is administered at a fixed regimen of 3 g twice nightly at four-hour interval. However, from a therapeutic perspective, GHB offers an advantage in the treatment of narcolepsy because by the time a patient wakes tip in the morning (i.e. 8 to 10 h after the fltst GHB dose), all GHB, including that from the second dose, will have been eliminated from the systemic circulation. GHB was also well tolerated by narcoleptic patients in this study. No adverse experience was reported.

12. Conclusions

The capacity limited elimination kinetics was observed in three out of six patients who had been administered two consecutive 3 g oral doses of GHB, 4 h apart. From a pharmacokinetic perspective, dividing the nightly GHB dose into two portions and administering the two portions to narcoleptic patients at a 2.5- to 4-h interval was rational because the elimination half-life of GHB was short (<1 h). The pharmacokinetic profiles of GHB in narcoleptic patients who had

been receiving this agent nightly for years appeared to be comparable to those in alcohol dependent patients (Ferrara, 1992).

EXAMPLE 4

Sodium Oxybate Formulation Study

I. Study Objectives

This example described ways that sodium oxybate may be prepared and tested for stability to determine preferred formulations. Various formulations of sodium oxybate in water were prepared under different conditions of mixing and with addition of selected acidulents at multiple pH levels (Neo-Pharm Laboratories, Blainville, Quebec). Selected formulations were placed on real time and accelerated stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high pH. Therefore several acidulents across a range of 6.0-9.0 were evaluated.

II. Study Design-Part I

The following experimental work is designed to be performed in two stages. Initial studies were conducted to evaluate the impact of conditions of formulation, pH and acidulent on the resultant levels of impurities, specified and unspecified, and potency of sodium oxybate. Sodium oxybate was prepared (MDS Neo-Pharm Laboratories, Quebec Canada), under different conditions of mixing and with addition of selected acidulents at multiple pH levels. These formulations of sodium oxybate acidulent were then tested.

A. Preliminary Studies

1. Formulations Description

All formulations were prepared at a concentration of 500 mg/cc of sodium oxybate in water. Three acidulents (HCl, malic acid, and phosphoric acid), were selected and tested at pH 6.0, 7.5 and 9.0.

2. Method of Formulation

Solutions, were prepared using the described methods:

a. Rapid Mix Method:

Sodium oxybate was dissolved in water and concentrated acidulent was added immediately, without temperature control. Temperature of solution was monitored and recorded prior to and during addition of acidulent. The time of equilibration to room temperature was also recorded. After the solution reached ambient room temperature, it was filtered through a 10 μm filter.

b. Cool Mix Method:

Sodium oxybate was dissolved in water. Acidulent was diluted to 10% and slowly added. The solution was cooled by water with jacket or ice bath. Monitor and record the temperature of the solution was monitored and recorded during addition of acidulent. The time of equilibrium from room temperature was also recorded. The preferred maximum temperature should be maintained at less than 40° C. The solution was filtered through a 10 μm filter.

c. Reverse Order of Addition:

Acidulent was added to water and cooled to room temperature. The sodium oxybate was dissolved in the diluted acidulent solution. The temperature of solution was monitored and recorded during addition of sodium oxybate. The solution was filtered through a 10 μm filter.

d. Sodium Oxybate Control:

Sodium oxybate was dissolved in water to a concentration of 500 mg/cc with no added acidulent. The final pH was recorded and the solution was filtered through a 10 μm (micron or micrometer) filter.

3. Solution Data:

Data was recorded for each solution which included: 1) date of preparation 2) date of analysis, 3) amount of acidulent required to achieve target pH, 4) length of time for dissolution of sodium oxybate, 5) temperature profile of solution over time of solution preparation to be recorded at 15 minute intervals, 6) final pH of solution.

4. Testing Requirements:

The following methods were used to test the prepared solutions: pH, HPLC (High Pressure Liquid Chromatography) for potency (sodium oxybate), and for impurities. Time 0 analysis was performed immediately (within 24 h). RRT= (relative retention time).

B. Summary of Part I:

1. Preliminary Evaluation of Sodium Oxybate Formulations

Tables 13, 14 and 15 provide test results for the three methods of preparation of sodium oxybate formulations.

Formulation Study/PR98068

Results of Formulation Study—Time Zero Determinations of Sodium Oxybate, GBL and Unspecified Impurities

TABLE 13

Preparation Method A					
Addition of Concentrated Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/cc % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (Apr. 23, 1998)	pH 9.0	9.0	509 mg/cc 101%	0.009%	RRT 4.88 = 0.01%
(10 drops over 2 minutes)					
(2.5 ml/4 minutes)	pH 7.5	7.5	507 mg/cc 101%	0.01%	RRT 4.89 = 0.02%
(45 ml/34 minutes)	pH 6.0	6.0	504 mg/cc 101%	0.033%	RRT 4.89 = 0.33%
Malic Acid (Apr. 24, 1998)	pH 9.0	9.1	498 mg/cc 99.6%	0.009%	RRT 4.89 = 0.01%
(0.12 gm)					
(1.6 gm)	pH 7.5	7.6	506 mg/cc 101%	0.009%	RRT 4.89 = 0.01%
(25 gm)	pH 6.0	6.2	493 mg/cc 98.6%	0.011%	RRT 4.89 = 0.01%
H_3PO_4 (Apr. 24, 1998)	pH 9.0	9.0	493 mg/cc 98.6%	0.009%	RRT 4.89 = 0.01%
(2 drops)					

TABLE 13-continued

Preparation Method A

Addition of Concentrated Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/cc % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
(1.0 ml)	pH 7.5	7.5	493 mg/cc 98.6%	0.009%	RRT 4.89 = 0.02%
(17.3 ml)	pH 6.0	6.1	497 mg/cc 99.4%	0.063%	RRT 4.89 = 0.02%
Sodium Oxybate Control No Acidulent	n.a.	9.8	500 mg/cc 100%	0.009%	RRT 4.89 = 0.04%

*Method A = Mix with Concentrated Acidulent and Temperature Monitoring

TABLE 14

Preparation Method B

Addition of Diluted Acidulent* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (25%) (Apr. 28, 1998) (20 drops)	pH 9.0	9.1	500 mg/cc 100%	0.009%	RRT 4.88 = 0.01%
(8.0 ml)	pH 7.5	7.6	499 mg/cc 99.8%	0.009%	RRT 4.88 = 0.01%
(175 ml)	pH 6.0	6.0	502 mg/cc 101%	0.016%	RRT 4.88 = 0.02%
H_3PO_4 (25%) (Apr. 29, 1998) (0.3 ml)	pH 9.0	8.9	499 mg/cc 99.8%	0.007%	RRT 4.92 = 0.02%
(4.0 ml)	pH 7.5	7.5	497 mg/cc 99.4%	0.008%	RRT 4.89 = 0.02%
(120 ml)	pH 6.0	6.0	499 mg/cc 99.8%	0.019%	RRT 4.89 = 0.01%
Malic Acid (500 mg/cc) (Apr. 30, 1998) (0.115 gm/0.23 ml)	pH 9.0	9.0	495 mg/cc 99%	0.008%	RRT 4.92 = 0.02%
(1.75 gm/3.5 ml)	pH 7.5	7.4	488 mg/cc 97.5%	0.009%	RRT 4.92 = 0.01%
(35 gm/70 ml)	pH 6.0	6.0	487 mg/cc 97.0%	0.013%	RRT 4.92 = 0.01%

*Acidulent added slowly at the rate of 2-3 drops/second

TABLE 15

Preparation Method C

Reverse Order of Addition* (Amount of Acidulent in 1000 ml) Date of Preparation/Date of Assay [Specification]	Target pH [Target ± 0.5]	Final pH	Sodium Oxybate mg/ml % [95-105%]	Impurities Specified % GBL [≦0.5%]	Impurities Unspecified % [≦0.1% Total]
HCl (May 1, 1998) (20 drops)	pH 9.0	9.0	497 mg/cc 99.4%	0.006%	RRT 4.92 = 0.03%
(2.4 ml)	pH 7.5	7.6	504 mg/cc 101%	0.004%	RRT 4.92 = 0.04%
(45 ml)	pH 6.0	6.0	493 mg/cc 98.6%	0.044%	RRT 4.92 = 0.04%
H_3PO_4 (May 4, 1998) (0.08 ml)	pH 9.0	8.9	496 mg/cc 99.2%	0.005%	RRT 4.91 = 0.03%
(1.0 ml)	pH 7.5	7.6	496 mg/cc 99.2%	0.004%	RRT 4.91 = 0.04%
(30 ml)	pH 6.0	6.1	489 mg/cc 97.8%	0.023%	RRT 4.91 = 0.04%
Malic Acid (May 5, 1998) (0.12 gm)	pH 9.0	9.0	495 mg/cc 99%	0.006%	RRT 4.93 = 0.02%
(1.6 gm)	pH 7.5	7.6	497 mg/cc 99.4%	0.004%	RRT 4.93 = 0.04%
(35 gm)	pH 6.0	6.2	495 mg/cc 99%	0.044%	RRT 4.93 = 0.04%

*Acidulent added to water first, GHB added second.

Review of the data indicated that the optimum method for preparation of sodium oxybate with minimal impurity levels is Method B: Controlled mixing with diluted acidulent. Method 2b resulted in formulations with lowest levels of GBL.

2. Conclusions.

Additional evaluations were carried out on selected formulations: 1) sodium oxybate with HCl as acidulent, at pH 7.5, and 2) sodium oxybate with malic acid as acidulent, pH 6.0, 7.5, and 9.0.

III. Study Design-Part II

Microbial Challenge and Stability Tested to determine the most preferred embodiments, the number of formulations was limited to three based on the data prepared from the above experiments.

A. Kinetic Stability Study with Selected Formulations

Samples of formulations are stored in tightly closed containers. Storage Conditions were 25° C., 40° C., and 60° C. Time points in brackets were tested at the inventor's discretion. The samples were tested according to the following schedule: at 25° C. storage temperature, the assay points will be 0, 14, 28, 45, 60 days and 120 days; at 40° C. storage temperature, the assay points will be 0, 7, 14, 28, 45, 60 days; at 60° C. storage temperature, the assay points will be at 0, 3, 7, 14, 28, 45 days, and, 60 days.

The testing requirements included pH, HPLC for sodium oxybate (duplicate injections of single sample preparation), and impurities, specified and unspecified.

B. Preservative Effectiveness Testing of Selected Formulations

Microbial challenge testing of formulations was preformed according to USP XXIII, <51>, Eighth Supplement. Solutions are determined to "Pass or Fail" based upon the USP criteria for preservative effectiveness which states: For Bacteria, "Not less than 1 log reduction from the initial microbial count at 14 days and no increase from the 14 days count at 28 days;" and for yeast and molds, "No increase from the initial calculated count at 14 and 28 days." Solutions which met these criteria were designated as "Pass" and those that did not meet these criteria were designated as "Fail".

C. Summary Stability Results:

1. Formulations Prepared with Malic Acid as Acidulents:

a. Malic Acid, pH 6.0 formulation (25°), GBL and impurity A levels were very low an Day 0, however, by Day 45 GBL levels had reached 2.8%. Impurity A increased from 0.01 to 1.0%, and pH increased from 6.0 to 6.3 by day 45. This formulation stored at 40° C. and 60° C. showed GBL levels up to 5.4%, impurity A levels increased to 2.3%, and pH increased to 6.3 by Day 14.

b. Malic Acid, pH 7.5 formulation (25° C.), GBL levels were 0.009% on Day 0, and increased to 0.17% by day 45. Impurity A increased from 0.01% to 0.1% and pH increased from 7.5 to 7.9. Malic acid, pH 7.5 GBL levels are reached (40° C.) and 60° C. a maximum of 0.22%. Impurity A levels reached 0.1% and pH increased to 8.0. Under accelerated conditions, all parameters reached an apparent maximum by Day 7 and did not increase significantly thereafter.

c. Malic Acid, pH 9.0 formulation (25° C.) GBL levels measure 0.008% on Day 0, and increased slightly to 0.013% on Day 45. Impurity A did not increase nor did pH increase. Under accelerated conditions, GBL increased from 0.008% to a maximum of 0.018% by Day 14. Impurity A increased slightly from 0.10 to 0.014% by Day 14.

2. Formulations Prepared with HCl as Acidulents.

HCl, pH 6.0 formulation (25°) GBL levels measured 2.8% by Day 30, and impurity A 0.004%. and pH 6.0. Accelerated storage conditions (40° C.) GBL levels were measured at 6.6%, and impurity A measured 3.1% by Day 30.

HCl, pH 7.5 formulation (25%) GBL levels measured 0.041% on Day 0, Impurity A measured 0.02%, and by Day 18 GBL measured to 0.12% and impurity A to 0.07%. Under accelerated conditions (40° C. and 60° C.), GBL increased to a maximum of 0.21%, impurity A increased from 0.02% to 0.1%, and pH increased from 7.5 to 8.0. As with Malic Acid at pH 7.5, the measured parameters reached maximum by Day 7 and did not increase significantly thereafter.

HCl, Ph 9.0 formulation (25° C.) GBL levels reached 0.022% by Day 18. Impurity A stayed constant at 0.01% for 18 days. Under accelerated conditions (40° C.) GBL levels were equivalent to 25° C. storage (0.21%). Impurity A showed no increase over 25° C. conditions.

3. Conclusions.

Formulations selected for microbial challenge testing were the following: HCl, Ph 7.5, and malic acid, Ph 7.5. The rationale for this decision was twofold. First, the formulations were selected based on minimal formation of GBL and impurity A. Second, the formulations were selected to maintain a Ph in the neutral range.

EXAMPLE 5

Further Evaluation of Sodium Oxybate Formulations

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of gamma-hydroxybutyrate.

Scope: Various formulations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple Ph levels. Solutions were prepared and tested at Neo-Pharm Laboratories, Blainville, Quebec. All formulations successfully prepared were placed on limited stability. Earlier studies have demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high Ph. Conditions of varying Ph and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Procedures: Solutions were prepared as summarized and microbial challenge testing carried out as follows:

B. Evaluation of Sodium Oxybate Formulations

Purpose: To prepare, test and evaluate multiple formulations of Sodium Oxybate and two formulations using alternative salts of gamma-hydroxybutyrate.

Scope: Various formulations of Sodium Oxybate in water were prepared with addition of selected acidulents at multiple Ph levels. Selected formulations were studied for limited stability. Earlier studies demonstrated that degradation products are formed in acidic conditions and that antimicrobial effectiveness is limited at high Ph. Conditions of varying Ph and concentrations of sodium oxybate previously not evaluated were prepared and tested.

Responsibility: It was the responsibility of Neo-Pharm Laboratories to prepare selected formulations and perform testing per this protocol. Orphan Medical, New Medicine Development and Quality Assurance were responsible for reviewing raw data at the defined decision point, defining which formulations will be included in stability testing. Orphan Medical was also responsible for reviewing final results (raw data) and the final report.

Procedure: The following formulations were prepared by scientists at Neo-Pharm following the steps listed below and dispensed into containers (amber PET 240 ml bottle, OMI

CS-460) and closures (Clic-Loc III, 24-400, OMI CS-470) to a volume of 200 ml each bottle. The bottles were tested by 28-day microbial challenge and by limited stability testing at 25° C. including appearance, Ph, potency, and impurity profile on day 1 (day of preparation) and day 28.

B. Formulations Prepared and Evaluated Using Sodium Oxybate:

TABLE 16

Formulations Prepared and Evaluated Using Sodium Oxybate

Formulation ID No.	Sodium Oxybate Concentration	Acidulent	Final Ph
1	500 mg/cc	Malic Acid	7.5
2	250 mg/cc	Malic Acid	7.5
3	350 mg/cc	Malic Acid	7.5
4	450 mg/cc	Malic Acid	7.5
5	550 mg/cc	Malic Acid	7.5
6	650 mg/cc	Malic Acid	7.5
7	500 mg/cc	Citric Acid	7.5
8	500 mg/cc	Malic Acid	5.0

1. Preparation: Method for Preparation of Various Formulations: As previously determined in PR98068, the method of choice for preparation of liquid formulations of sodium oxybate was the following:
   a. For a one liter quantity of product, add the sodium oxybate in 500 ml of purified and stir until dissolved. Prepare a 10% solution of the acid (Malic or Citric) and add slowly to the solution of sodium oxybate. The solution should be monitored for Ph and temperature and both variables recorded at reasonable intervals (every 10 or 15 minutes). When the target Ph is attained, the solution will be Q. S. to 1 liter and Ph rechecked and recorded.
   b. The final solutions will be filtered through 10 μm filters and 200 Ml dispensed into 5 amber PET bottles with closures (□rovide by Orphan Medical, Inc.). Two bottles will be used for microbial challenge studies and the remaining three bottles will be placed on limited stability.
2. Testing: Formulations were tested by two methods of evaluation:
   a. Limited stability evaluation:
      (1) Storage Conditions: 25° C.
      (2) Pull Points: Day 0 (day of preparation), and day 28
      (3) Testing Requirements:

Test	Method
Appearance	Visual
Potency	HPLC Neopharm 764
Impurities	HPLC Neopharm 793DT
Ph	USP <791>

   b. Microbial challenge:
      (1) Storage Conditions: Microbial challenge studies of above formulations were set up with 5 microorganisms and stored for 28 days at 20-25° C., per USP <51> Eighth Supplement.
      (2) Microorganisms: After a sufficient quantity of each formulation is prepared, aliquots were inoculated with 5 microorganisms at a concentration of at least 10^5 microorganisms/cc:
         (a) *Escherichia coli*, ATCC 8739
         (b) *Pseudomonas aeruginosa*, ATCC 9027
         © *Staphylococcus aureus*, ATCC 6538
         (d) *Aspergillus niger*, ATCC 18404
         (e) *Candida albicans*, ATCC 10231
      (3) Time Points: A determination of the viable cell concentration in each inoculated container was performed after 0, 1, 3, 7, 14, 21 and 28 days.

B. Formulations To Be Prepared From Alternative Salts of Gamma-Hydroxybutyrate: This work may be staged to take place at a later time than the work described above.

TABLE 17

Formulation Detail

Formulation ID No.	Salt of GHB	Concentration of Salt of GHB	Acidultent	Final pH
9	Calcium salt	500 mg/cc (Or maximum possible*)	Malic Acid (If compatible)	7.5

1. Solubility determination: Little information is available about the solubility of this alternative salt of gamma-hydroxybutyrate and a determination of solubility was done in advance of efforts to prepare formulations for evaluation by stability and microbial challenge. Maximum solubility is evaluated for pH unadjusted solutions and within the pH range desired for this formulation (pH 6.0-8.0). If solubility is limited, the formulation will be changed to accommodate the solubility limitations. The preferred acidulent for this work is Malic acid. If acid is not compatible with the salt, then an alternative acid can be selected.
2. Preparation: Method for preparation of alternative salt formulations:
   a. The previously described method (Part A) is used for preparation of formulations of calcium gamma-hydroxybutyrate at the concentrations and specified pH determined by solubility experiments.
   b. The final solutions were filtered through 10 μm filters and dispensed into 5 amber PET bottles with closures (provided by Orphan Medical, Inc.). Two bottles are used for microbial challenge studies and two bottles are placed on limited stability. The remaining bottles are retained for any additional studies at a future time.
3. Testing: Formulations are tested as described above.

C. Reporting of Results: The results will be reported for the Stability and Microbial Challenge results in standard format as defined by the described Orphan Medical Development. Copies of HPLC chromatograms and any raw data from these studies will be provided with results.

D. Acceptance Criteria: Specific acceptance criteria for this study can be described analogous to those for sodium oxybate.

Results: Summarized as follows in Tables 18, 19 and 20 for various studies.

TABLE 18

Result Summary
Results of Protocol 98126 Microbial Challenge Study

Lot Number MCH1064-33						
GHB, pH 7.50, 500 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	490,000	5,500	<100	<10	<10	<10
P. aeruginosa	141,000	21,600	<100	<10	<10	<10
S. aureus	1,035,000	405,000	79,500	8,300	1,645	375
C. albicans	835,000	147,000	<100	<10	<10	<10
A. niger	370,000	285,000	120,500	246,500	148,500	183,000
Lot Number MCH1064-35						
GHB, pH 7.50, 250 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	705,000	229,500	<100	<10	<10	<10
P. aeruginosa	224,500	5,200	<100	<10	<10	<10
S. aureus	1,135,000	390,000	262,500	31,500	4,250	155
C. albicans	705,000	435,000	52,000	850	<10	<10
A. niger	510,000	515,000	155,500	176,000	147,500	184,000
Lot Number MCH1064-37						
GHB, pH 7.50, 300 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	365,000	310,000	13,400	<10	<10	<10
P. aeruginosa	205,000	15,600	50	<10	<10	<10
S. aureus	1,170,500	605,000	67,500	<60	60	<10
C. albicans	870,000	355,000	8,300	<10	<10	<10
A. niger	540,000	525,000	172,000	155,500	155,500	163,500
Lot Number MCH1064-43						
GHB, pH 7.50, 550 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	425,000	63,500	700	<10	<10	<10
P. aeruginosa	171,500	211,550	250	<10	<10	<10
S. aureus	1,020,000	520,000	41,500	1,050	180	10
C. albicans	880,000	157,500	800	<10	<10	<10
A. niger	545,000	505,000	131,000	156,500	205,000	187,500
Lot Number MCH1064-45						
GHB, pH 7.50, 550 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	660,000	58,500	450	<10	<10	<10
P. aeruginosa	896,000	14,450	900	<10	<10	<10
S. aureus	860,000	132,000	19,750	935	110	45
C. albicans	1,125,000	166,000	<100	<10	<10	<10
A. niger	530,000	530,000	105,500	153,000	157,500	177,000
Lot Number MCH1064-47						
GHB, pH 7.50, 650 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	630,000	119,000	1,350	<10	<10	<10
P. aeruginosa	183,500	5,900	50	<10	<10	<10
S. aureus	890,000	650,000	76,000	14,550	510	1,150
C. albicans	675,000	145,500	<100	<10	<10	<10
A. niger	535,000	385,000	103,000	162,000	187,000	173,000
Lot Number MCH1064-85						
Ca-Oxybate, pH 7.50, 500 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	425,000	121,000	1,650	<10	<10	<10
P. aeruginosa	420,000	22,000	300	<10	<10	<10
S. aureus	265,000	2,000	<100	<10	<10	<10

TABLE 18-continued

Result Summary Results of Protocol 98126 Microbial Challenge Study						
C. albicans	565,000	440,000	29,500	<1000	<10	<10
A. niger	1,310,000	965,000	370,000	640,000	690,000	675,000
Lot Number MCH1064-49						
GHB, pH 7.50, 500 mg/cc Malic Acid	0	Day 1	Day 7	Day 14	Day 21	Day 28
E. coli	615,000	6,500	<100	<10	<10	<10
P. aeruginosa	69,500	14,600	<100	<10	<10	<10
S. aureus	650,000	305,000	1,700	<10	<10	<10
C. albicans	720,000	107,000	<100	<10	<10	<10
A. niger	375,000	380,000	99,500	178,500	212,500	165,500

TABLE 19

Result Summary Data from Dec. 30, 1997									
GHB (pH 7.5) 750 mg/cc	(n = 3) Inoculu	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	
E. coli	470,000	160,000	64,500	4,300	420	<10	<10	<10	
P. aeruginosa	437,500	152,000	3,500	10	<10	<10	<10	<10	
S. aureus	447,500	330,000	24,500	42,000	8,050	1,935	15	10	
C. albicans	375,000	234,500	28,000	1,950	<10	<10	10	<10	
A. niger	475,500	395,000	395,000	229,000	101,500	161,500	101,000	202,000	
750 mg/cc + 0.2% MP/PP, pH 7.50									
E. coli	470,000	127,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	61,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	350,000	3,000	4,050	<10	<10	<10	<10	
C. albicans	375,000	103,500	<1,000	<10	<10	<10	<10	<10	
A. niger	457,500	315,000	415,000	35,500	79,500	38,500	87,500	6,400	
750 mg/cc + 0.1% MP/PP, pH 7.5									
E. coli	470,000	157,000	7,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	90,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	239,000	5,500	16,950	600	<10	<10	<10	
C. albicans	375,000	169,000	<1,000	<100	<10	<10	<10	<10	
A. niger	457,500	335,000	425,000	34,500	168,500	90,500	95,500	99,000	
750 mg/cc + 0.2% Potassium sorbate, pH 7.5									
E. coli	470,000	180,000	735,000	6,200	475	<10	<10	<10	
P. aeruginosa	437,500	152,000	1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	264,000	27,500	49,800	14,550	2,370	<10	<10	
C. albicans	375,000	300,000	41,500	3,800	<10	<10	<10	<100	
A. niger	457,500	325,000	360,000	25,000	202,000	500,000	345,000	425,000	
GHB (pH 6.0) 500 mg/cc	Inoculu	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28	Results
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10	
P. aeruginosa	437,500	172,000	3,000	<10	<10	<10	<10	<10	
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10	
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10	
A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600	
									PASS
500 mg/cc + 0.2% MP/PP, pH 6.0									
E. coli	470,000	163,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	60,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	243,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	150,500	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	400,000	38,000	<10	<10	<10	<10	<10	
									PASS
500 mg/cc + 0.1% MP/PP, pH 6.0									
E. coli	470,000	206,000	<1,000	<10	<10	<10	<10	<10	
P. aeruginosa	437,500	118,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	330,000	<1,000	<10	<10	<10	<10	<10	
C. albicans	375,000	221,000	<1,000	<100	<10	<10	<10	<10	
A. niger	475,500	355,000	93,500	59,000	8,700	315	35	>10	
									PASS
500 mg/cc + 0.2% Potassium sorbate, pH 6.0									
E. coli	470,000	222,000	46,500	150	<10	<10	<10	<10	
P. aeruginosa	437,500	136,000	<1,000	<10	<10	<10	<10	<10	
S. aureus	447,500	410,000	<1,000	130	<10	<10	<10	<10	

TABLE 19-continued

Result Summary									
C. albicans	375,000	395,000	28,500	<100	<10	<10	<10	<10	
A. niger	475,500	405,000	270,000	63,000	51,000	49,500	39,000	11,150	
									PASS

TABLE 20

Result Summary								
Data from Study Dated Dec. 30, 1997								
GHB (pH 6.0) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	470,000	221,000	40,000	100	<10	<10	<10	<10
P. aeruginosa	437,500	172,000	3,000	<10	<10	<10	<10	<10
S. aureus	447,500	320,000	<1,000	30	<10	<10	<10	<10
C. albicans	375,000	310,000	14,000	100	<10	<10	<10	<10
A. niger	475,500	270,000	355,000	84,000	120,000	48,500	41,000	8,600
Data From Study Begun Mar. 12, 1998								
GHB (pH 6.0) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	500,000	370,000	Nd	Nd	<100	<10	<10	<10
P. aeruginosa	350,000	198,500	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	480,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	340,000	Nd	Nd	<100	<10	<10	<10
A. niger	450,000	445,000	Nd	Nd	9,050	20,500	9,450	1,120
E. coli	500,000	199,000	Nd	Nd	<100	<10	<10	<10
P. acruginosa	350,000	192,500	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	300,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	370,000	Nd	nd	<100	<10	<10	<10
A. niger	450,000	445,000	Nd	Nd	10,100	22,750	3,800	4,050
Data From Study Begun Mar. 12, 1998								
GHB (pH 9.0) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	500,000	320,000	Nd	Nd	<100	<10	<10	<10
P. aeruginosa	350,000	12,000	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	495,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	380,000	Nd	Nd	<100	<10	<10	<10
A. niger	450,000	355,000	Nd	Nd	12,550	157,500	365,000	365,000
GHB (pH 6.0 + Excipients) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	500,000	96,000	Nd	Nd	<100	<10	<10	<10
P. aeruginosa	350,000	26,000	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	155,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	205,000	Nd	Nd	<100	<10	<10	<10
A. niger	450,000	131,500	Nd	Nd	6,250	1,825	870	370
GHB (pH 6.0 + Excipients) 500 mg/cc	Inoculum	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	500,000	93,000	Nd	Nd	<100	<10	<10	<10
P. aeruginosa	350,000	30,500	Nd	Nd	<100	<10	<10	<10
S. aureus	280,000	185,000	Nd	Nd	<100	<10	<10	<10
C. albicans	450,000	135,000	Nd	Nd	<100	<10	<10	<10
A. niger	450,000	121,500	Nd	Nd	5,400	1,785	795	505

TABLE 21

Result Summary

Jul. 2, 1998 Start Date

GHB (pH 7.50) 500 mg/cc	HCl Initial Cone	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	97000	82000	19200	Nd	1000	<10	<10	<10
P. aeruginosa	48500	29500	520	Nd	<10	<10	<10	<10
S. aureus	54500	58000	42350	Nd	4950	245	<10	<10
C. albicans	58500	38500	1060	Nd	<100	<10	<10	<10
A. niger	77500	48000	21450	Nd	46000	46000	38000	54000
GHB (pH 7.50) 500 mg/cc	Malic Acid Initial Cone	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	97000	83000	44450	Nd	3050	70	<10	<10
P. aeruginoas	48500	15650	545	Nd	<10	<10	<10	<10
S. aureus	54500	59500	48400	Nd	17400	6500	820	505
C. albicans	58500	44000	6200	Nd	500	<10	<10	<10
A. niger	77500	35500	24100	Nd	28000	49000	44500	44000

For Category IC Products:
Bacteria: Not less than 1 log reduction from the initial count at 14 days, and no increase from the 14 days count at 28 days.
Yeast and Molds: No increase from the initial calculated count at 14 and 28 days.

Jul. 2, 1998 Start Date

GHB (pH 7.50) 500 mg/cc	HCl Initial Co	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	9.70E+04	8.20E+04	1.92E+04	nd	1.00E+03	<10	<10	<10
P. aeruginosa	4.85E+04	2.95E+04	5.20E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.80E+04	4.24E+04	nd	4.95E+03	2.45E+02	<10	<10
C. albicans	5.85E+04	3.85E+04	1.06E+03	nd	<100	<10	<10	<10
A. niger	7.75E+04	4.80E+04	2.15E+04	nd	4.60E+04	4.60E+04	3.80E+04	5.40E+04
GHB (pH 7.50) 500 mg/cc	Malic Acid Initial Co	0	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
E. coli	9.70E+04	8.30E+04	4.45E+04	nd	3.05E+03	7.00E+01	<10	<10
P. aeruginosa	4.85E+04	1.57E+04	5.45E+02	nd	<10	<10	<10	<10
S. aureus	5.45E+04	5.95E+04	4.84E+04	nd	1.74E+04	6.50E+03	8.20E+02	5.05E+02
C. albicans	5.85E+04	4.40E+04	6.20E+03	nd	5.00E+02	<10	<10	<10
A. niger	7.75E+04	3.55E+04	2.41E+04	nd	2.80E+04	4.90E+04	4.45E+04	4.40E+04

TABLE 22

pH Variable Result Summary

GHB, pH 7.5 750 mg/cc Dec. 30, 1997	Inoculum	0	Day 14	Day 28	GHB, pH 6.0 500 mg/cc Dec. 30, 1997	Inoculum	0	Day 14	Day 28
E. coli	470,000	160,000	<10	<10	*E. coli*	470,000	221,000	<10	<10
P. aeruginosa	437,500	152,000	<10	<10	*P. aeruginosa*	437,500	172,000	<10	<10
S. aureus	447,500	330,000	1,935	10	*S. aureus*	447,500	320,000	<10	<10
C. albicans	375,000	234,500	<10	<10	*C. albicans*	375,000	310,000	<10	<10
A. niger	475,500	395,000	161,500	202,000	*A. niger*	475,500	270,000	48,500	8,600
GHB, pH 7.5 750 mg/cc + 0.2% MP/PP Dec. 30, 1997					GHB, pH 6.0 500 mg/cc + 0.2% MP/PP Dec. 30, 1997				
E. coli	470,000	127,000	<10	<10	*E. coli*	470,000	163,000	<10	<10
P. aeruginosa	437,500	61,000	<10	<10	*P. aeruginosa*	437,500	60,000	<10	<10
S. aureus	447,500	350,000	<10	<10	*S. aureus*	447,500	243,000	<10	<10
C. albicans	375,000	103,500	<10	<10	*C. albicans*	375,000	150,500	<10	<10
A. niger	457,500	315,000	38,500	6,400	*A. niger*	475,500	400,000	<10	<10

TABLE 22-continued

pH Variable Result Summary

GHB, pH 7.5 750 mg/cc + 0.1% MP/PP					GHB, pH 6.0 500 mg/cc + 0.1% MP/PP Dec. 30, 1997				
E. coli	470,000	157,000	<10	<10	*E. coli*	470,000	200,000	<10	<10
P. aeruginosa	437,500	90,000	<10	<10	*P. aeruginosa*	437,500	118,000	<10	<10
S. aureus	447,500	239,000	<10	<10	*S. aureus*	447,500	330,000	<10	<10
C. albicans	375,000	169,000	<10	<10	*C. albicans*	375,000	221,000	<10	<10
A. niger	457,500	335,000	90,500	99,000	*A. niger*	475,500	355,000	315	<10
GHB, pH 7.5 750 mg/cc + 0.2% Potassium sorbate	xxxxxx				GHB, pH 6.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coli					*E. coli*				
P. aeruginosa					*P. aeruginosa*				
S. aureus					*S. aureus*				
C. albicans					*C. albicans*				
A. niger					*A. niger*				
GHB, pH 6.0 500 mg/cc + 0.2% Potassium sorbate Dec. 30, 1997					GHB, pH 6.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coli	470,000	222,000	<10	<10	*E. coli*	500,000	199,000	<10	<10
P. aeruginosa	437,500	136,000	<10	<10	*P. aeruginosa*	350,000	192,500	<10	<10
S. aureus	447,500	410,000	<10	<10	*S. aureus*	280,000	300,000	<10	<10
C. albicans	375,000	395,000	<10	<10	*C. albicans*	450,000	370,000	<10	<10
A. niger	475,500	405,000	49,500	11,150	*A. niger*	450,000	445,000	22,750	4,050
GHB, pH 6.0 500 mg/cc + Excipients Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 6.0 500 mg/cc + Excipients Mar. 12, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	93,000	<10	<10	*E. coli*	500,000	96,000	<10	<10
P. aeruginosa	350,000	30,500	<10	<10	*P. aeruginosa*	350,000	26,000	<10	<10
S. aureus	280,000	185,000	<10	<10	*S. aureus*	280,000	155,000	<10	<10
C. albicans	450,000	135,000	<10	<10	*C. albicans*	450,000	205,000	<10	<10
A. niger	450,000	121,500	1,785	505	*A. niger*	450,000	131,500	1,825	370
GHB, pH 9.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 7.50 500 mg/cc HCl Jul. 2, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	320,000	<10	<10	*E. coli*	97000	82000	<10	<10
P. aeruginosa	350,000	12,000	<10	<10	*P. aeruginosa*	48500	29500	<10	<10
S. aureus	280,000	530,000	<10	<10	*S. aureus*	54500	58000	245	<10
C. albicans	450,000	510,000	<10	<10	*C. albicans*	58500	38500	<10	<10
A. niger	450,00	345,000	158,500	110,500	*A. niger*	77500	48000	46000	54,000
GHB, pH 9.0 500 mg/cc Mar. 12, 1998	Inoculum	0	Day 14	Day 28	GHB, pH 7.5 500 mg/cc, Malic Acid Jul. 2, 1998	Inoculum	0	Day 14	Day 28
E. coli	500,000	305,000	<10	<10	*E. coli*	97000	83000	70	<10
P. aeruginosa	350,000	20,000	<10	<10	*P. aeruginosa*	48500	15650	<10	<10
S. aureus	280,000	495,000	<10	<10	*S. aureus*	54500	59500	6500	505
C. albicans	450,000	380,000	<10	<10	*C. albicans*	58500	44000	<10	<10
A. niger	450,000	355,000	157,500	365,000	*A. niger*	77500	35500	49000	44,000

Short term stability testing was carried out as described in Appendix A and results are summarized in—Results of Limited Stability Testing—XYREM® oral solution—are shown as follows:

TABLE 23-A

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333198

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	512 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.068%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.021%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.02%	NPLC-793D
		RRT 3.79: 0.007%	
PH	Report	7.6	USP <791>
Challenge Test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 1: 500 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328841

TABLE 23-B

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331347

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	510 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.36%	NPLC-793-D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.23%	NPLC-793-D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.1%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:

28 days (25° C., 60% RH)

Formulation 1: 500 mg/cc; Malic acid; pH 7.5

*A: RRT 1.30: 0.02%

RRT 3.93: 0.008%

TABLE 23-C

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333197

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	258 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.045%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.016%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.79: 0.009%	NPLC-793D
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 2: 250 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328845

TABLE 23-D

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331346

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
(28 DAY CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	256 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.18%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.13%	NPLC-793D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.03%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:

28 days (25° C., 60% RH)

Formulation 2: 250 mg/cc; Malic acid; pH 7.5

*A: RRT 1.29: 0.007%

RRT 3.93: 0.008%

TABLE 23-E

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333196

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	360 mg/ml (103%)	NPLC-793
Impurities total	≦2.0%	0.050%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.017%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.006%	NPLC-793D
		RRT 3.79: 0.007%	
PH	Report	7.7	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 3: 350 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328847

TABLE 23-F

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331345

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORMULATION
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-3
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	363 mg/ml (104%)	NPLC-793-D
Impurities total	≦2.0%	0.21%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.14%	NPLC-793D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.05%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	8.0	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
Formulation 3: 350 mg/cc; Malic acid; pH 7.5
*A: RRT 1.29: 0.009%
RRT 3.93: 0.008%

TABLE 23-G

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333195

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE: 1741
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	461 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.065%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.018%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.02%	NPLC-793D
		RRT 3.79: 0.007%	
PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 4: 450 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328875

TABLE 23-H

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331343

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	454 mg/ml (101%)	NPLC-793-D
Impurities total	≦2.0%	0.40%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.26%	NPLC-793D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.1%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)

Formulation 4: 450 mg/cc; Malic acid; pH 7.5

*A: RRT 1.30: 0.03%

RRT 3.93: 0.008%

TABLE 23-I

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333194

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	563 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.077%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.020%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.29: 0.03%	NPLC-793D
		RRT 3.79: 0.007%	
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 5: 550 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328883

TABLE 23-J

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO.: 331341

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	561 mg/ml (102%)	NPLC-793-D
Impurities total	≦2.0%	0.56%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.31%	NPLC-793D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.2%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)

Formulation 5: 550 mg/cc; Malic acid; pH 7.5

*A: RRT 1.30: 0.04%

RRT 3.93: 0.007%

TABLE 23-K

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333193

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	666 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.10%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.025%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 1.28: 0.05%	NPLC-793D
		RRT 3.78: 0.007%	
PH	Report	7.6	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 6: 650 mg/cc; Malic acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 328885

TABLE 23-L

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331336

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	660 mg/ml (102%)	NPLC-764
Impurities total	≦2.0%	0.81%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.43%	NPLC-793D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.3%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
PH	Report	7.8	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)

Formulation 6: 650 mg/cc; Malic acid; pH 7.5

*A: RRT 1.30: 0.07%

RRT 3.93: 0.007%

TABLE 23-M

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Jan. 1999
NO: 333192

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	518 mg/ml (104%)	NPLC-793
Impurities total	≦2.0%	0.065%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.45: 0.018%	NPLC-793D
GBL-RRT 1.6	(RRT = 1.6): ≦0.5%	RRT 4.17: 0.02%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.79: 0.007%	NPLC-793D
		RRT 5.99: 0.02%	
PH	Report	7.5	USP <791>
Challenge test	Conforms to USP (0, 1, 7, 14, 21, 28 days)	Conforms	USP 23 <51> S.8

COMMENTS:

Initial test

Formulation 7: 500 mg/cc; Citric acid; pH 7.5

THIS CERTIFICATE CORRECTS AND REPLACES CERTIFICATE 329033

TABLE 23-N

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 21 Jan. 1999
NO: 331335

CERTIFICATE OF ANALYSIS

OXYBATE SODIUM, LIQUID
FORMULATION
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-4
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	515 mg/ml (103%)	NPLC-793-D
Impurities total	≦2.0%	0.38%	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.27%	NPLC-793D
	(RRT = 1.6): ≦0.5%	RRT 4.31: 0.1%	
	Impurity A (RRT 4.3): ≦0.5%		
Impurities unspecified	Ind. imp. ≦0.1%	RRT 3.93: 0.007%	NPLC-793D
PH	Report	7.9	USP <791>

COMMENTS:

28 DAYS (25° C., 60% RH)

Formulation 7: 500 mg/cc; Malic acid; pH 7.5

TABLE 23-O

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 09 Feb. 1999
NO: 330721

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM LIQUID FORM.
(28 DAYS CHALLENGE TEST)
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Challenge Test	Conforms to USP (0, 1, 7, 14, 21 and 28 days)	Conforms	USP 23 <51> S.8
Potency	Report	501 mg/ml (100%)	NPLC-793
Impurities total	≦2.0%	1.2%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
Impurities specified	Gamma-Butyrolactone	RRT 1.46: 0.013%	NPLC-793D
GBL-RRT 1.6	Report:		
PH	Report	7.3	USP <791>
Solubility study	Report	*B	PR 98126 IIA

COMMENTS:
Initial test
500 mg/cc; Malic acid; pH 7.5
*A: RRT 1.31: 0.02% RRT 1.67: 0.008%
RRT 1.91: Interference with peak dilution solvent cannot calculate
RRT 3.47: 0.1% RRT 3.79: 0.009% RRT 3.84: 0.01%
RRT 4.18: 0.06% RRT 5.10: 0.008% RRT 5.35: 0.02%
RRT 6.74: 0.9% RRT 6.90: 0.08% RRT 7.41: 0.006%
*B: Maximum solubility: 700 mg/ml no pH adjustment.

TABLE 23-P

ORPHAN MEDICAL INC.
13911, Ridgedale Drive
Minnetonka, (MN) 55305
USA

DATE: 26 Feb. 1999
NO: 331307

CERTIFICATE OF ANALYSIS

OXYBATE CALCIUM LIQUID FORM.
PROTOCOL 98126
ORPHAN MEDICAL

LOT: MCH1064-85
CODE:
REQUISITION: 1741

TEST	SPECIFICATION	RESULT	PROCEDURE
Description	Clear to slightly opalescent solution.	Conforms	ORGANOLEPTIC
Potency	Report	508 mg/ml (102%)	NPLC-793
Impurities total	≦2.0%	0.70%	NPLC-793D
Impurities unspecified	Ind. imp. ≦0.1%	*A	NPLC-793D
Impurities specified	Gamma-Butyrolactone Report:	RRT 1.37: 0.054%	NPLC-793D
PH	Report	7.6	USP <791>

COMMENTS:
28 DAYS (25° C., 60% RH)
500 mg/ml cc; Malic acid; pH 7.5
*A: RRT 1.17: 0.03% RRT 3.47: 0.2%
RRT 5.46: 0.01% RRT 6.87: 0.3%
RRT 7.04: 0.007%
RRT 1.78: Can not calculate because it interfere with a dilution solvent peak.

This report summarizes the results of the above described study and provides a summary of previous development work which evaluated conditions other than those evaluated in this study. The purposes of this information is to define the scope and limitations of the self-preserving properties of Xyrem® oral solution for completion of patent application.

II. Summary of Results:

A. Preparation of Various Formulations of Sodium Oxybate and Formulations Using an Alternative Salt of GHB.

1. Various formulations of sodium oxybate were prepared as directed in the above Protocol. Sodium oxybate. 500 mg/cc with Malic Acid was not soluble at pH 5.0, and further evaluation of this solution was discontinued. All other solutions were successfully prepared as described.
2. The preparation of an alternative salt of gamma-hydroxybutyrare was described as the calcium salt, prepared at 500 mglcc (or maximum possible) with Malic Acid at pH 7.5.
   a. The calcium salt of gamma-hydroxybutyrate was prepared by Toronto Research and shipped to NeoPharm for determination of solubility and evaluation according to the Protocol. The absolute limit of solubility,

without pH adjustment, was determined to be 700 mg/cc. The pH of this solution was 8.4. Solutions of lower pH were more difficult to prepare at 500 mg/cc using Malic acid, as acidulant. When pH was adjusted to 6.0 with Malic acid. the solubility of the calcium oxybate was limited (longer stifling required to solubilize). The desired solution of 500 mg/cc, pH 7.5 was prepared with Malic acid as acidulant without difficulty. Appearance of the final solution was slightly yellow in color. Copies of the laboratory record for preparation of these solutions is available.

B. Microbial Challenge Testing of the Various Formulations Prepared by MDS NeoPharm.

The microbial challenge testing was carried as specified in the Protocol and the following table summarizes the results of microbial challenge testing of various formulations of sodium oxybate and the single calcium oxybate formulation prepared.

TABLE 24

Testing of Sodium and Calcium GHB Salts

	pH of Solution	Microbial Challenge Result
Sodium Oxybate Concentration		
1. 500 mg/cc	7.5 (Malic acid)	Pass
2. 250 mg/cc	7.5 (Malic acid)	Pass
3. 350 mg/cc	7.5 (Malic acid)	Pass
4. 450 mg/cc	7.5 (Malic acid)	Pass
5. 550 mg/cc	7.5 (Malic acid)	Pass
6. 650 mg/cc	7.5 (Malic acid)	Pass
7. 500 mg/cc	7.5 (Citric acid)	Pass
Calcium Oxybate Conctration		
500 mg/cc	7.5	Pass

C. Short Term Stability Evaluation of Various Formulations of Sodium Oxybate and a Formulation of Calcium Oxybate.

Solutions were tested on day zero (preparation doy) and day 28 according to the described Protocol. The results of the stability evaluation are summarized in Table 25 below:

TABLE 25

Sodium and Calcium GHB Evaluation

Sodium oxybate solution	Potency mg/cc (%)	Impurities (Total)	Impurities (Unspecified)	Impurities (Specified - GBL)	pH
500 mg/cc pH 7.5 Malic Acid Day 0	512 mg/cc (102%)	0.68%	0.041%	0.027%	7.6
Day 28	510 mg/cc (103%)	0.36%	0.33%	0.028%	7.9
250 mg/cc pH 7.5 Malic Acid Day 0	258 mg/cc (103%)	0.045%	0.009%	0.026%	7.6
Day 28	256 mg/cc (102%)	0.18%	0.015%	0.16%	7.9
350 mg/cc pH 7.5 Malic Acid Day 0	360 mg/cc (103%)	0.050%	0.013%	0.037%	7.7
Day 28	363 mg/cc (104%)	0.21%	0.017%	0.19%	8.0

TABLE 25-continued

Sodium and Calcium GHB Evaluation

Sodium oxybate solution	Potency mg/cc (%)	Impurities (Total)	Impurities (Unspecified)	Impurities (Specified - GBL)	pH
450 mg/cc pH 7.5 Malic Acid Day 0	461 mg/cc (102%)	0.065%	0.027%	0.038%	7.5
Day 28	454 mg/cc (101%)	0.40%	0.038%	0.36%	7.8
550 mg/cc pH 7.5 Malic Acid Day 0	563 mg/cc (102%)	0.077%	0.037%	0.040%	7.6
Day 28	561 mg/cc (102%)	0.56%	0.047%	0.51%	7.9
650 mg/cc pH 7.5 Malic Acid Day 0	666 mg/cc (102%)	0.10%	0.057%	0.045%	7.6
Day 28	660 mg/cc (102%)	0.81%	0.077%	0.73%	7.8
500 mg/cc pH 7.5 Citric Acid Day 0	518 mg/cc (104%)	0.065%	0.027%	0.038%	7.5
Day 28	515 mg/cc (103%)	0.38%	0.007%	0.37%	7.9
500 mg/cc pH 7.5 Malic Acid Day 0	501 mg/cc (100%)	1.2%	>0.1% (See C of A Attached)	0.013%	7.3
Day 28	508 mg/cc (102%)	0.70%	>0.1% (See C of A)	0.054%	7.6

D. Summary of Pertinent Solubility and Microbial Challenge Data are Shown in Tables 26 and 27.

TABLE 26

Limits of Solubility

	pH of Solution	Comments
Sodium oxybate Maximum Solubility		
450 mg/cc	pH 4 (HCl)	25°
500 mg/cc	pH 5 (HCl)	25°
600 mg/cc	pH 6 (HCl)	25°
750 mg/cc	pH 6.8 (HCl)	25°
1000 mg/cc	pH (unadjusted)	65° Soluble, 25° gel
Calcium oxybate Maximum Solubility		
700 mg/cc	pH 8.4 (unadjusted)	25°
500 mg/cc	pH 6.0	25°

TABLE 27

Microbial Challenge Results

	pH of Solution	Microbial Challenge Results
Sodium oxybate Concentration (Date)		
750 mg/cc (December 1997)	7.5 (HCl)	pass
500 mg/cc (December 1997)	6.0 (HCl)	pass
500 mg/cc + Excipients (Xylitol) (March 1998)	6.0 (Malic Acid)	pass

TABLE 27-continued

Microbial Challenge Results

	pH of Solution	Microbial Challenge Results
500 mg/cc (March 1998)	9.0 (HCl)	pass (Borderline *aspergillus*)
150 mg/cc (BDL 1995)	5.0 (HCl)	fail (*aspergillus* only)
150 mg/cc (BDL 1995)	7.0 (HCl)	fail (*aspergillus* and *staph*)
150 mg/cc (BDL 1995)	3.0 (HCl)	fail (*aspergillus* only)
150 mg/cc (BDL 1995)	10.3 (HCl)	fail (*aspergillus* and *staph*)
500 mg/cc (May 1998)	6.0 (Malic Acid)	discontinued
500 mg/cc (May 1998)	7.5 (Malic Acid)	pass
500 mg/cc (May 1998)	9.0 (Malic Acid)	discontinued
500 mg/cc (May 1998)	7.5 (HCl)	pass
500 mg/cc	7.5 (Malic Acid)	pass
250 mg/cc	7.5 (Malic Acid)	pass
350 mg/cc	7.5 (Malic Acid)	pass
450 mg/cc	7.5 (Malic Acid)	pass
550 mg/cc	7.5 (Malic Acid)	pass
650 mg/cc	7.5 (Malic Acid)	pass
500 mg/cc	7.5 (Citric Acid)	pass
Calcium oxybate Concentration (Date)		
500 mg/cc	7.5 (Malic Acid)	pass

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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What is claimed is:

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.

2. The method of claim **1**, wherein said salt is sodium gamma-hydroxybutyrate.

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

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, hyrochloric acid, phosphoric acid, sulfuric acid, and nitric acid.

5. The method of claim **1**, wherein the concentration is from about 450 to about 600 mg/ml.

6. The method of claim **1**, wherein the concentration is about 500 mg/ml.

7. The method of claim **1**, wherein the components are admixed sequentially.

8. The method of claim **1**, wherein the components are admixed simultaneously.

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 and resistant to microbial growth, wherein the medium does not contain a preservative.

10. A method of rendering an aqueous medium comprising a salt of gamma-hydroxybutyrate resistant to microbial growth, said method comprising 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.

11. The method of claim **9** or **10**, wherein the salt is sodium gamma-hydroxybutyrate.

12. The method of claim **9** or **10**, wherein said pH-adjusting agent is an organic acid.

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.

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.

15. The method of claim **9** or **10**, wherein the concentration of the gamma-hydroxybutyrate salt is about 500 mg/ml.

16. The method of claim **1**, wherein the medium does not contain a preservative.

* * * * *

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
Amneal Pharmaceuticals, LLC

County of Residence of First Listed Defendant Somerset, NJ
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE 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 and 13-391

DATE 09/12/2013

SIGNATURE OF ATTORNEY OF RECORD 

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

107632 7590 09/17/2013

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

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

DATE MAILED: 09/17/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/595,676	08/27/2012	Dayton T. Reardan	101.031US10	1006

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	$1780	$0	$0	$1780	12/17/2013

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 09/17/2013
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.
13/595,676	08/27/2012	Dayton T. Reardan	101.031US10	1006

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	$1780	$0	$0	$1780	12/17/2013

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 credit 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 form 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: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information 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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/595,676	08/27/2012	Dayton T. Reardan	101.031US10	1006

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EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

DATE MAILED: 09/17/2013

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.

PTOL-85 (Rev. 02/11)

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. 13/595,676	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 *5/31/13*.
   ☐ 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 *1-26*. 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 20130311; 20130528
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

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Attorneys for Plaintiff
Jazz Pharmaceuticals, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC., **Plaintiff,** **v.** **AMNEAL PHARMACEUTICALS, LLC,** **Defendant.**	**Civil Action No. _____** **(Filed Electronically)**

FED. R. CIV. P. 7.1 DISCLOSURE STATEMENT

Pursuant to Fed. R. Civ. P. Rule 7.1, counsel for Plaintiff Jazz Pharmaceuticals, Inc. certifies the following:

1. The full name of the party represented by me is: Jazz Pharmaceuticals, Inc.

2. Jazz Pharmaceuticals, Inc. is a wholly-owned subsidiary of Jazz Pharmaceuticals plc, which is a publicly traded company.

Dated: September 12, 2013

By: s/ Charles M. Lizza
Charles M. Lizza
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Modified form PTO/SB/08A(04-07) OMB 651-0031
US Patent & Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (Use as many sheets as necessary)	*Complete if Known*	
	Application Number	13/592,202
	Filing Date	August 22, 2012
	First Named Inventor	Dayton T. Reardan Ph.D
	Group Art Unit	3686
	Examiner Name	Lena Najarian
Sheet 1 of 1	Attorney Docket No: 101.031US9	

OTHER DOCUMENTS – NON PATENT LITERATURE DOCUMENTS		
Examiner Initial *	**Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.**	**T 1**
	"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 **DATE CONSIDERED**

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

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Attorneys for Defendant/Counterclaim Plaintiff
Amneal Pharmaceuticals, LLC

Document Filed Electronically

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC.,	:	
	:	Civil Action No. 13-391-ES-SCM
Plaintiff/Counterclaim Defendant,	:	
	:	District Judge Esther Salas
v.	:	Magistrate Judge Steven C. Mannion
	:	
AMNEAL PHARMACEUTICALS, LLC,	:	
	:	
Defendant/Counterclaim Plaintiff.	:	
	x	

DEFENDANT AMNEAL PHARMACEUTICALS, LLC'S
ANSWER, DEFENSES, AND COUNTERCLAIMS

Defendant-Counterclaim Plaintiff Amneal Pharmaceuticals, LLC ("Amneal") for its Answer, Defenses, and Counterclaims to the Complaint of Plaintiff-Counterclaim Defendant Jazz Pharmaceuticals, Inc. ("Jazz"), alleges as follows:

Nature of the Action

1. Admitted in part and denied in part. Amneal admits only that the Complaint purports to be a civil action alleging infringement of United States Patent Nos. 6,472,431 ("the '431 patent"), 6,780,889 ("the '889 patent"), 7,262,219 ("the '219 patent"), 7,851,506 ("the '506 patent"), 7,895,059 ("the '059 patent"), 8,263,650 ("the '650 patent"), and 8,324,275 ("the '275 patent") (collectively, "patents-in-suit") in response to Amneal's submission of Abbreviated New Drug Application ("ANDA") No. 203631 with the United States Food and Drug Administration ("FDA") for approval to market sodium oxybate oral solution 500 mg/mL. Amneal denies any remaining allegations or legal conclusions in Paragraph 1, and specifically denies that this action states a proper cause of action for patent infringement and denies that it has infringed, infringes, or will infringe any valid claim of the patents-in-suit.

The Parties

2. On information and belief, admitted.

3. Admitted.

Jurisdiction and Venue

4. Paragraph 4 contains conclusions of law to which no response is required. Amneal states that it will not contest subject-matter jurisdiction for purposes of this action only. To the extent any further response is required, Amneal denies any remaining allegations or legal conclusions in Paragraph 4.

5. For purposes of this action, Amneal consents to this Court's personal jurisdiction. Amneal denies all other allegations contained in paragraph 5 of the Complaint.

6. Paragraph 6 contains conclusions of law to which no response is required. Amneal will not contest venue for purposes of this action only. To the extent any further

response is required, Amneal denies any remaining allegations or legal conclusions in Paragraph 6.

The Patents-In-Suit

7. Admitted in part and denied in part. Amneal admits that the '431 patent states on its face that it is titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy", that it issued on October 29, 2002, and it lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan as inventors. Amneal admits that a purported copy of the '431 patent is attached to the Complaint as Exhibit A. Amneal is without knowledge or information sufficient to form a belief as to the remaining allegations of Paragraph 7, and on that basis denies those allegations. Amneal specifically denies that the '431 patent was duly and legally issued or that its claims are valid and enforceable.

8. Admitted in part and denied in part. Amneal admits that the '889 patent states on its face that it is titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy", that it issued on August 24, 2004, and it lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan as inventors. Amneal admits that a purported copy of the '889 patent is attached to the Complaint as Exhibit B. Amneal is without knowledge or information sufficient to form a belief as to the remaining allegations of Paragraph 8, and on that basis denies those allegations. Amneal specifically denies that the '889 patent was duly and legally issued or that its claims are valid and enforceable.

9. Admitted in part and denied in part. Amneal admits that the '219 patent states on its face that it is titled "Microbiologically Sound and Stable Solutions of

Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy", that it issued on August 28, 2007, and it lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan as inventors. Amneal admits that a purported copy of the '219 patent is attached to the Complaint as Exhibit C. Amneal is without knowledge or information sufficient to form a belief as to the remaining allegations of Paragraph 9, and on that basis denies those allegations. Amneal specifically denies that the '219 patent was duly and legally issued or that its claims are valid and enforceable.

10. Admitted in part and denied in part. Amneal admits that the '506 patent states on its face that it is titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy", that it issued on December 14, 2010, it lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton Reardan as inventors, and it lists Jazz Pharmaceuticals, Inc. as the assignee. Amneal admits that a purported copy of the '506 patent is attached to the Complaint as Exhibit D. Amneal is without knowledge or information sufficient to form a belief as to the remaining allegations of Paragraph 10, and on that basis denies those allegations. Amneal specifically denies that the '506 patent was duly and legally issued or that its claims are valid and enforceable.

11. Admitted in part and denied in part. Amneal admits that the '059 patent states on its face that it is titled "Sensitive Drug Distribution System and Method", that it issued on February 22, 2011, it lists Dayton T. Reardan, Patti A. Engle and Bob Gagne as inventors, and it lists Jazz Pharmaceuticals, Inc. as the assignee. Amneal admits that a purported copy of the '059 patent is attached to the Complaint as Exhibit E. Amneal is without knowledge or information sufficient to form a belief as to the remaining allegations of Paragraph 11, and on

that basis denies those allegations. Amneal specifically denies that the '059 patent was duly and legally issued or that its claims are valid and enforceable.

12. Admitted in part and denied in part. Amneal admits that the '650 patent states on its face that it is titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy", that it issued on September 11, 2012, it lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton T. Reardan as inventors, and it lists Jazz Pharmaceuticals, Inc. as the assignee. Amneal admits that a purported copy of the '650 patent is attached to the Complaint as Exhibit F. Amneal is without knowledge or information sufficient to form a belief as to the remaining allegations of Paragraph 12, and on that basis denies those allegations. Amneal specifically denies that the '650 patent was duly and legally issued or that its claims are valid and enforceable.

13. Admitted in part and denied in part. Amneal admits that the '275 patent states on its face that it is titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy", that it issued on December 4, 2012, it lists Harry Cook, Martha Hamilton, Douglas Danielson, Colette Goderstad and Dayton T. Reardan as inventors, and it lists Jazz Pharmaceuticals, Inc. as the assignee. Amneal admits that a purported copy of the '275 patent is attached to the Complaint as Exhibit G. Amneal is without knowledge or information sufficient to form a belief as to the remaining allegations of Paragraph 13, and on that basis denies those allegations. Amneal specifically denies that the '275 patent was duly and legally issued or that its claims are valid and enforceable.

The XYREM® Drug Product

14. Admitted in part and denied in part. Amneal admits that Jazz sells sodium oxybate oral solution under the registered trade name Xyrem®. Amneal is without knowledge or information sufficient to form a belief as to the remaining allegations of Paragraph 14, and on that basis denies those allegations.

15. Admitted in part and denied in part. Amneal admits only that the '889, '219, '506, '059, '650, and '275 patents are listed in the FDA's Orange Book. Amneal is without knowledge or information sufficient to form a belief as to the remaining allegations of Paragraph 15, and on that basis denies those allegations.

Acts Giving Rise to This Suit

16. Admitted in part and denied in part. Amneal admits that it filed ANDA No. 203631 ("Amneal's ANDA") with the FDA under § 505 of the Food, Drug, and Cosmetic Act ("FDCA") seeking approval to engage in the commercial use, manufacture, sale, offer for sale or importation of 500 mg/mL sodium oxybate oral solution ("Amneal's ANDA Product"). Amneal denies the remaining allegations of Paragraph 16.

17. Admitted in part and denied in part. Amneal admits that Amneal's ANDA contained a written certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Amneal's Paragraph IV Certification") that the claims of the '889,'219,'506,'059, '650, and '275 patents are invalid, unenforceable, and/or will not be infringed by Amneal's ANDA Product. Amneal admits that Amneal's Paragraph IV Certification also stated that the claims of U.S. Patent Nos. 7,668,730 ("the '730 patent"), 7,765,106 ("the '106 patent"), and 7,765,107 ("the '107 patent") are invalid, unenforceable, and/or will not be infringed by Amneal's ANDA Product. Amneal denies the remaining allegations of Paragraph 17.

18. Admitted in part and denied in part. Amneal admits that on December 7, 2012 it sent written notice to Jazz ("Amneal's Notice Letter") that the claims of the '889, the '219, the '506, the '059, the '650, the '730, the '106, and the '107 patents are invalid, unenforceable, and/or will not be infringed by Amneal's ANDA Product. Amneal admits that Amneal's Notice Letter states that Amneal seeks approval to engage in the commercial manufacture, use, and/or sale of 500 mg/mL sodium oxybate oral solution before the expiration of the '889, the '219, the '506, the '059, the '650, the '730, the '106, and the '107 patents. Amneal denies the remaining allegations of Paragraph 18.

Count I: Alleged Infringement of the '431 Patent

19. Amneal repeats and realleges its responses to Paragraphs 1-18 of the Complaint.

20. Admitted in part and denied in part. Amneal admits that it included a Paragraph IV Certification for the '889, '219, '506, '059, '650, '730, '106, and'107 patents to obtain approval to engage in the commercial manufacture, use, and/or sale of 500 mg/mL sodium oxybate. Amneal also admits that based on Jazz's filing of the Complaint, and Amneal's denial thereof, there is an actual, substantial, and continuing justiciable controversy between Amneal and Jazz having adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaratory judgment regarding whether Amneal has infringed any valid enforceable claim of the '431 patent. Amneal denies the remaining allegations of Paragraph 20.

21. Denied.

22. Admitted.

23. Denied.

24. Denied.

25. Denied.

26. Denied.

27. Denied.

28. Denied.

Count II: Alleged Infringement of the '889 Patent

29. Amneal repeats and realleges its responses to Paragraphs 1-28 of the Complaint.

30. Denied.

31. Admitted.

32. Denied.

33. Denied.

34. Denied.

35. Denied.

36. Denied.

37. Denied.

Count III: Alleged Infringement of the '219 Patent

38. Amneal repeats and realleges its responses to Paragraphs 1-37 of the Complaint.

39. Denied.

40. Admitted.

41. Denied.

42. Denied.

43. Denied.

44. Denied.

45. Denied.

46. Denied.

Count IV: Alleged Infringement of the '506 Patent

47. Amneal repeats and realleges its responses to Paragraphs 1-46 of the Complaint.

48. Denied.

49. Admitted.

50. Denied.

51. Denied.

52. Denied.

53. Denied.

54. Denied.

55. Denied.

Count V: Alleged Infringement of the '059 Patent

56. Amneal repeats and realleges its responses to Paragraphs 1-55 of the Complaint.

57. Denied.

58. Admitted.

59. Denied.

60. Denied.

61. Denied.

62. Denied.

63. Denied.

64. Denied.

Count VI: Alleged Infringement of the '650 Patent

65. Amneal repeats and realleges its responses to Paragraphs 1-64 of the Complaint.

66. Denied.

67. Admitted.

68. Denied.

69. Denied.

70. Denied.

71. Denied.

72. Denied.

73. Denied.

Count VII: Alleged Infringement of the '275 Patent

74. Amneal repeats and realleges its responses to Paragraphs 1-73 of the Complaint.

75. Denied.

76. Admitted.

77. Denied.

78. Denied.

79. Denied.

80. Denied.

81. Denied.

82. Denied.

PRAYER FOR RELIEF

Amneal denies that Jazz is entitled to any judgment or relief against Amneal and, therefore, specifically denies paragraphs (A) through (K) of Jazz's Prayer for Relief.

AMNEAL'S DEFENSES

An allegation of any defense below is not an admission that Amneal bears the burden of proof or persuasion on any claim or issue.

First Defense – Noninfringement of the '431 Patent

83. Amneal's proposed product described in ANDA No. 203631 has not infringed, does not infringe, will not infringe, and will not contribute to or induce infringement of any valid and/or enforceable claim of the '431 patent, literally or under the Doctrine of Equivalents.

Second Defense – Invalidity of the '431 Patent

84. Upon information and belief, each claim of the '431 patent is invalid for failure to comply with the conditions and requirements of the patent laws of the United States, including without limitations, 35 U.S.C. §§ 101, 102, 103, and/or 112.

Third Defense – Noninfringement of the '889 Patent

85. Amneal's proposed product described in ANDA No. 203631 has not infringed, does not infringe, will not infringe, and will not contribute to or induce infringement of any valid and/or enforceable claim of the '889 patent, literally or under the Doctrine of Equivalents.

Fourth Defense – Invalidity of the '889 Patent

86. Upon information and belief, each claim of the '889 patent is invalid for failure to comply with the conditions and requirements of the patent laws of the United States, including without limitations, 35 U.S.C. §§ 101, 102, 103, and/or 112.

Fifth Defense – Noninfringement of the '219 Patent

87. Amneal's proposed product described in ANDA No. 203631 has not infringed, does not infringe, will not infringe, and will not contribute to or induce infringement of any valid and/or enforceable claim of the '219 patent, literally or under the Doctrine of Equivalents.

Sixth Defense – Invalidity of the '219 Patent

88. Upon information and belief, each claim of the '219 patent is invalid for failure to comply with the conditions and requirements of the patent laws of the United States, including without limitations, 35 U.S.C. §§ 101, 102, 103, and/or 112.

Seventh Defense – Noninfringement of the '506 Patent

89. Amneal's proposed product described in ANDA No. 203631 has not infringed, does not infringe, will not infringe, and will not contribute to or induce infringement of any valid and/or enforceable claim of the '506 patent, literally or under the Doctrine of Equivalents.

Eighth Defense – Invalidity of the '506 Patent

90. Upon information and belief, each claim of the '506 patent is invalid for failure to comply with the conditions and requirements of the patent laws of the United States, including without limitations, 35 U.S.C. §§ 101, 102, 103, and/or 112.

Ninth Defense – Noninfringement of the '059 Patent

91. Amneal's proposed product described in ANDA No. 203631 has not infringed, does not infringe, will not infringe, and will not contribute to or induce infringement of any valid and/or enforceable claim of the '059 patent, literally or under the Doctrine of Equivalents.

Tenth Defense – Invalidity of the '059 Patent

92. Upon information and belief, each claim of the '059 patent is invalid for failure to comply with the conditions and requirements of the patent laws of the United States, including without limitations, 35 U.S.C. §§ 101, 102, 103, and/or 112.

Eleventh Defense – Noninfringement of the '650 Patent

93. Amneal's proposed product described in ANDA No. 203631 has not infringed, does not infringe, will not infringe, and will not contribute to or induce infringement of any valid and/or enforceable claim of the '650 patent, literally or under the Doctrine of Equivalents.

Twelfth Defense – Invalidity of the '650 Patent

94. Upon information and belief, each claim of the '650 patent is invalid for failure to comply with the conditions and requirements of the patent laws of the United States, including without limitations, 35 U.S.C. §§ 101, 102, 103, and/or 112.

Thirteenth Defense – Noninfringement of the '275 Patent

95. Amneal's proposed product described in ANDA No. 203631 has not infringed, does not infringe, will not infringe, and will not contribute to or induce infringement of any valid and/or enforceable claim of the '275 patent, literally or under the Doctrine of Equivalents.

Fourteenth Defense – Invalidity of the '275 Patent

96. Upon information and belief, each claim of the '275 patent is invalid for failure to comply with the conditions and requirements of the patent laws of the United States, including without limitations, 35 U.S.C. §§ 101, 102, 103, and/or 112.

Fifteenth Defense – No Relief Available

97. Jazz is barred from obtaining relief pursuant to one or more provisions of 35 U.S.C. § 1, *et seq.*, including but not limited to §§ 286 and 287.

98. Jazz has not suffered any damages.

99. Jazz is not suffering an irreparable injury.

Sixteenth Defense – Failure to State a Claim

100. The Complaint, in whole or in part, fails to state a claim upon which relief can be granted.

Reservation of Rights

101. Amneal reserves the right to assert such other defenses, including but not limited to defenses of unenforceability as well as defense(s) raised by another defendant in this action or any other action concerning the patents-in-suit, and damages that may appear as discovery proceeds in this case.

AMNEAL'S COUNTERCLAIMS

Counterclaim Plaintiff Amneal Pharmaceuticals, LLC ("Amneal"), for its counterclaims against Counterclaim Defendant Jazz Pharmaceuticals, Inc., ("Jazz"), allege as follows:

The Parties

1. Amneal is a limited liability company organized under the laws of Delaware having its principal place of business at 440 U.S. Highway 22 West, Suite 104, Bridgewater, New Jersey, 08807.

2. On information and belief, Counterclaim Defendant Jazz 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.

Jurisdiction and Venue

3. These counterclaims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, under the United States Patent Laws, 35 U.S.C. § 1 *et seq.*, and under 21 U.S.C.

§ 355(j)(5)(C).

4. This Court has subject-matter jurisdiction based on 28 U.S.C. §§ 1331 and 1338(a), 2201, and 2202, and 21 U.S.C. § 355(j)(5)(C).

5. Jazz has submitted to personal jurisdiction in this Court by suing Amneal, and previously Roxane Laboratories Inc. over the same patents, in this District. On information and belief, Jazz sells products here, including the Xyrem® product at issue in this case, and Jazz regularly conducts business in this District.

6. This Court is the proper venue under 28 U.S.C. §§ 1391, 1400(b), and 21 U.S.C. § 355(j)(5)(C)(i)(II).

7. This is an action for declaratory relief seeking a declaration of noninfringement and invalidity of U.S. Patent Nos. 6,472,431 ("the '431 patent"), 6,780,889 ("the '889 patent"), 7,262,219 ("the '219 patent"), 7,851,506 ("the '506 patent"), 7,895,059 ("the '059 patent"), 8,263,650 ("the '650 patent"), 8,324,275 ("the '275 patent"), 7,668,730 ("the '730 patent"), 7,765,106 ("the '106 patent"), and 7,765,107 ("the '107 patent") (collectively, "the counterclaim patents").

Background

8. The face of the '431 patent, titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," indicates that it issued on October 29, 2002.

9. On information and belief, Jazz purports to be the owner of the '431 patent.

10. The face of the '889 patent, titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," indicates that it issued on August 24, 2004.

11. On information and belief, Jazz purports to be the owner of the '889 patent.

12. The face of the '219 patent, titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," indicates that it issued on August 28, 2007.

13. On information and belief, Jazz purports to be the owner of the '219 patent.

14. The face of the '506 patent, titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," indicates that it issued on December 14, 2010.

15. On information and belief, Jazz purports to be the owner of the '506 patent.

16. The face of the '059 patent, titled "Sensitive Drug Distribution System and Method," indicates that it issued on February 22, 2011.

17. On information and belief, Jazz purports to be the owner of the '059 patent.

18. The face of the '650 patent, titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," indicates that it issued on September 11, 2012.

19. On information and belief, Jazz purports to be the owner of the '650 patent.

20. The face of the '275 patent, titled "Microbiologically Sound and Stable Solutions of Gamma-Hydroxybutyrate Salt for the Treatment of Narcolepsy," indicates that it issued on December 4, 2012.

21. On information and belief, Jazz purports to be the owner of the '275 patent.

22. The face of the '730 patent, titled "Sensitive Drug Distribution System and Method," indicates that it issued on February 23, 2010. A true and correct copy of the '730 patent as it issued is attached to this Answer as Exhibit 1.

23. On information and belief, Jazz purports to be the owner of the '730 patent.

24. The face of the '106 patent, titled "Sensitive Drug Distribution System and Method," indicates that it issued on July 27, 2010. A true and correct copy of the '106 patent as it issued is attached to this Answer as Exhibit 2.

25. On information and belief, Jazz purports to be the owner of the '106 patent.

26. The face of the '107 patent, titled "Sensitive Drug Distribution System and Method," indicates that it issued on July 27, 2010. A true and correct copy of the '107 patent as it issued is attached to this Answer as Exhibit 3.

27. On information and belief, Jazz purports to be the owner of the '107 patent.

28. Under 21 U.S.C. § 355(b)(1)(G) and 21 C.F.R. § 314.53, respectively, an NDA holder, here Jazz, must provide to the FDA the patent number and expiration date of any patent(s) that it believes "claims the drug for which the applicant submitted the application or which claims a method of using such drug" and "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."

29. The FDA publishes patent(s) in an electronic, publicly available database called APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, also known as the "Orange Book." The FDA does not evaluate whether the claims of the disclosed patents actually cover the drug or method of using such drug, or whether the patent is valid; its actions are "purely ministerial." *aaiPharma Inc. v. Thompson*, 296 F.3d 227, 243 (4th Cir. 2002).

30. Amneal submitted ANDA No. 203631 ("Amneal's ANDA") to the FDA seeking approval to engage in the commercial manufacture, use, and/or sale of 500 mg/mL sodium oxybate oral solution ("Amneal's ANDA Product").

31. Each of the counterclaim patents, except for the '431 patent, are listed in the FDA's Orange Book.

32. Amneal submitted ANDA No. 203631 to the FDA seeking permission to market the proposed 500 mg/mL sodium oxybate oral solution.

33. Amneal's ANDA contains a certification ("Amneal's Paragraph IV Certification") under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that the claims of the '889,'219,'506,'059,'650, '275, '730, '106, and '107 patents are invalid, unenforceable, and/or will not be infringed by Amneal's ANDA Product.

34. Jazz filed its Complaint in this Court alleging that Amneal's act of submitting ANDA No. 203631 infringes the patents-in-suit.

35. Amneal denies that it infringes any valid and enforceable claim of the patents-in-suit, as well as the '730 patent, the '106 patent, and the '107 patent.

36. The present suit by Jazz impairs Amneal's ability to obtain approval of its ANDA No. 203821 and market the proposed sodium oxybate product described therein.

37. There remains a real and definite threat that Jazz may assert the '730, '106, and '107 patents against Amneal.

38. To the extent that any of the counterclaim patents, including the '730, '106, and/or '107 patents, forms the basis for a prior ANDA applicant's eligibility for 180-exclusivity under 21 USC 355(j)(5)(B)(iv), they will preclude the approval of Amneal's ANDA No. 203631 unless Amneal secures a final court decision of noninfringement, invalidity or unenforceability as to these patents.

39. Based on Jazz's filing of the Complaint, and Amneal's denial thereof, there is an actual, substantial, and continuing justiciable controversy between Amneal and Jazz having

adverse legal interests of sufficient immediacy and reality to warrant the issuance of a declaratory judgment regarding whether Amneal has infringed any valid and enforceable claim of the counterclaim patents.

40. Unless enjoined, Jazz will continue to assert that Amneal infringes the claims of the counterclaim patents, and Jazz is free to assert that Amneal infringes the claims of the '730,'106, and '107 patents. Amneal believes that this will continue to interfere with Amneal's business with respect to 500 mg/mL sodium oxybate oral solution.

41. Amneal will be irreparably harmed if Jazz is not enjoined from asserting the counterclaim patents against Amneal.

Count I

(Declaratory Judgment of Noninfringement)

42. Amneal repeats and realleges its responses in Paragraphs 1-41 of the Counterclaims as if fully set forth herein.

43. Amneal's proposed sodium oxybate product described in ANDA No. 203631 has not infringed, does not infringe, will not infringe, and will not contribute to or induce the infringement of any valid claim of the '431, '889, '219, '506, '059, '650, '275, '730, '106, and/or '107 patents, either literally or under the doctrine of equivalents.

44. Pursuant to the Federal Declaratory Judgment Act, 28 U.S.C. § 2201 *et seq.*, Amneal requests a declaration from the Court that Amneal does not infringe the claims of the '431, '889, '219, '506, '059, '650, '275, '730, '106, and/or '107 patents.

Count II

(Declaratory Judgment of Patent Invalidity)

45. Amneal repeats and realleges its responses in Paragraphs 1-45 of the Counterclaims as if fully set forth herein.

46. Each claim of the '431, '889, '219, '506, '059, '650, '275, '730, '106, and '107 patents is invalid for failure to comply with one or more of the conditions and requirements for patentability under Title 35 of the United States Code, including but not limited to, 35 U.S.C. §§ 101, 102, 103 and/or 112.

47. Pursuant to the Federal Declaratory Judgment Act, 28 U.S.C. § 2201 *et seq.*, Amneal requests a declaration from the Court that the claims of the '431, '889, '219, '506, '059, '650, '275, '730, '106, and/or'107 patents are invalid.

DEMAND FOR JUDGMENT

WHEREFORE, Amneal respectfully requests that this Court enter judgment in its favor and against Counterclaim Defendant Jazz and grant the following relief:

A. Dismiss Jazz's Complaint with prejudice and deny each and every prayer for relief contained therein;

B. Declare that by filing ANDA No. 203631, Amneal has not infringed, is not infringing, and will not infringe, nor contribute to or induce infringement of, literally or under the Doctrine of Equivalents, any valid and enforceable claim of the '431, '889, '219, '506, '059, '650, '275, '730, '106, and'107 patents and that Amneal has a lawful right to obtain FDA approval of its ANDA No. 203631 for 500 mg/mL sodium oxybate oral solution;

C. Declare that the claims of the '431, '889, '219, '506, '059, '650, '275, '730, '106, and'107 patents are invalid;

D. Enjoin Jazz, its officers, employees, agents, representatives, attorneys and others acting on its behalf, from threatening or initiating infringement litigation against Amneal or its customers, dealers or suppliers, or any prospective or present sellers, dealers, distributors or customers of Amneal, or charging them either verbally or in writing with infringement of any patent with respect to the sodium oxybate product described in ANDA No. 203631;

E. Declare that this is an exceptional case, and that Amneal be awarded its attorneys' fees and costs pursuant to 35 U.S.C. § 285 based on, among other things, Jazz's lack of good faith in filing its Complaint;

F. Award costs and expenses to Amneal; and

G. Award Amneal such further relief as this Court may deem necessary, just and proper.

Respectfully submitted,

LERNER, DAVID, LITTENBERG, KRUMHOLZ & MENTLIK, LLP
Attorneys for Defendant/Counterclaim Plaintiff Amneal Pharmaceuticals, LLC

Dated: April 15, 2013

By: s/ Paul H. Kochanski
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CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 11.2

I hereby certify pursuant to Local Civil Rule 11.2, that to the best of my knowledge, information, and belief one or more of the patents at issue in this action are at issue in other actions.

1. *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, case no. 10-6108 (D.N.J.) (Newark), before Judge Esther Salas. Plaintiff's complaint asserts United States Patent Nos. 6,780,889; 7,262,219; 7,668,730; 7,765,106; and 7,765,107.

2. *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, case no. 11-0660 (D.N.J.) (Newark), before Judge Esther Salas. Plaintiff's complaint asserts United States Patent Nos. 6,472,431 and 7,851,506. This action was consolidated with case no. 10-6108 (D.N.J.) (Newark) on April 5, 2011.

3. *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, case no. 11-2523 (D.N.J.) (Newark), before Judge Esther Salas. Plaintiff's complaint asserts United States Patent No. 7,895,059. This action was consolidated with case no. 10-6108 (D.N.J.) (Newark) on June 30, 2011.

4. *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, case no. 12-6761 (D.N.J.) (Newark), before Judge Esther Salas. Plaintiff's complaint asserts United States Patent No. 8,263,650.

5. *Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc.*, case no. 12-7459 (D.N.J.) (Newark), before Judge Esther Salas. Plaintiff's complaint asserts United States Patent No. 8,324,275.

Dated: April 15,2013

LERNER, DAVID, LITTENBERG, KRUMHOLZ & MENTLIK, LLP
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Document Filed Electronically

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC.,	:	
	:	Civil Action No. 13-391-ES-SCM
Plaintiff/Counterclaim Defendant,	:	
	:	District Judge Esther Salas
v.	:	Magistrate Judge Steven C. Mannion
	:	
AMNEAL PHARMACEUTICALS, LLC,	:	
	:	
Defendant/Counterclaim Plaintiff.	x	

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)

Pursuant to Fed. R. Civ. P. 41(a)(1)(A)(i) and 41(c), Defendant Amneal Pharmaceuticals, LLC hereby dismisses, without prejudice, its counterclaims pertaining to U.S. Patent Nos. 7,668,730; 7,765,106; and 7,765,107 (as contained in Counts I and II) against Plaintiff Jazz Pharmaceuticals, Inc. who has not yet served an answer or filed a motion for summary judgment pertaining to these counterclaims. The foregoing dismissal is expressly conditioned on the Covenant Not to Sue filed by Plaintiff Jazz on even date herewith, in this action. Amneal expressly

reserves the right to reassert claims for declaratory relief of noninfringement and invalidity if Jazz's convent not to sue is voided for any reason.

LERNER, DAVID, LITTENBERG
KRUMHOLZ & MENTLIK, LLP
Attorneys for Defendant/Counterclaim Plaintiff Amneal Pharmaceuticals, LLC

Dated: July 15, 2013

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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:	Eric B. Andersland/Valerie Murphy
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:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	17244031
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:	Eric B. Andersland/Valerie Murphy
Filer Authorized By:	Eric B. Andersland
Attorney Docket Number:	101.031US9
Receipt Date:	28-OCT-2013
Filing Date:	22-AUG-2012
Time Stamp:	15:47:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	2590
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 1.17 (Patent application and reexamination processing fees)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13592202_SIDS_10-28-13.pdf	215532 18ff7ab0950582cb9c8fcca45887cbfbc90b1619	yes	4
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Miscellaneous Incoming Letter		1	1	
	Transmittal Letter		2	3	
	Information Disclosure Statement (IDS) Form (SB08)		4	4	
Warnings:					
Information:					
2	Non Patent Literature	0001_answerdefensescounterclaims_41513.pdf	2638445 4eed8a2eb0721c20680f6dfbb26a0ca6b764fda7	no	22
Warnings:					
Information:					
3	Non Patent Literature	0002_noticevoluntarydismissal_71513.pdf	184312 ece6d8b7664fdf46f35ad990ee1d819acb62ebba	no	2
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30346 a13b1f8ce5f79201e44c2085ac5e0251b4ade727	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3068635		

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

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		

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

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

In compliance with the duty imposed by 37 C.F.R. § 1.56, and in accordance with 37 C.F.R. §§ 1.97 *et. seq*., the enclosed materials are brought to the attention of the Examiner for consideration in connection with the above-identified patent application. Applicants respectfully request that this Information Disclosure Statement be entered and the documents listed on the attached PTO 1449 Form be considered by the Examiner and made of record. Pursuant to the provisions of MPEP 609, 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(c)(2), Applicants hereby authorize the Commissioner to charge the fee of $180.00 as set forth in 37 C.F.R. § 1.17(p), to Deposit Account No. 19-0743. Please charge any additional fees or deficiencies, or credit any overpayment to Deposit Account No. 19-0743.

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

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

Respectfully submitted,

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

Date October 28, 2013 By /David D'Zurilla/
David D'Zurilla
Reg. No. 36,776

DDZ:vam

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Dayton T. Reardan Ph.D et al.

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

Docket No.:	101.031US9	Serial No.:	13/592,202
Filed:	August 22, 2012	Due Date:	N/A
Examiner:	Lena Najarian	Group Art Unit:	3686
Customer No.:	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 (2).

X Authorization to charge Deposit Account 19-0743 in the amount of $180.00 to cover the fee for consideration of Information Disclosure Statement under 37 C.F.R. § 1.97(c).

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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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 10/31/2013

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

EXAMINER	
NAJARIAN, LENA	
ART UNIT	PAPER NUMBER
3686	

NOTIFICATION DATE	DELIVERY MODE
10/31/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

slw@blackhillsip.com
uspto@slwip.com

Office Action Summary	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 --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/25/13*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-22 and 27-34* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☒ Claim(s) *2* is/are allowed.

7)☒ Claim(s) *1,3-22 and 27-34* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

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)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20130725; 20130924*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

Notice to Applicant

1. This communication is in response to the amendment filed 7/25/13. Claims 1 and 2 have been amended. Claims 23-26 have been canceled. Claims 29-34 are newly added. Claims 1-22 and 27-34 are pending.

Allowable Subject Matter

2. Claim 2 is allowed.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*,

686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 30-34 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 2, and 7-11 of of U.S. Patent No. 7,668,730 and claims 1, 6, 9, and 12-14 of U.S Patent No. 7,895,059. Although the claims at issue are not identical, they are not patentably distinct from each other because they contain similar limitations.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, 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. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 3-15, 19, and 27-29 are rejected under 35 U.S.C. 103(a) as being 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).

(A) Referring to claim 1, Moradi discloses a computer-implemented system for treatment of a 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 (para. 27 & 31 of Moradi);

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 (para. 27 & 43-45 of Moradi);

said patient fields, contained within the database schema, storing information sufficient to identify the patient for whom the company's prescription drug is prescribed (para. 27 & 43-45 of Moradi);

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 (para. 27 & 43-45 of Moradi);

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 (para. 31 and 37-38 of Moradi).

Moradi does not disclose that the patient is narcoleptic 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.

Talk About Sleep teaches that the patient is narcoleptic (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

Rosenblum discloses 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 (para. 100, 105 and 111 of Rosenblum).

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 and Rosenblum within Moradi. The motivation for doing so would have been to provide medications to only those that need it (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com) and so that all discrepancies may be resolved (para. 111 of Rosenblum)

(B) Referring to claim 3, Moradi discloses wherein the data processor is configured to process a second database query that identifies a potential misuse, abuse or diversion by the patient (para. 43, 45, 6, and Fig. 3 of Moradi).

Moradi does not disclose that the patient is narcoleptic.

Talk About Sleep teaches that the patient is narcoleptic (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned feature of Talk About Sleep within Moradi. The motivation for doing so would have been to provide medications to only those that need it (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

(C) Referring to claim 4, Moradi discloses wherein the data processor selectively blocks shipment of the prescription drug to the patient based upon said identifying by the database query (para. 45-46 of Moradi).

(D) Referring to claim 5, Moradi discloses wherein the prescription drug is shipped to the patient if no potential misuse, abuse or diversion is found for the patient (para. 43-45 and para. 6 of Moradi).

Moradi does not disclose that the patient is narcoleptic.

Talk About Sleep teaches that the patient is narcoleptic (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned feature of Talk About Sleep within Moradi.

The motivation for doing so would have been to provide medications to only those that need it (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

(E) Referring to claim 6, Moradi discloses wherein the single computer database is an exclusive database that receives data associated with all patients being prescribed the prescription drug that are associated with the company (para. 27 of Moradi).

(F) Referring to claim 7, Moradi discloses wherein the exclusive central pharmacy controls the single computer database (para. 24 & 35 of Moradi).

(G) Referring to claim 8, Moradi does not disclose wherein the prescription drug comprises gamma hydroxyl butyrate (GHB).

Talk About Sleep discloses wherein the prescription drug comprises gamma hydroxyl butyrate (GHB). (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned feature of Talk About Sleep within Moradi. The motivation for doing so would have been to treat narcoleptic patients (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

(H) Referring to claim 9, Moradi discloses wherein the single computer database comprises a relational database (para. 43 of Moradi).

(I) Referring to claim 10, Moradi discloses where the single computer database is distributed among multiple computers provided the database query that operates over all data relating to said prescription fields, prescriber fields, and patient fields for the prescription drug (para. 27, 31, 43-45 of Moradi).

(J) Referring to claim 11, Moradi discloses 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 (para. 27, 31, and 43-45 of Moradi).

(K) Referring to claim 12, Moradi discloses wherein the data processor is configured to process a second database query that identifies an expected date for a refill of the prescription drug (para. 25, 42, and 46 of Moradi).

(L) Referring to claim 13, Moradi discloses wherein the expected date is based on a prescription for the prescription drug and a date of a previous filling of the prescription (para. 25, 42, and 46 of Moradi).

(M) Referring to claim 14, Moradi discloses wherein the prescription identifies an amount of the prescription drug to be provided and a schedule for consumption of the prescription drug (para. 25, 42, and 46 of Moradi).

(N) Referring to claim 15, Moradi discloses 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 (para. 25 & 193 of Moradi).

(O) Referring to claim 19, Moradi does not expressly disclose wherein additional controls for distribution are selected in a negotiation with an approval body to garner the approval of distribution.

Talk About Sleep discloses wherein additional controls for distribution are selected in a negotiation with an approval body to garner the approval of distribution (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned feature of Talk About Sleep within Moradi. The motivation for doing so would have been to obtain permission to provide medications to those that need it (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

(P) Referring to claim 27, Moradi discloses 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 (para. 27 and 43-45 of Moradi).

(Q) Referring to claim 28, Moradi discloses 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 (para. 27 and 43-45 of Moradi).

(R) Claim 29 differs from claim 1 (see above rejection, incorporated herein) by reciting: 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.

Moradi discloses 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 (para. 31 and 37-38 of Moradi).

Rosenblum discloses 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 (Fig. 8 and para. 100, 105 and 111 of Rosenblum).

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 and Rosenblum within Moradi. The motivation for doing so would have been to provide medications to only those that need it (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com) and so that all discrepancies may be resolved (para. 111 of Rosenblum)

6. Claims 16-18, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Talk About Sleep ("An Interview with Orphan Medical about Xyrem"), in view of Rosenblum (US 2003/0050731 A1), and further in view of Lilly et al. (US 2004/0176985 A1).

(A) Referring to claims 16 and 17, Moradi, Talk About Sleep, and Rosenblum do not expressly disclose 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 and wherein one or more controls for distribution of the prescription drug are selected based on the identified pattern.

Lilly discloses 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 and wherein one or more controls for distribution of the prescription drug are selected based on the identified pattern (para. 33, 69, 54, 57-58, 61, and 11 of Lilly).

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 Lilly within Moradi, Talk About Sleep, and Rosenblum. The motivation for doing so would have been to immediately detect problems related to abuse, fraud, and misuse of medications (para. 57 of Lilly).
(B) Referring to claims 18 & 21, Moradi does not expressly disclose wherein the one or more controls are submitted to an approval body for approval of distribution of the prescription drug and wherein the approval body is the Food and Drug Administration (FDA) or the Drug Enforcement Agency (DEA).

Talk About Sleep discloses disclose wherein the one or more controls are submitted to an approval body for approval of distribution of the prescription drug and wherein the approval body is the Food and Drug Administration (FDA) or the Drug Enforcement Agency (DEA). (see “An Interview with Orphan Medical about Xyrem,” talkaboutsleep.com).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned feature of Talk About Sleep within Moradi. The motivation for doing so would have been to obtain permission from the government

to provide medications to those that need it (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

(C) Referring to claim 20, Moradi, Talk About Sleep, and Rosenblum do not expressly disclose wherein the data processor is used to add further controls until approval is obtained.

Lilly discloses wherein the data processor is used to add further controls until approval is obtained (para. 43 & 54 of Lilly).

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 Lilly within Moradi, Talk About Sleep, and Rosenblum. The motivation for doing so would have been to detect problems related to abuse, fraud, and misuse of medications (para. 57 of Lilly).

7. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Talk About Sleep ("An Interview with Orphan Medical about Xyrem"), in view of Rosenblum (US 2003/0050731 A1), and further in view of Brinkley et al. (5,963,919).

(A) Referring to claim 22, Moradi, Talk About Sleep, and Rosenblum do not expressly disclose wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent.

Brinkley discloses wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent (col. 4, line 62 – col. 5, line 8 of Brinkley).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to combine the aforementioned feature of Brinkley within Moradi, Talk About Sleep, and Rosenblum. The motivation for doing so would have been to trigger replenishment (col. 4, line 62 - col. 5, line 8 of Brinkley).

Response to Arguments

Applicant's arguments with respect to claims 1 and 22 have been considered but are moot because the arguments do not apply to any of the references being used in the current rejection.

Applicant's additional arguments filed 7/25/13 have been fully considered but they are not persuasive. Applicant's arguments will be addressed hereinbelow in the order in which they appear in the response filed 7/25/13.

(1) Applicant argues that Moradi and Xyrem do not teach or suggest the data processor selectively blocking shipment of the prescription drug to the patient based upon said identifying by the database query.

(A) As per the first argument, the Examiner respectfully submits that the claims do not state *how* the blocking is done. Moradi teaches a refill data calculator and performing a

check to make sure that the patient's prescription is not filled twice (see paragraph 45-46 of Moradi). As such, it is unclear how the language of the claims differs from the prior art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LENA NAJARIAN whose telephone number is (571)272-7072. The examiner can normally be reached on Monday - Friday, 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Elaine Gort can be reached on (571) 272-6781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LENA NAJARIAN/
Primary Examiner, Art Unit 3686
10/23/13

Notice of References Cited	Application/Control No. 13/592,202	Applicant(s)/Patent Under Reexamination REARDAN ET AL.	
	Examiner LENA NAJARIAN	Art Unit 3686	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2003/0050731	03-2003	Rosenblum, Ken	700/232
*	B	US-5,963,919	10-1999	Brinkley et al.	705/28
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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**
	"Application Serial No. 13/595,676, Notice of Allowance mailed 09-17-13", 8 pgs	
	"Civil Cover Sheet", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey), (9/12/13), 2 pgs	
	"Complaint for Patent Infringement with Exhibit A", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey), (9/12/2013), 76 pgs	
	"Fed. R. Civ. P. Rule 7.1 Disclosure Statement", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey), (9/12/13), 2 pgs	
	"Notice of Electronic Filing: Civil Inital Pleadings (Attorney/Credit Card) USE CASE 33-1)", Jazz Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, (United States District Court, District of New Jersey [LIVE]), (9/12/13), 1 pg	

EXAMINER /Lena Najarian/ **DATE CONSIDERED** 10/22/2013

* 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./

Modified form PTO/SB/08A(04-07) OMB 651-0031
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	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**

FOREIGN PATENT DOCUMENTS				
Examiner Initial *	**Foreign Document Number**	**Publication Date**	**Name of Patentee or Applicant of cited Document**	**T 1**

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 , Response filed 05-31-13 to Non Final Office Action mailed 03-21-13", 14 pgs	
	"Application Serial No. 13/595,676, Examiner Interview Summary mailed 05-30-13", 3 pgs	

/Lena Najarian/ 10/22/2013

EXAMINER **DATE CONSIDERED**

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

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

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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						
	1	÷	✓	✓						
	2	÷	✓	=						
	3	÷	✓	✓						
	4	÷	✓	✓						
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	12	÷	✓	✓						
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	22	÷	✓	✓						
	23	÷	N	-						
	24	÷	N	-						
	25	÷	N	-						
	26	÷	N	-						
	27		✓	✓						
	28		✓	✓						
	29			✓						
	30			✓						
	31			✓						
	32			✓						
	33			✓						
	34			✓						

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S9	42	inventory same reconcil$ same prescription	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/10/22 14:34
S14	62	cash with (pay$) with (drug or pharm$ or medicine or medication or pill or prescri$) with (alert$ or fraud or indicat$ or note or abuse or diver$ or misus$ or flag$)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/10/22 16:04
S17	66	cycle adj1 count$3 same inventory and (drug or prescription or medication or medicine or pharmaceutical)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/10/22 16:37
S18	66	cycle adj1 count$3 same inventory and (drug or prescription or medication or medicine or pharmaceutical)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/10/22 19:13
S19	16	cycle adj1 count$3 same inventory and (drug or prescription or medication or medicine or pharmaceutical) and reconcil$ same inventory	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/10/22 19:14
S20	358	(payment) same method same (drug or pharm$ or medicine or medication or pill or prescri$) same (alert$ or fraud or indicat$ or note or abuse or diver$ or misus$)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/10/23 12:40
S21	57	(payment) adj2 method same (drug or pharm$ or medicine or medication or pill or prescri$) same (alert$ or fraud or indicat$ or note or abuse or diver$ or misus$)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/10/23 12:40
S22	96	(payment) adj2 method with cash with (alert$ or fraud or indicat$ or note or abuse or diver$ or misus$)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/10/23 12:44

10/23/2013 4:42:07 PM
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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 No.: 101.031US9	
Customer No.: 107632		Confirmation No.: 5805	

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

TERMINAL DISCLAIMER

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

I, David D'Zurilla, am an attorney of record for the above-identified patent application as evidenced by the Power of Attorney filed in the present application on August 22, 2012. This Terminal Disclaimer is submitted on behalf of Jazz Pharmaceuticals, Inc., the assignee of the present invention. As an attorney of record, I am empowered to act on behalf of the assignee and, in accordance with 37 C.F.R. § 1.321(b)(1)(iv), to sign this Terminal Disclaimer.

Certificate Under 37 C.F.R. § 3.73(b)

The assignee, Jazz Pharmaceuticals, Inc., hereby certifies that it is the owner of the entire right, title and interest in and to both the above-identified application (U.S. Application Serial No. 13/592,202) and to U.S. Patent No. 7,668,730, by virtue of the executed and filed assignment transferring title of both of these applications. The above-identified application (U.S. Application Serial No. 13/592,202) is a continuation of U.S. Application Serial No. 13/013,680 (now abandoned), which is a continuation of U.S. Patent No. 7,895,059. U.S. Patent No. 7,895,059 is a continuation of U.S. Patent No. 7,668,730. The assignment for U.S. Patent No. 7,668,730 was recorded on December 22, 2010 at Reel 025604, Frames 0903 - 0906. That assignment assigned the application underlying U.S. Patent No. 7,668,730, as well as, *inter alia*, all continuations and divisionals based upon that application. The above-identified application was thus assigned to the assignee by the identified assignment.

The undersigned representative of the assignee has reviewed the evidentiary documents of title and certifies that to the best of assignee's knowledge and belief, title is in the assignee seeking to take the action set forth in this disclaimer.

Terminal Disclaimer

The assignee of the above-identified application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the above-identified patent application, which would extend beyond the expiration date of the full statutory term, as presently shortened by any terminal disclaimers, of U.S. Patent No. 7,668,730. The assignee hereby agrees that any patent to be granted on the above-identified application shall be enforceable only for and during such period as such patent is commonly owned with U.S. Patent No. 7,668,730. This agreement shall run with any patent granted on the above-identified application and shall be binding upon the assignee's successors and assigns.

Limitations on the Disclaimer

The assignee does not disclaim any terminal part of any patent granted on the above-identified application prior to the expiration date of the full statutory term as presently shortened by any terminal disclaimer of U.S. Patent No. 7,668,730 in the event that it later expires before such term for failure to pay a maintenance fee, is held unenforceable, is found invalid, is statutorily disclaimed, is the subject of a reexamination certificate cancelling all claims, or is otherwise terminated prior to the expiration date of its statutory term as presently shortened by any terminal disclaimer.

Fee Status

Please charge Deposit Account 19-0743 in the amount of $160.00 which is required under 37 C.F.R. § 1.20(d) to file a statutory disclaimer. The Commissioner of Patents and Trademarks is hereby authorized to 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 December 31, 2013

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

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 No.: 101.031US9	
Customer No.: 107632		Confirmation No.: 5805	

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

TERMINAL DISCLAIMER

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

I, David D'Zurilla, am an attorney of record for the above-identified patent application as evidenced by the Power of Attorney filed in the present application on August 22, 2012. This Terminal Disclaimer is submitted on behalf of Jazz Pharmaceuticals, Inc., the assignee of the present invention. As an attorney of record, I am empowered to act on behalf of the assignee and, in accordance with 37 C.F.R. § 1.321(b)(1)(iv), to sign this Terminal Disclaimer.

Certificate Under 37 C.F.R. § 3.73(b)

The assignee, Jazz Pharmaceuticals, Inc., hereby certifies that it is the owner of the entire right, title and interest in and to both the above-identified application (U.S. Application Serial No. 13/592,202) and to U.S. Patent No. 7,895,059, by virtue of the executed and filed assignment transferring title of both of these applications. The above-identified application (U.S. Application Serial No. 13/592,202) is a continuation of U.S. Application Serial No. 13/013,680 (now abandoned), which is a continuation of U.S. Patent No. 7,895,059. U.S. Patent No. 7,895,059 is a continuation of U.S. Patent No. 7,668,730. The assignment for U.S. Patent No. 7,668,730 was recorded on December 22, 2010 at Reel 025604, Frames 0903 - 0906. That assignment assigned the application underlying U.S. Patent No. 7,668,730, as well as, *inter alia*, all continuations and divisionals based upon that application. The above-identified application was thus assigned to the assignee by the identified assignment.

The undersigned representative of the assignee has reviewed the evidentiary documents of title and certifies that to the best of assignee's knowledge and belief, title is in the assignee seeking to take the action set forth in this disclaimer.

Terminal Disclaimer

The assignee of the above-identified application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the above-identified patent application, which would extend beyond the expiration date of the full statutory term, as presently shortened by any terminal disclaimers, of U.S. Patent No. 7,895,059. The assignee hereby agrees that any patent to be granted on the above-identified application shall be enforceable only for and during such period as such patent is commonly owned with U.S. Patent No. 7,895,059. This agreement shall run with any patent granted on the above-identified application and shall be binding upon the assignee's successors and assigns.

Limitations on the Disclaimer

The assignee does not disclaim any terminal part of any patent granted on the above-identified application prior to the expiration date of the full statutory term as presently shortened by any terminal disclaimer of U.S. Patent No. 7,895,059 in the event that it later expires before such term for failure to pay a maintenance fee, is held unenforceable, is found invalid, is statutorily disclaimed, is the subject of a reexamination certificate cancelling all claims, or is otherwise terminated prior to the expiration date of its statutory term as presently shortened by any terminal disclaimer.

Fee Status

Please charge Deposit Account 19-0743 in the amount of $160.00 which is required under 37 C.F.R. § 1.20(d) to file a statutory disclaimer. The Commissioner of Patents and Trademarks is hereby authorized to 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 December 31, 2013

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

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	

AMENDMENT & RESPONSE UNDER 37 C.F.R. 1.116

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

In response to the Final Office Action dated October 31, 2013, please amend the application as follows.

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.

REMARKS

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

Claims 1, 4, 5, 6, 10, 12, 29, and 30 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.

Double Patenting Rejection

Claims 30-34 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 2, and 7-11 of U.S. Patent No. 7,668,730 and claims 1, 6, 9, and 12-14 of U.S Patent No. 7,895,059.

Applicant does not admit that claims 30-34 are unpatentable in view of claims 1, 2, and 7-11 of U.S. Patent No. 7,668,730. Applicant does not admit that claims 30-34 are unpatentable in view of claims 1, 6, 9, and 12-14 of U.S. Patent No. 7,895,059. Notwithstanding, a Terminal Disclaimer in compliance with 37 C.F.R. § 1.321(b) is being submitted to obviate these rejections. Applicant respectfully submits that the Terminal Disclaimer places claims 30-34 into a condition for allowance, and Applicant respectfully requests a notice to that effect.

The Rejection of Claims Under § 103

Claims 1, 3-15, 19, and 27-29 are rejected under 35 U.S.C. 103(a) as allegedly being 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).

Claims 16-18, 20, and 21 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Talk About Sleep ("An Interview with Orphan Medical about Xyrem"), in view of Rosenblum (US 2003/0050731 A1), and further in view of Lilly et al. (US 2004/0176985 A1).

Claim 22 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Talk About Sleep ("An Interview with Orphan Medical

about Xyrem"), in view of Rosenblum (US 2003/0050731 A1), and further in view of Brinkley et al. (5,963,919).

Applicant gratefully acknowledges the notice in the Final Office Action that dependent claim 2 is allowed. Applicant has incorporated the features of claim 2 into claim 1. Applicant respectfully submits that this places claims 1, 4-22, and 27-28 into a condition for allowance, and respectfully requests a notice to that effect.

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 December 31, 2013

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

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

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:				
Statutory or Terminal Disclaimer	1814	2	160	320
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**320**

Electronic Acknowledgement Receipt	
EFS ID:	17790293
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:	31-DEC-2013
Filing Date:	22-AUG-2012
Time Stamp:	15:27:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$320
RAM confirmation Number	2364
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		101031us9_resp_123113.pdf	213317 96975783b58a3836c71c30eab5a468d5327ffd66	yes	18

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Miscellaneous Incoming Letter	1	1
	Terminal Disclaimer Filed	2	4
	Terminal Disclaimer Filed	5	7
	Response After Final Action	8	8
	Claims	9	15
	Applicant Arguments/Remarks Made in an Amendment	16	18

Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30358 3f935620d744d0df676b1bc93ad9def2077c50c3	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	243675		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Dayton T. Reardan Ph.D et al.

Title: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

Docket No.:	101.031US9	Serial No.:	13/592,202
Filed:	August 22, 2012	Due Date:	January 31, 2014
Examiner:	Lena Najarian	Group Art Unit:	3686
Customer No.:	107632	Confirmation No.:	5805

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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 Amendment and Response under 37 C.F.R. § 1.116 (11 pgs.)
X Terminal Disclaimer over U.S. Patent No. 7,895,059 (3 pgs.)
X Terminal Disclaimer over U.S. Patent No. 7,668,730 (3 pgs.)
X Authorization to charge Deposit Account 19-0743 in the amount of $320.00 to cover the fee for the Terminal Disclaimer

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

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 527 027 A1**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number : **92307070.0**

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(51) Int. Cl.[5] : **A01C 23/04,** A01M 7/00, B05B 7/32

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(71) Applicant : **HUNTING ENGINEERING LIMITED**
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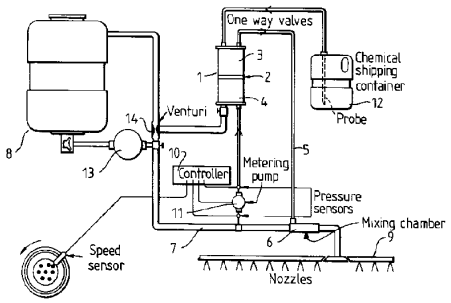
(54) **Fluid dispenser.**

(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.

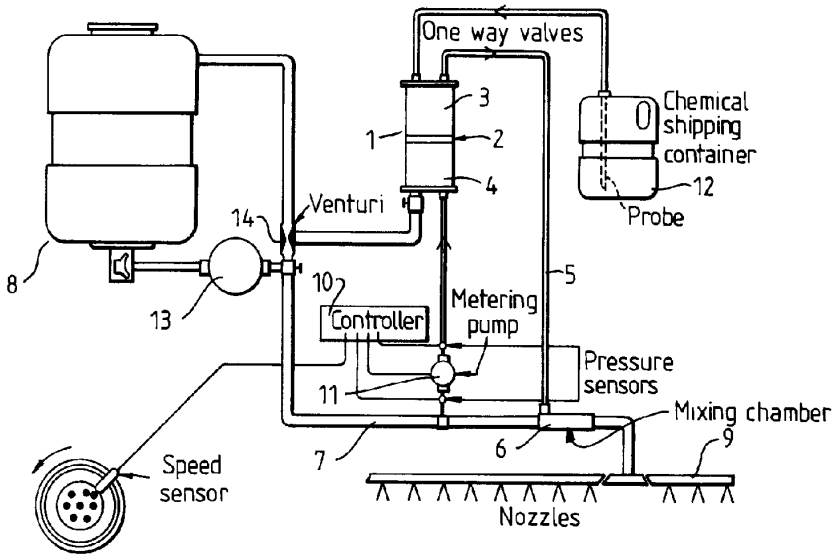


FIG. 2

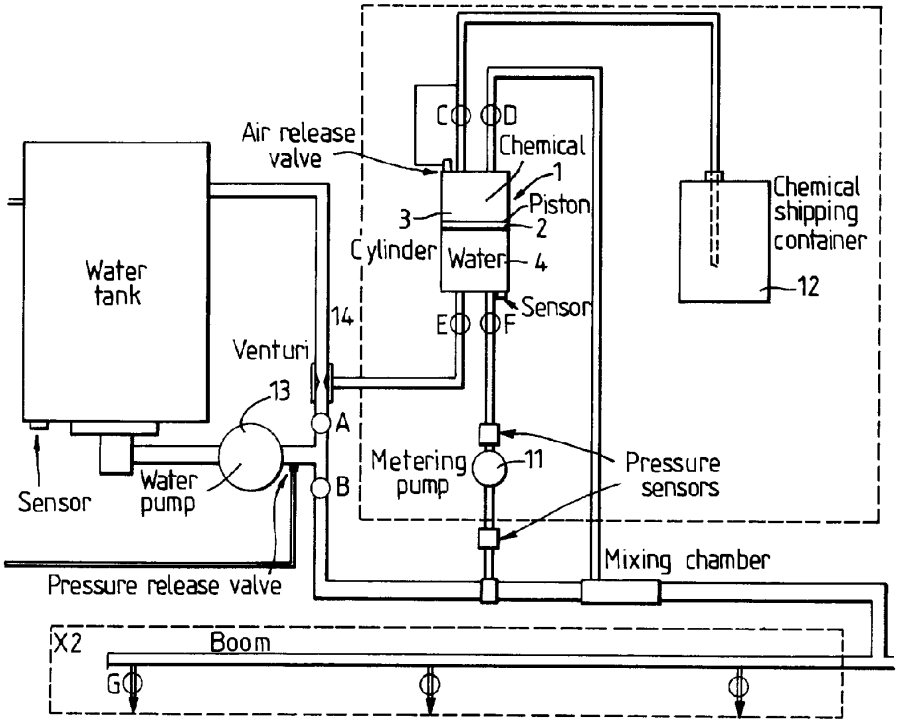


FIG. 3

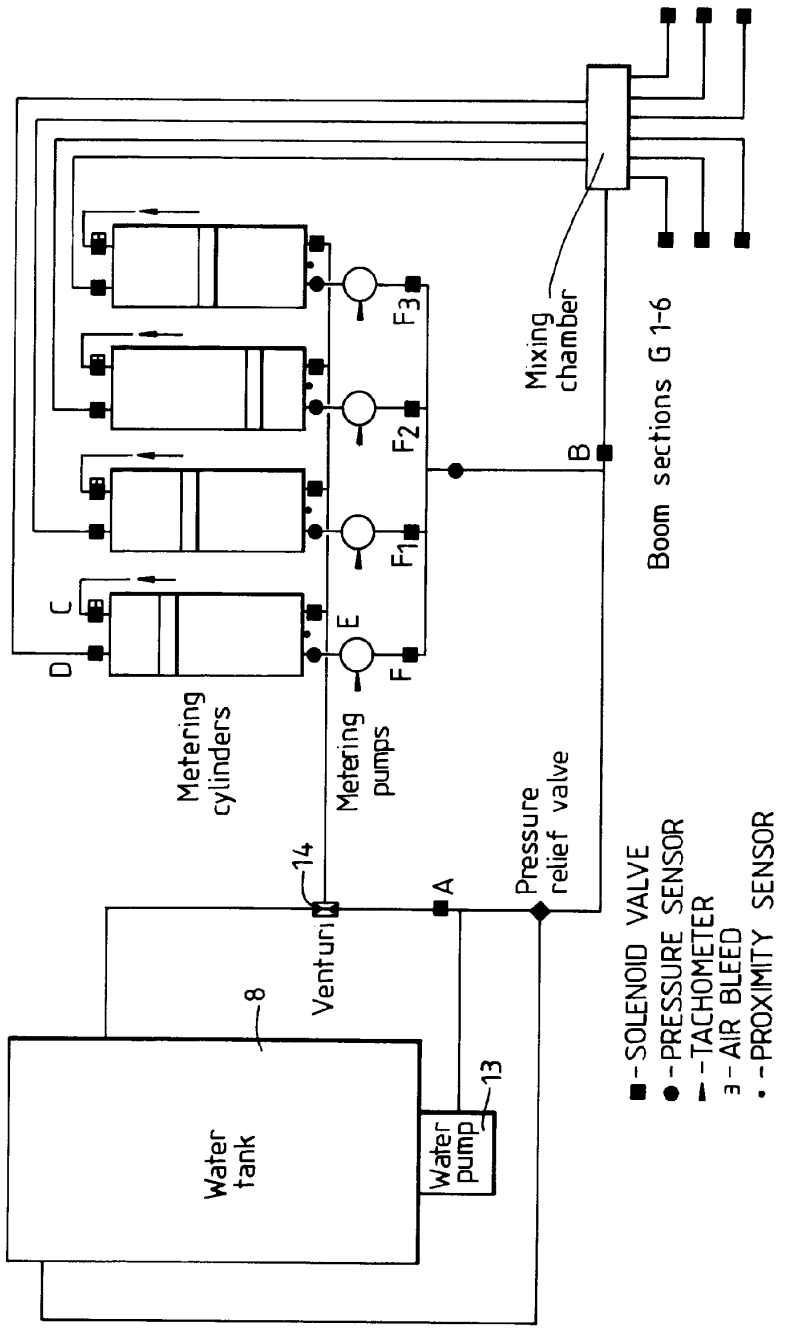
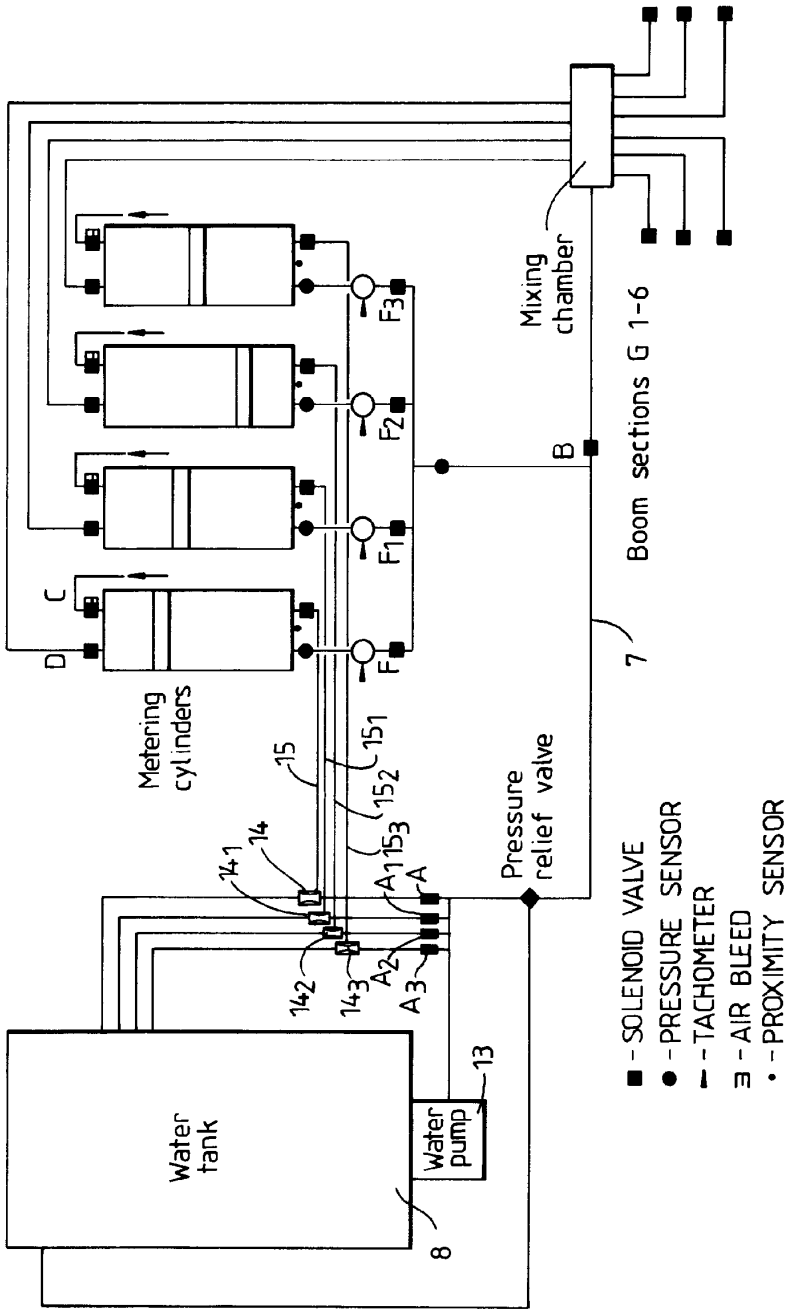


FIG. 4



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

EPO FORM 1503 03.82 (P0401)

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	
	"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 **DATE CONSIDERED**

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

IN THE UNITED STATES 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

Respectfully submitted,

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CERTIFICATE OF SERVICE

This is to certify that on November 7, 2013, a true and correct copy of **DEFENDANT'S PRELIMINARY INVALIDITY CONTENTIONS** was served by electronic mail and Fed Ex on the following counsel of record:

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Dated: November 7, 2013

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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		

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR 1.97(i)

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. Since a Notice of Allowance has been issued, Applicants understand that the enclosed material may be placed in the file and may not be considered by the U.S. Patent Office. Kindly consider this submission in accordance with USPTO procedure, e.g., MPEP609.

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, the Commissioner is hereby authorized to charge the required fees to Deposit Account No. 19-0743 if deemed necessary.

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,

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/ /

Date December 31, 2013 By _____
David D'Zurilla
Reg. No. 36,776

DDZ:vam

Electronic Acknowledgement Receipt

EFS ID:	17790304
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:	Eric B. Andersland/Valerie Murphy
Filer Authorized By:	Eric B. Andersland
Attorney Docket Number:	101.031US9
Receipt Date:	31-DEC-2013
Filing Date:	22-AUG-2012
Time Stamp:	15:28:31
Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	no

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		13592202_SIDS_12-31-13.pdf	270849 7e7cd2f69daa40533d56745d8e93273dea07fc36	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Miscellaneous Incoming Letter	1	1
	Transmittal Letter	2	3
	Information Disclosure Statement (IDS) Form (SB08)	4	4

Warnings:					
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2	Foreign Reference	0001_ep0527027a1.pdf	867338 3a0fcede67cc0f0fbc90d7d15c8671c6117433da	no	8
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Information:					
3	Non Patent Literature	0002_amnealspreliminvalidityttentions_110713_.pdf	811439 c9544c3751ab5142b1240447a865820ca335662b	no	182
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Warnings:					
Information:					
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Information:					
8	Non Patent Literature	0007_oxtoby_1996.pdf	2860931 c12a6270b2c81f4bd39aec602047db8f529c1877	no	7
Warnings:					

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Total Files Size (in bytes):	37726102

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.

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

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CONFIDENTIAL

November 20, 2013

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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

VIA REGISTERED EXPRESS MAIL
RETURN RECEIPT REQUESTED

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 acid, 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 facie 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.

[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, Col. 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, col. 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; confinning 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).

e. 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 "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). 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 Borssand, 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; *see 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 treatment~~ 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;