IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS LLC, Defendant.	)	C.A. No. 21-691 (MN)
JAZZ PHARMACEUTICALS, INC. and JAZZ PHARMACEUTICALS IRELAND LIMITED, Plaintiffs, v. AVADEL CNS PHARMACEUTICALS LLC, Defendant.	)	C.A. No. 21-1138 (MN)
JAZZ PHARMACEUTICALS, INC. and JAZZ PHARMACEUTICALS IRELAND LIMITED, Plaintiffs, v. AVADEL CNS PHARMACEUTICALS LLC, Defendant.	)	C.A. No. 21-1594 (MN)

JOINT CLAIM CONSTRUCTION APPENDIX

Jazz's Exhibits

EXHIBIT	DESCRIPTION
Exhibit 1	U.S. Patent No. 10,758,488
Exhibit 2	March 6, 2020 Response to Office Action in U.S. Patent Application No. 16/025,487
Exhibit 3	Dictionary of Pharmacy (2004), definition of "sustained release"
Exhibit 4	Webster's New Explorer Medical Dictionary (2006), definition of "sustained release"
Exhibit 5	U.S. Patent No. 11,077,079
Exhibit 6	Srikanth, M.V., et al., Ion-exchange resins as controlled drug delivery carriers, Journal of Scientific Research. 2010;2(3):597
Exhibit 7	U.S. Patent No. 11,147,782
Exhibit 8	June 18, 2021 Office Action in U.S. Patent Application No. 17/210,064
Exhibit 9	European Medicines Agency, Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (November 20, 2014)
Exhibit 10	U.S. Patent No. 8,731,963
Exhibit 11	Merriam-Webster's Collegiate Dictionary (10th Ed. 2001), definition of "cash"
Exhibit 12	Random House Webster's College Dictionary (2001), definitions of "database" and "system"
Exhibit 13	The American Heritage Dictionary of the English Language (4th Ed. 2000), definitions of "database" and "system"
Exhibit 14	The New Oxford American Dictionary (2001), definitions of "database" and "system"
Exhibit 15	Macmillan English Dictionary (2002), definitions of "database" and "system"
Exhibit 16	U.S. Patent No. 7,895,059
Exhibit 17	U.S. Patent No. 7,765,106

Avadel's Exhibits

EXHIBIT	DESCRIPTION
A	Application No. 16/025,487 File History, 3/6/2020 Amendments
B	Application No. 16/025,487 File History, 3/6/2020 Applicant Remarks
C	Application No. 16/025,487 File History, 3/6/2020 Declaration of Clark Allphin
D	*Sensormatic Electronics, LLC v. Genetec (USA) Inc.*, C.A. No. 20-760-MN, D.I. 68 (D. Del Sep. 29, 2021)
E	Excerpt of Cambridge Dictionary of American English
F	*Cirba Inc. v. VMware, Inc.*, C.A. No. 19-742-LPS, D.I. 1160 (D. Del. Feb. 24, 2022)
G	Excerpt of Wiley Electrical and Electronics Dictionary
H	U.S. Patent No. 7,765,106
I	U.S. Patent No. 8,457,988
J	*Amneal Pharm. LLC v. Jazz Pharm., Inc.*, IPR2015-01903, Paper 14, Patent Owner Response (Jun. 3, 2016)
K	U.S. Patent No. 8,771,735
L	Excerpt of The Concise Oxford Dictionary of Current English
M	Excerpt of Random House Webster's Dictionary of American English
N	Application No. 10,322,348 File History, 12/3/2007 Reply Brief
O	Application No. 10,322,348 File History, 10/3/2005 Applicant Remarks
P	Application No. 10,322,348 File History, 3/29/2006 Applicant Remarks
Q	Application No. 13/592,202 File History, 7/25/2013 Applicant Remarks
R	Application No. 14/219,904 (U.S. Patent Application Pub. No. US 2014/0207480 A1)
S	Application No. 14/219,904, File History, 3/2/2015 Office Action
T	Application No. 14/219,904, File History, 7/8/2015 Applicant Remarks
U	*Jazz Pharm., Inc. v. Watson Labs. Inc.*, C.A. No. 14-7757, D.I. 20 at 12 (D.N.J. Apr. 20, 2015)

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EXHIBIT 1

US010758488B2

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

(10) **Patent No.: US 10,758,488 B2**
(45) **Date of Patent: Sep. 1, 2020**

(54) **CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES**

(71) Applicant: **JAZZ PHARMACEUTICALS, INC.**, Palo Alto, CA (US)

(72) Inventors: **Clark Allphin**, Seattle, WA (US); **James Pfeiffer**, Palo Alto, CA (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.: **16/025,487**

(22) Filed: **Jul. 2, 2018**

(65) **Prior Publication Data**

US 2018/0318222 A1 Nov. 8, 2018

Related U.S. Application Data

(63) Continuation of application No. 13/071,369, filed on Mar. 24, 2011, now abandoned.

(60) Provisional application No. 61/317,212, filed on Mar. 24, 2010.

(51) **Int. Cl.**

A61K 9/20	(2006.01)
A61K 9/28	(2006.01)
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A61K 9/24	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 9/2054*** (2013.01); ***A61K 9/209*** (2013.01); ***A61K 9/284*** (2013.01); ***A61K 9/286*** (2013.01); ***A61K 9/2833*** (2013.01); ***A61K 9/2846*** (2013.01); ***A61K 9/2853*** (2013.01); ***A61K 9/2866*** (2013.01); ***A61K 9/2893*** (2013.01); ***A61K 31/19*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Controlled release dosage forms are described herein. The controlled release formulations described herein provide prolonged delivery of high dose drugs that are highly water soluble and highly hygroscopic. In specific embodiments, controlled release dosage forms for delivery of a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. The controlled release dosage forms described herein may incorporate both controlled release and immediate release formulations in a single unit dosage form.

12 Claims, 9 Drawing Sheets

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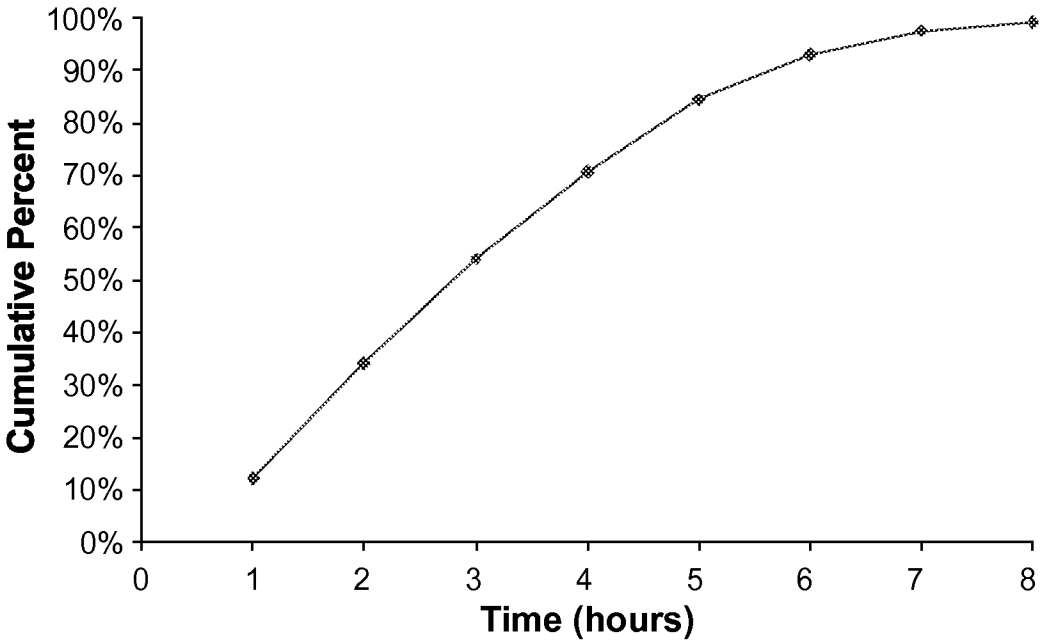

Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)

FIG. 1

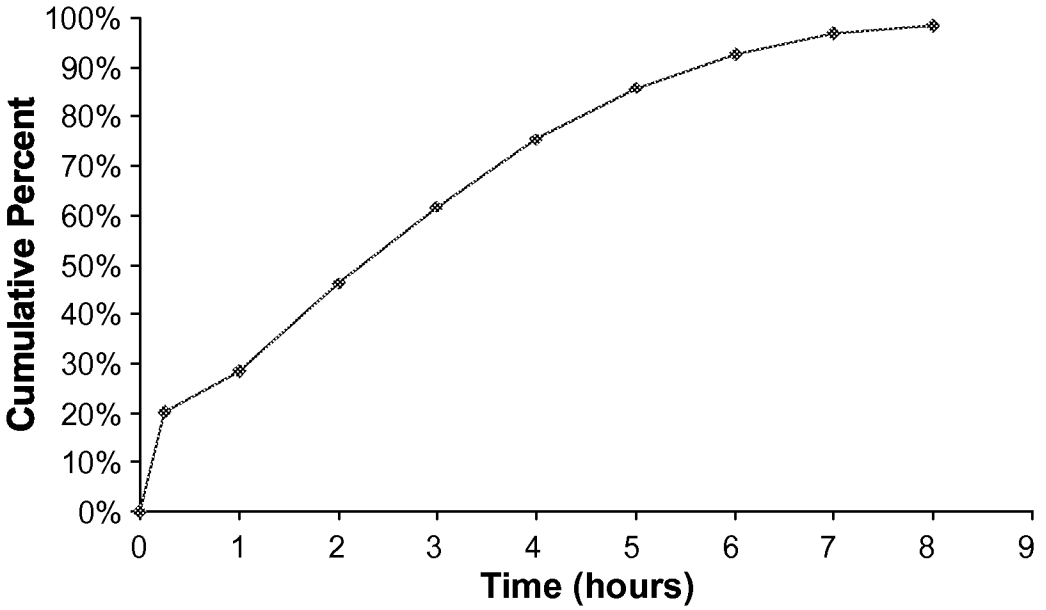

Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
9
Time (hours)

FIG. 2

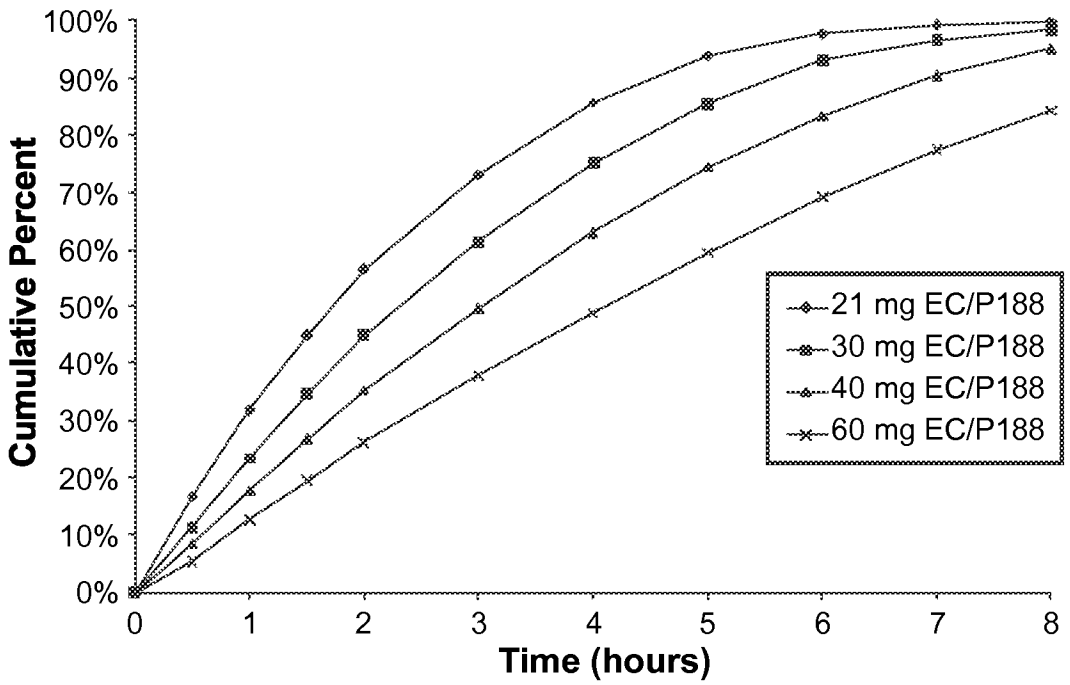

Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
21 mg EC/P188
30 mg EC/P188
40 mg EC/P188
60 mg EC/P188

FIG. 3

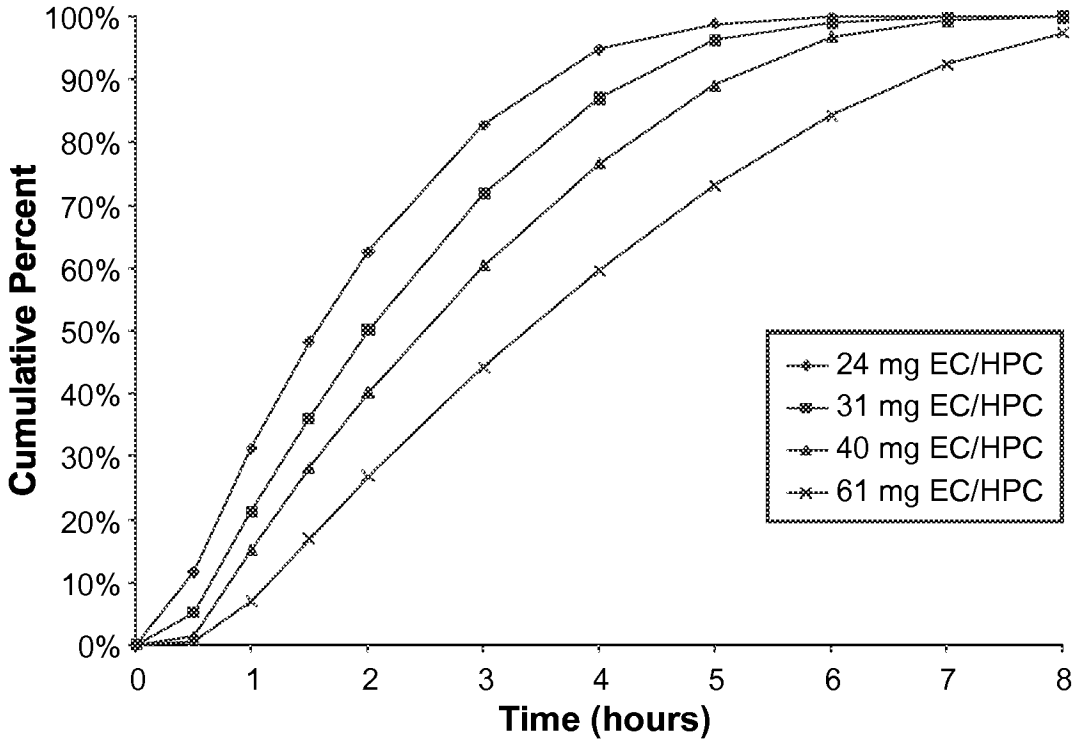

Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
24 mg EC/HPC
31 mg EC/HPC
40 mg EC/HPC
61 mg EC/HPC

FIG. 4

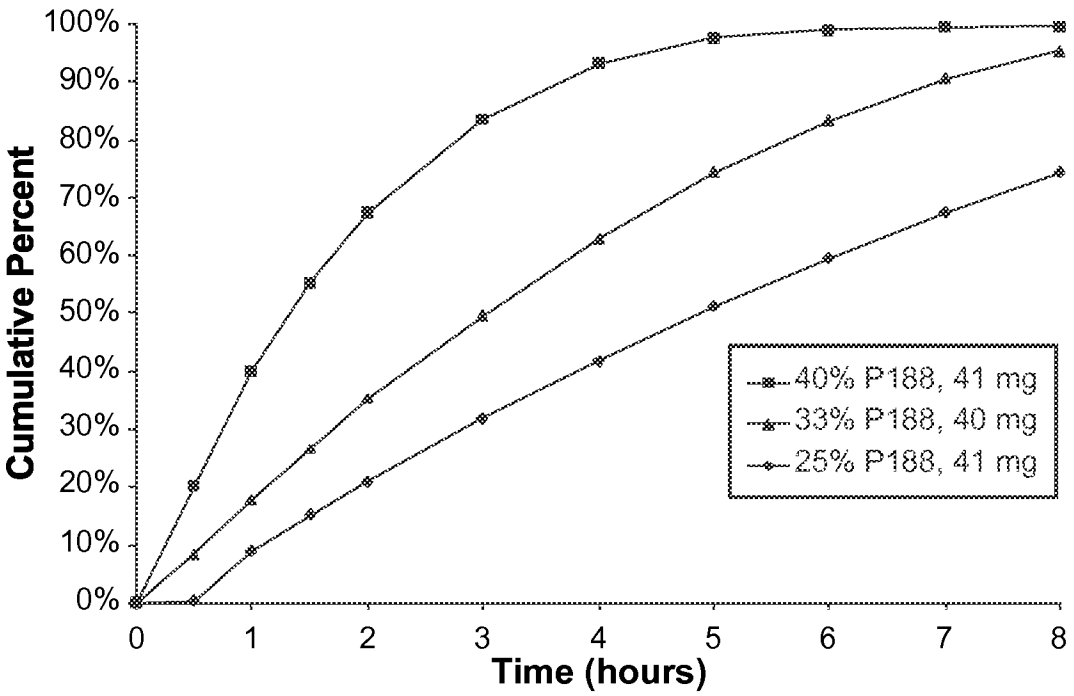

Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
40% P188, 41 mg
33% P188, 40 mg
25% P188, 41 mg

FIG. 5

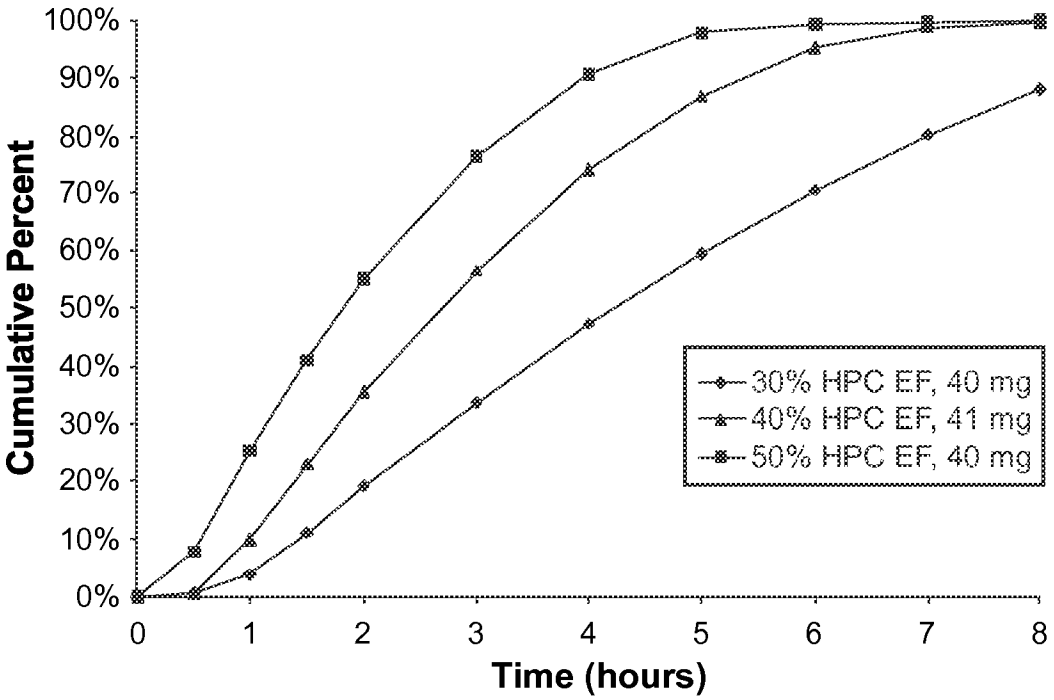
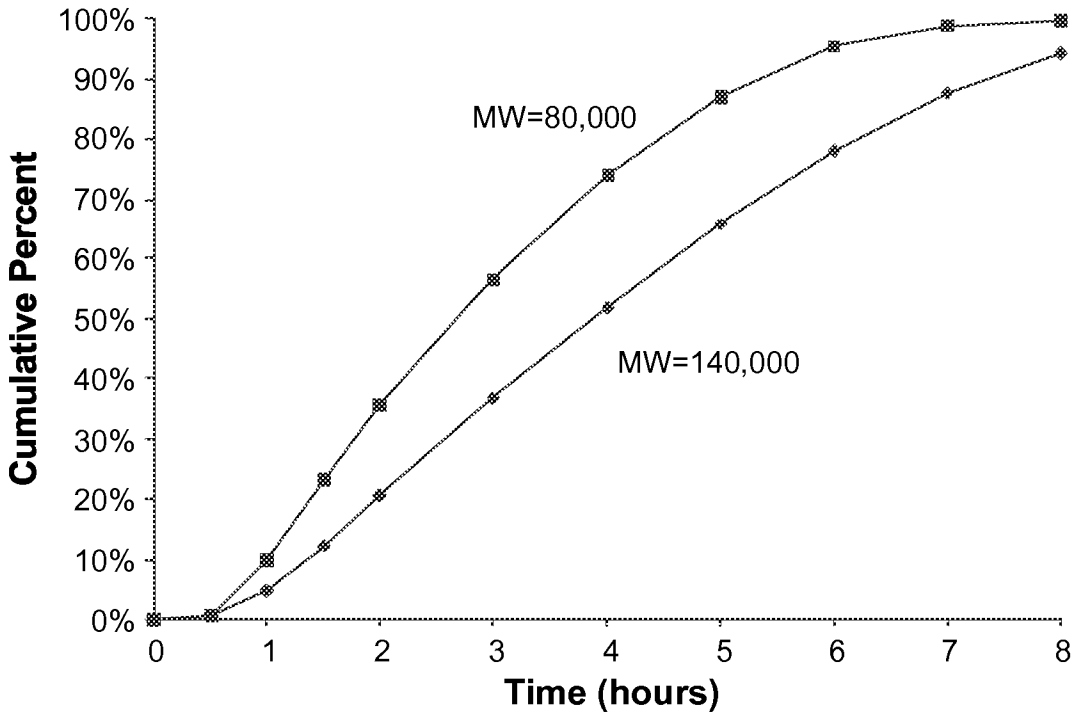

Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
30% HPC EF, 40 mg
40% HPC EF, 41 mg
50% HPC EF, 40 mg

FIG. 6


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
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MW=140,000
0
1
2
3
4
5
6
7
8
Time (hours)

FIG. 7

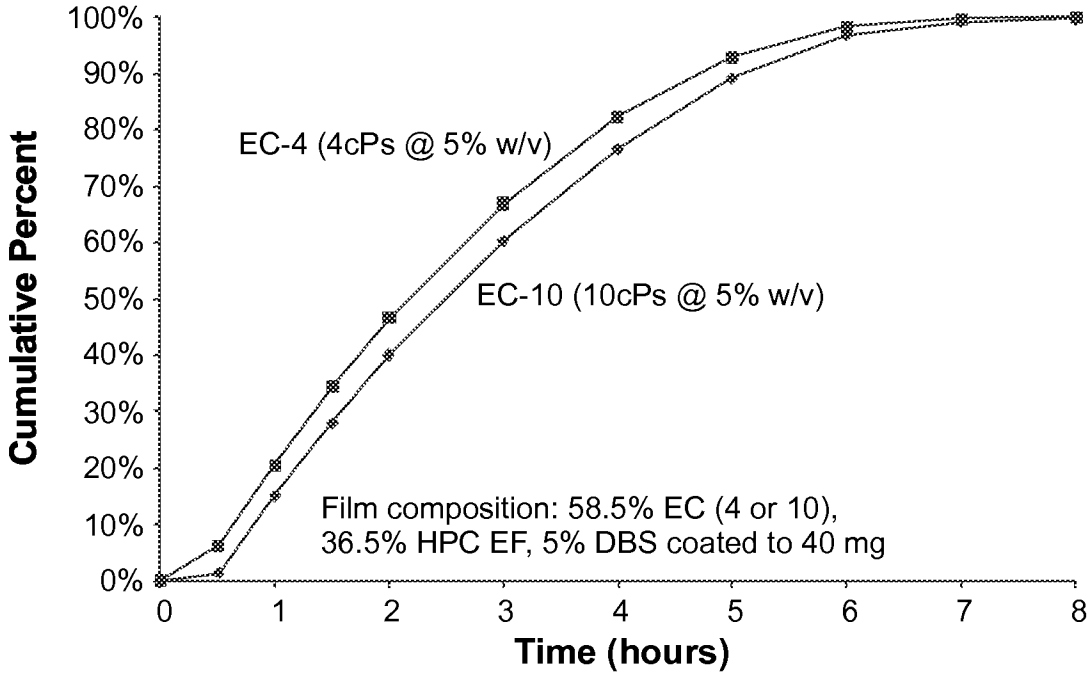

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
EC-4 (4cPs @ 5% w/v)
EC-10 (10cPs @ 5% w/v)
Film composition: 58.5% EC (4 or 10),
36.5% HPC EF, 5% DBS coated to 40 mg
0
1
2
3
4
5
6
7
8
Time (hours)

FIG. 8

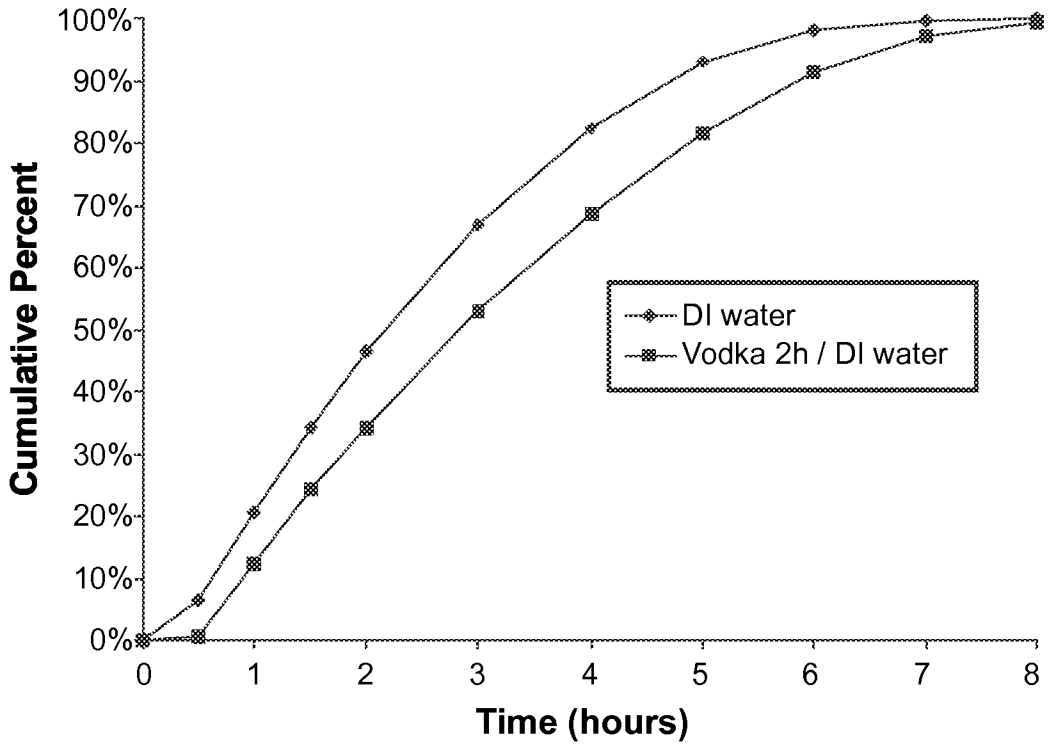

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9A

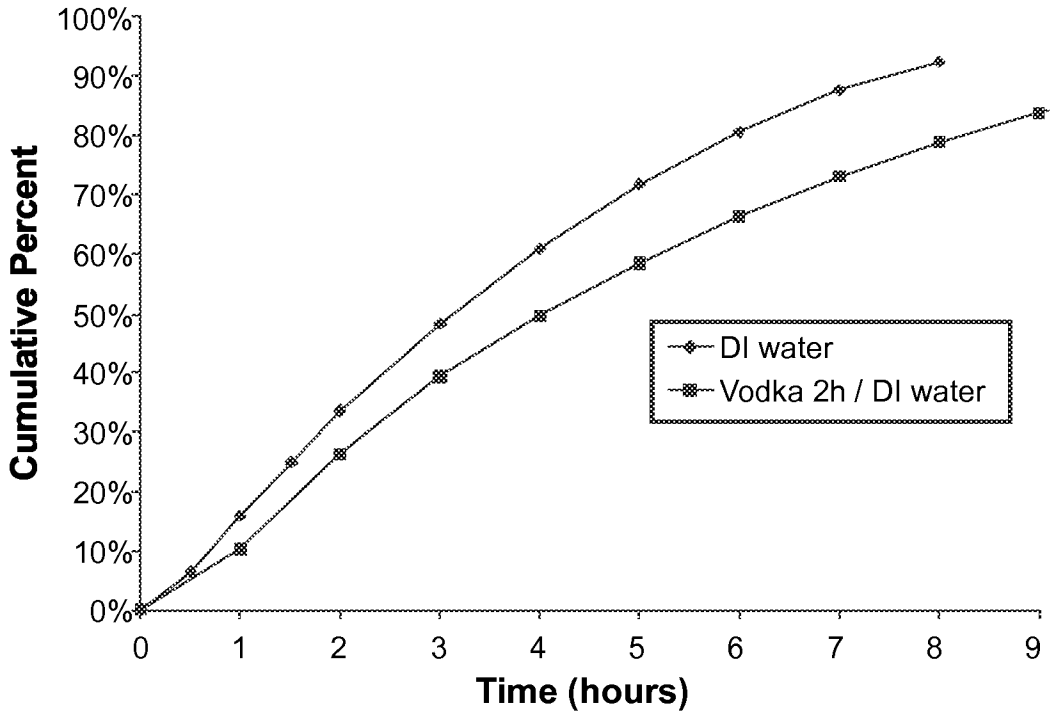

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
9
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9B

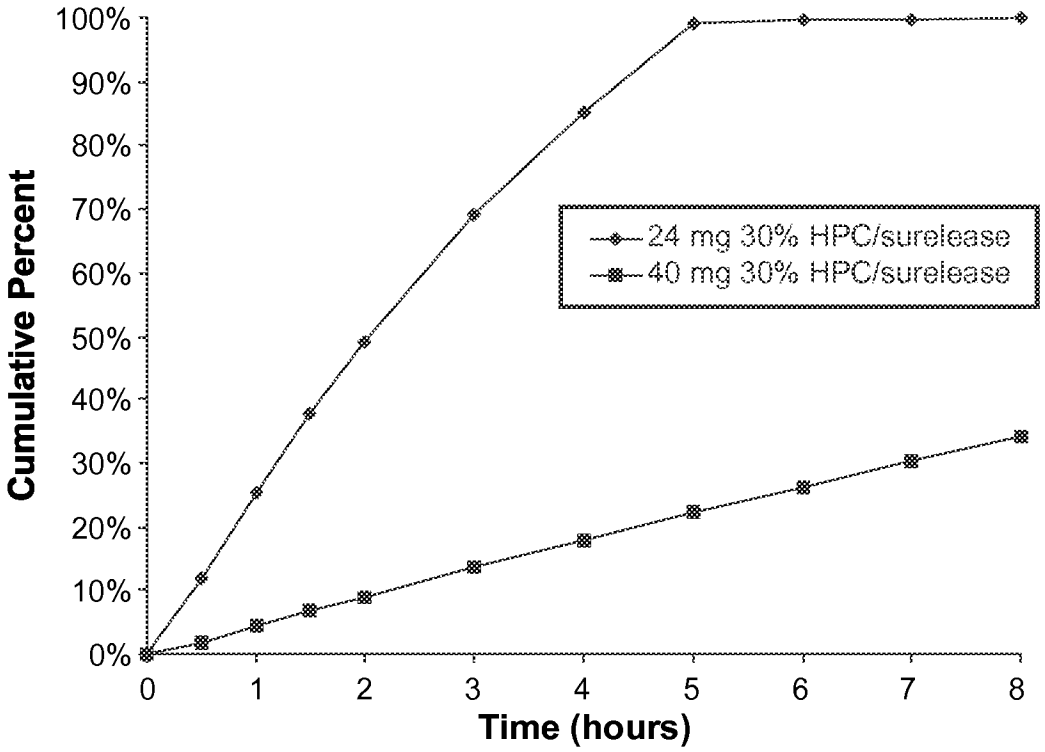

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
24 mg 30% HPC/surelease
40 mg 30% HPC/surelease

FIG. 10

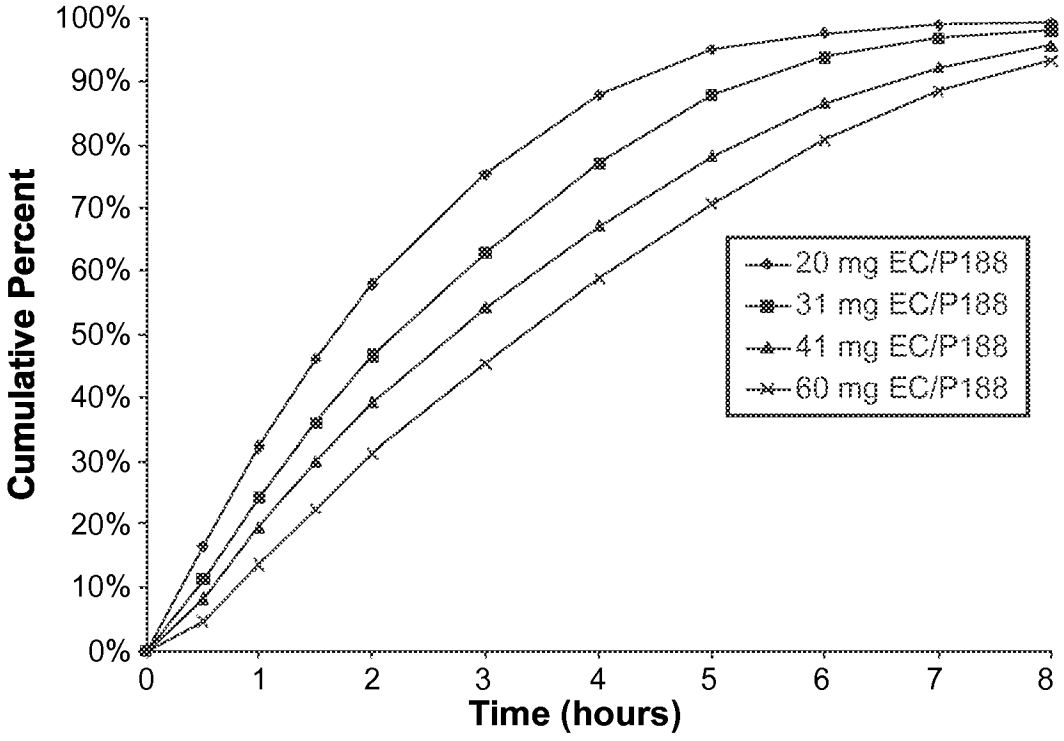

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
20 mg EC/P188
31 mg EC/P188
41 mg EC/P188
60 mg EC/P188

FIG. 11

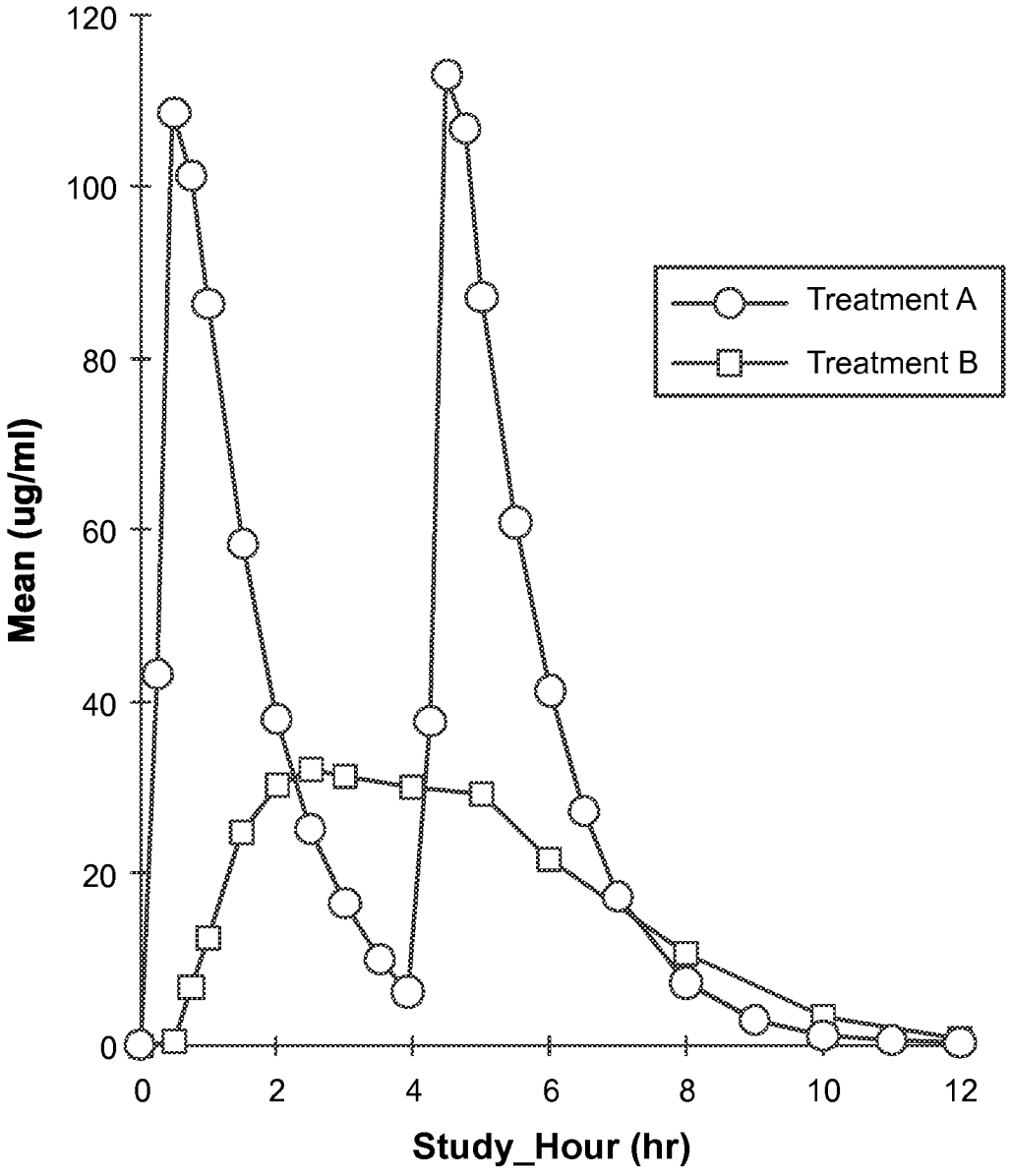
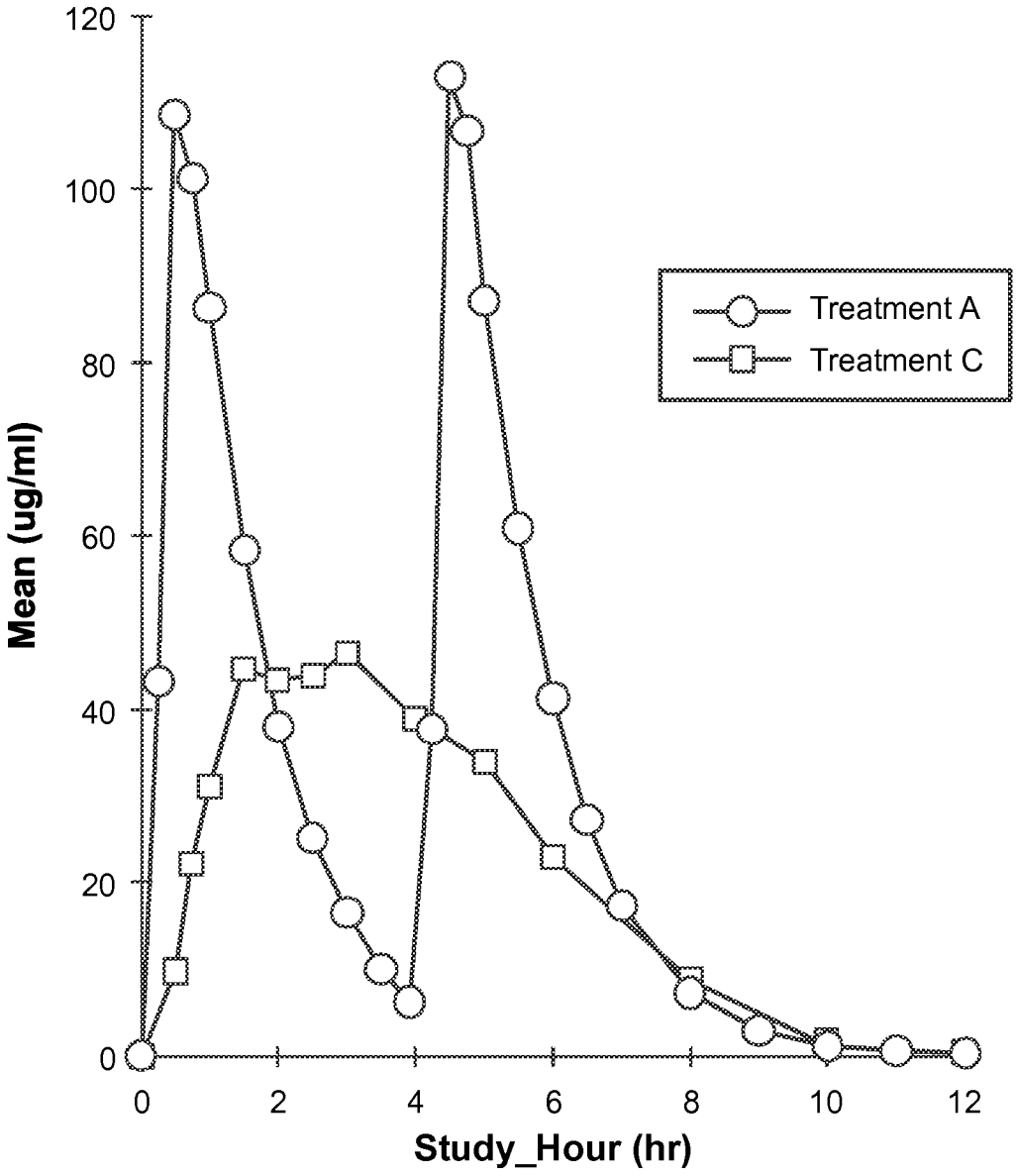

120
100
80
60
40
20
0
Mean (ug/ml)
0
2
4
6
8
10
12
Study_Hour (hr)
Treatment A
Treatment B

FIG. 12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100
80
60
40
20
0
Mean (ug/ml)
0
2
4
6
8
10
12
Study_Hour (hr)
Treatment A
Treatment C

FIG. 13

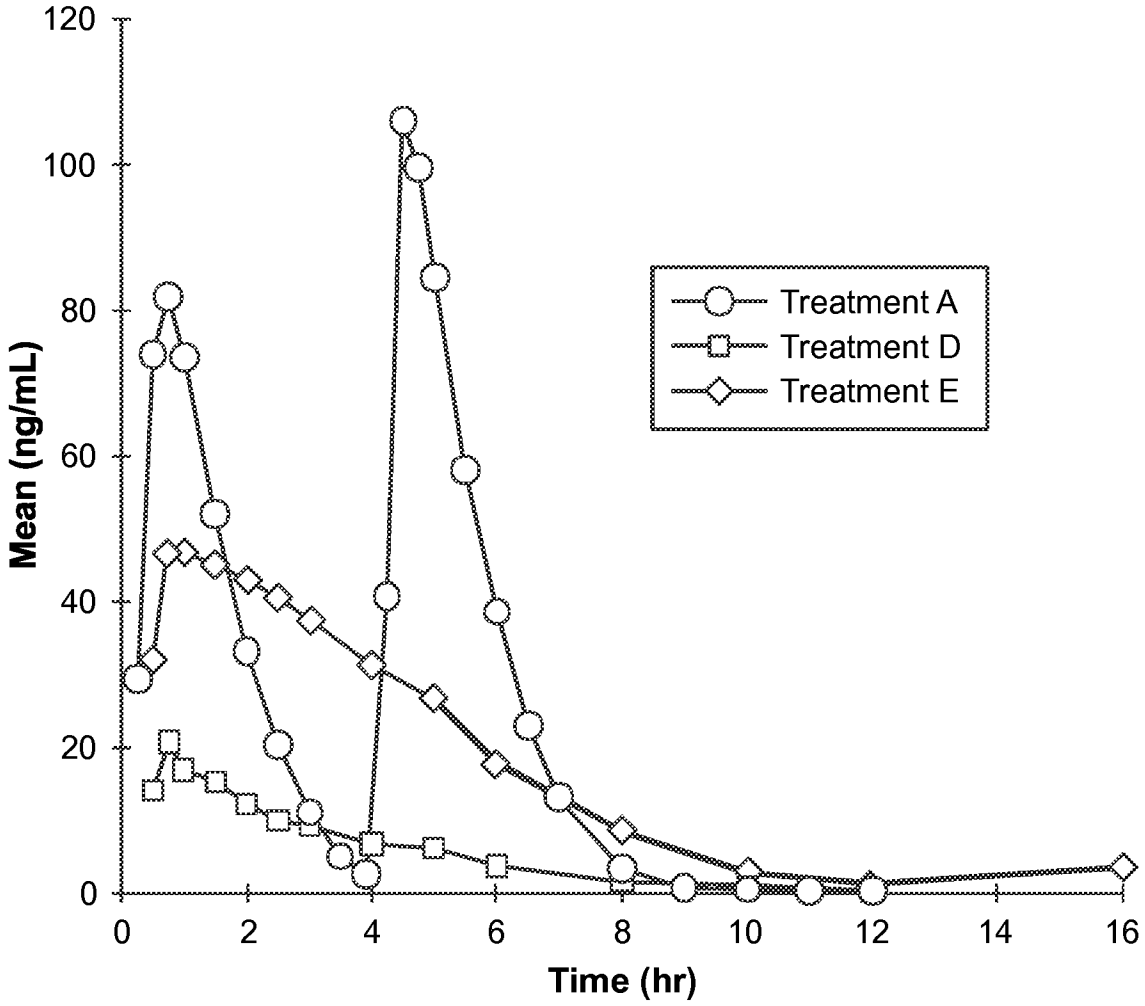

120
100
80
60
40
20
0
Mean (ng/mL)
0
2
4
6
8
10
12
14
16
Time (hr)
Treatment A
Treatment D
Treatment E

FIG. 14

CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 13/071,369, filed Mar. 24, 2011, which claims the benefit of U.S. Provisional Application No. 61/317,212, filed on Mar. 24, 2010, the contents of each of which are incorporated herein by reference

TECHNICAL FIELD

This disclosure relates to controlled release drug compositions.

BACKGROUND

For some drugs, it is difficult to formulate a controlled release dosage form that maintains an effective concentration of the drug over a sustained period of time. In particular, drugs that are administered at a high dose, drugs having a low molecular weight, and drugs with high water solubility make formulation of a controlled release dosage form challenging. For example, in the context of a controlled release drug formulation produced as a unit dosage form for oral administration, drugs that must be administered at a high dose constrain the amount of rate controlling excipients that can be used in formulating a drug composition that is both capable of sustained delivery of therapeutic doses of the drug and exhibits a size and shape suited to oral administration. Low molecular weight and high-solubility drugs may also readily permeate films and matrices that might otherwise be used to control release, and high solubility drugs are not suited to some drug delivery approaches, particularly where zero-order release kinetics are desired. An example of a drug that is administered at a high dose, has a low molecular weight, and high water solubility, is gamma-hydroxy butyrate (GHB), particularly the sodium salt of GHB.

Initial interest in the use of GHB as a potential treatment for narcolepsy arose from observations made during the use of GHB for anesthesia. Unlike traditional hypnotics, GHB induces sleep that closely resembles normal, physiologic sleep (Mamelak et al., Biol Psych 1977:12:273-288). Therefore, early investigators administered GHB to patients suffering from disorders of disturbed sleep, including narcolepsy (Broughton et al. in Narcolepsy, NY, N.Y.: Spectrum Publications, Inc. 1976:659-668), where it was found to increase total nocturnal sleep time, decrease nocturnal awakenings and increase Stage 3-4 (slow wave) sleep. Three open-label and two placebo-controlled studies provided a body of evidence demonstrating that improvements in nocturnal sleep were associated with a reduction in cataplexy and improvements in excessive daytime sleepiness (Broughton et al., Can J. Neurol Sci 1979; 6:1-6, and Broughton et al., Can J. Neurol Sci 1980; 7:23-30).

An estimated 6 million Americans suffer the often baffling symptoms of fibromyalgia or chronic fatigue syndrome. Patients with fibromyalgia, also referred to as fibromyalgia syndrome, FMS or fibrositis syndrome, report widespread musculoskeletal pain, chronic fatigue, and non-restorative sleep. These patients show specific regions of localized tenderness in the absence of demonstrable anatomic or biochemical pathology, and patients suffering from fibromyalgia typically describe light and/or restless sleep, often

reporting that they awaken feeling unrefreshed with pain, stiffness, physical exhaustion, and lethargy. See, H. D. Moldofsky et al., J. Muscoloskel. Pain, 1, 49 (1993). In a series of studies, Moldofsky's group has shown that aspects of the patients' sleep pathology are related to their pain and mood symptoms. That is, patients with fibrositis syndrome show an alpha (7.5 to 11 Hz) electroencephalographic (EEG), non-rapid-eye-movement (NREM) sleep anomaly correlated with musculoskeletal pain and altered mood. Moldofsky has interpreted this alpha EEG NREM sleep anomaly to be an indicator of an arousal disorder within sleep associated with the subjective experience of non-restorative sleep. See H. D. Moldofsky et al., Psychosom. Med., 37, 341 (1975).

Fibromyalgia patients frequently report symptoms similar to those of patients with post-infectious neuromyasthenia, also referred to as chronic fatigue syndrome (CFS). CFS is a debilitating disorder characterized by profound tiredness or fatigue. Patients with CFS may become exhausted with only light physical exertion. They often must function at a level of activity substantially lower than their capacity before the onset of illness. In addition to these key defining characteristics, patients generally report various nonspecific symptoms, including weakness, muscle aches and pains, excessive sleep, malaise, fever, sore throat, tender lymph nodes, impaired memory and/or mental concentration, insomnia, and depression. CFS can persist for years. Compared with fibromyalgia patients, chronic fatigue patients have similarly disordered sleep, localized tenderness, and complaints of diffuse pain and fatigue.

Scharf et al. conducted an open-label study to evaluate the effects of GHB on the sleep patterns and symptoms of non-narcoleptic patients with fibromyalgia (Scharf et al., J Rheumatol 1998; 25: 1986-1990). Eleven patients with previously confirmed diagnosis of fibromyalgia who reported at least a 3-month history of widespread musculoskeletal pain in all body quadrants and tenderness in a least 5 specific trigger point sites participated in the study. Results showed that patients reported significant improvements in the subjective assessments of their levels of pain and fatigue over all 4 weeks of GHB treatment as compared to baseline, as well as a significant improvement in their estimates of overall wellness before and after GHB treatment.

WO 2006/053186 to Frucht describes an open label study of 5 patients with hyperkinetic movement disorders including ethanol responsive myoclonus and essential tremor. Sodium oxybate, a sodium salt of GHB, was reported to produce dose-dependent improvements in blinded ratings of ethanol responsive myoclonus and tremor and was said to be tolerated at doses that provided clinical benefit.

XYREM® sodium oxybate oral solution, the FDA approved treatment for cataplexy and excessive daytime sleepiness associated with narcolepsy, contains 500 mg sodium oxybate/ml water, adjusted to pH=7.5 with malic acid. In man, the plasma half-life of sodium oxybate given orally is about 45 minutes and doses of 2.25 grams to 4.5 grams induce about 2 to 3 hours of sleep (See, L. Borgen et al., *J. Clin. Pharmacol.,* 40, 1053 (2000)). Due to the high doses required and very short half-life of sodium oxybate, optimal clinical effectiveness in narcolepsy typically requires dosing of the drug twice during the night, with administration typically recommended at 2.5 to 4 hour intervals. For each dose, a measured amount of the oral solution is removed from the primary container and transferred to a separate container where it is diluted with water before administration. The second dose is prepared at bedtime and stored for administration during the night.

Liang et al. (published U.S. patent application US 2006/0210630 A1) disclose administration of GHB using an immediate release component and a delayed release component. The delayed release component of the formulations taught in Liang et al., however, function in a pH dependent manner.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the delivery profile of sodium oxybate controlled release formulations as described herein.

FIG. **2** shows the delivery profile of integrated dosage forms as described herein having an immediate release component and a controlled release component.

FIG. **3** provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the coating weight of a functional coating.

FIG. **4** provides a graph further illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the coating weight of a functional coating.

FIG. **5** provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the amount of pore former included within a functional coating.

FIG. **6** provides a graph further illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the amount of pore former included within a functional coating.

FIG. **7** provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by varying the molecular weight of a pore former included within a functional coating.

FIG. **8** provides a graph illustrating that suitable controlled release profiles from dosage forms prepared according to the present description can be achieved even with functional coatings formed using different grades of the same base polymer material.

FIG. **9**A and FIG. **9**B provide graphs illustrating the effects of alcohol on the delivery profile of sustained-release formulations prepared as described herein.

FIG. **10** provides a graph illustrating the controlled release performance achieved by dosage forms as described herein having functional coatings prepared from aqueous dispersions of ethylcellulose as the base polymer.

FIG. **11** provides a graph illustrating the controlled release performance achieved by dosage forms as described herein incorporating calcium oxybate as the drug.

FIG. **12** provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein (Treatment B).

FIG. **13** provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein (Treatment C).

FIG. **14**. provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein dosed at 4 g (Treatment D) and 8 g (Treatment E).

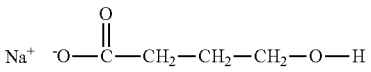
DETAILED DESCRIPTION

Formulations and dosage forms for the controlled release of a drug are described herein. Formulations described herein are suited to the controlled release of high dose drugs that are highly water soluble. In addition, in certain embodiments, the formulations described herein provide controlled release of drugs that are highly hygroscopic, even where such drugs must be administered at relatively high doses. In particular embodiments, the controlled release formulations are provided as a unit dosage form, and in one such embodiment, the controlled release formulation is provided as a coated tablet.

The formulations and dosage forms of the present invention can also include an immediate release component. The immediate release component can form part of a controlled release (CR) unit dosage form or may be a separate immediate release composition. Therefore, an immediate release (IR) component may be provided, for example, as a dry powder formulation, an immediate release tablet, an encapsulated formulation, or a liquid solution or suspension. However, the IR component may also be formulated as part of a single dosage form that integrates both the IR and CR components. In such an embodiment, the pharmaceutical formulation may be provided in the form of the coated tablet or capsule.

In specific embodiments, controlled release and immediate release formulations can be dosed together to a subject to provide quick onset of action, followed by maintenance of therapeutic levels of the drug substance over a sustained period of time. However, because the controlled release component and immediate release component described herein need not be present in a single dosage form, as it is used herein, the phrase "dosed together" refers to substantially simultaneous dosing of the controlled release and immediate release components, but not necessarily administration in the same dosage form. Dosing the controlled release and immediate release components together offers increased convenience, allowing patients to quickly achieve and maintain therapeutic levels of a drug over a sustained period of time, while reducing the frequency with which the drug must be dosed. Furthermore, dosing the controlled release and immediate release components together may avoid the disadvantages of dosing regimens and formulations that result in highly pulsatile plasma concentrations.

An example of a drug that may be used with the controlled release dosage forms described herein is GHB. It should be noted that embodiments of controlled release dosage forms comprising GHB, and other drugs, are presented herein for purposes of example only and not for purposes of limitation. The formulations and unit dosage forms provided herein can be utilized to achieve controlled release of GHB, as well as pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. Suitable salts of GHB include the calcium, lithium, potassium, sodium and magnesium salts. The structure of the sodium salt of GHB, sodium oxybate, is given as formula (I):



Methods of making GHB salts are described, for example, in U.S. Pat. No. 4,393,236, which is incorporated herein by reference.

Formulating GHB into a unit dosage form presents various challenges, and such challenges are magnified in the context of formulating a unit dosage form providing controlled release of GHB. For instance, GHB is very soluble, generally requires a relatively high dose, has a low molecu-

lar weight, and exhibits a short circulating half-life once administered. Therefore, a controlled release unit dosage form of GHB should be configured to deliver large doses of drug over a prolonged period of time, while being acceptably sized for oral administration. However, controlled release formulations typically require the addition of significant amounts of excipients or rate controlling materials to control the delivery of drug, and the presence and need for such materials often limits the drug loading available for a given controlled release technology. Additionally, low molecular weight drugs, such as GHB, typically exhibit high permeability through films and matrices. Even further, high water solubility increases drug mobility and may preclude the use of some approaches utilized to achieved a controlled release dosage form.

Another challenge to achieving a formulation capable of delivering GHB over a sustained period of time is the fact that some forms of GHB, such as the sodium salt of GHB, sodium oxybate, are extremely hygroscopic. As used herein, the term "hygroscopic" is used to describe a substance that readily absorbs and attracts water from the surrounding environment. The hygroscopic nature of sodium oxybate presents significant challenges to the formulation, production, and storage of dosage forms capable of delivering sodium oxybate over a sustained period of time. Despite the challenges noted, formulations and unit dosage forms providing controlled release of GHB are described herein.

A. Controlled Release Formulations

As used herein, the term "controlled release" describes a formulation, such as, for example, a unit dosage form, that releases drug over a prolonged period of time. The controlled release compositions described herein may be provided as a unit dosage form suitable for oral administration. In each embodiment of the controlled release compositions described herein, the drug incorporated in such compositions may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB.

In certain embodiments, the controlled release compositions described herein are formulated as unit dosage forms that deliver therapeutically effective amounts of drug over a period of at least 4 hours. For example, controlled release unit dosage forms as described herein may be formulated to deliver therapeutically effective amounts of drug over a period selected from about 4 to about 12 hours. In specific embodiments, the controlled release dosage forms described herein deliver therapeutically effective amounts of drug over a period selected from about 4, about 5, about 6, about 7, about 8, about 9, about 10 hours, and about 12 hours. In other such embodiments, the controlled release dosage forms deliver therapeutically effective amounts of drug over a period selected from a range of about 4 to about 10 hours, about 5 to about 10 hours, about 5 to about 12 hours, about 6 to about 10 hours, about 6 to about 12 hours, about 7 to about 10 hours, about 7 to about 12 hours, about 8 to about 10 hours, and from about 8 to about 12 hours. In yet other embodiments, the controlled release dosage forms deliver therapeutically effective amounts of drug over a period selected from a range of about 5 to about 9 hours, about 5 to about 8 hours, about 5 to about 7 hours, and about 6 to about 10 hours, about 6 to about 9 hours, and about 6 to about 8 hours.

The compositions described herein facilitate production of controlled release dosage forms that provide a substantially constant drug release rate. In one embodiment, the controlled release dosage forms may be formulated to deliver not more than approximately 30% of the drug initially contained within the controlled release dosage form in the first hour post-administration. When referencing the amount of drug initially contained in the controlled release dosage form or "initial drug content" of the controlled release dosage form, for purposes of the present description, such amount refers to the total amount of drug included in the controlled release composition prior to administration to a patient.

As is detailed herein, the controlled release dosage forms according to the present description include a controlled release component (also referred to as a controlled release "formulation") and, optionally, an immediate release component (also referred to as an immediate release "formulation" or an immediate release "coating"). In specific embodiments, the controlled release dosage forms described herein may be formulated to deliver drug to the gastro-intestinal tract at desired rates of release or release profiles. For example, in some embodiments, controlled release dosage forms as described herein are formulated to release to the gastro-intestinal tract not more than about 10% to about 60% of the drug initially contained within the controlled release component of the controlled release dosage form during the first two hours post-administration, and not more than about 40% to about 90% of the drug initially contained within the controlled release component of the controlled release dosage form during the first four hours post-administration. In other embodiments, controlled release dosage forms as described herein are formulated to release to the gastro-intestinal tract not more not more than about 40% of the drug initially contained within the controlled release component in the first hour post-administration, not more than about 60% of the drug initially contained within the controlled release component during the first two hours post-administration, and not more than about 90% of the drug initially contained within the controlled release component during the first four hours post-administration. In still other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 30% of the initial drug content in the controlled release component in the first hour post-administration, not more than about 60% of the initial drug content in the controlled release component during the first two hours post-administration, and not more than about 90% of the initial drug content of the controlled release component during the first four hours post-administration. In other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 50% of the initial drug content of the controlled release component during the first hour post-administration, between about 50 and about 75% of the initial drug content of the controlled release component after two hours, and not less than 80% of the initial drug content of the controlled release component after four hours post administration. In still other embodiments, a controlled release dosage form as described herein may be formulated release to the gastro-intestinal tract not more than about 20% of the initial drug content of the controlled release component during the first hour post-administration, between about 5 and about 30% of the initial drug content of the controlled release component after two hours, between about 30% and about 50% of the initial drug content of the controlled release component after 4 hours, between about 50% and about 70% of the initial drug content of the controlled release component after 6 hours, and not less than about 80% of the initial drug content of the controlled release component after 10 hours post administration. In yet other embodiments, a controlled release dosage form as described

herein may be formulated to release to the gastro-intestinal tract not more than about 20% of the initial drug content of the controlled release component after the first hour post-administration, between about 20% and about 50% of the initial drug content of the controlled release component after 2 hours, between about 50% and about 80% of the initial drug content of the controlled release component after 4 hours, and not less than 85% of the initial drug content of the controlled release component after 8 hours post-administration. The rate and extent of the absorption of GHB varies along the length of the GI tract with lower amounts absorbed in the more distal portions (i.e., the ileum and the colon).

Due to the rapid clearance of GHB from the plasma, when GHB is administered in an immediate release formulation, even large doses of the drug (e.g., a dose of between about 2.25 g and 4.5 g) generally result in plasma levels below 10 ug/mL within 4 hours of ingestion. In order to achieve therapeutic efficacy, therefore, a second, equal, dose is often required within 4 hours after administration of the first dose, and some patients may require administration of a second as soon as 2.5 hours after administration of the first dose. In such an instance, in order to maintain therapeutic efficacy, 4.5 g to 9 g of drug must be administered to the patient in two separate doses within 2 to 5 hours. This also requires that the second dose be administered during the night, which requires that the patient be awakened to take the second dose. The result is that the Cmax/Cmin ratio of GHB over an six hour period can be greater than 4 and is often greater than 8. In certain embodiments, for a given dose of GHB, administration of GHB using controlled release dosage forms as described herein can achieve a rapid rise in plasma concentrations of GHB, but with a prolonged duration of plasma levels above 10 μg/mL. In certain such embodiments, a GHB controlled release dosage form as described herein provides a Cmax to Cmin ratio of GHB over a prolonged period of time after administration selected from less than 3 and less than 2. Therefore, in specific embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a Cmax to Cmin ratio of GHB selected from less than 3 and less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours. For example, in particular embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a Cmax to Cmin ratio of GHB selected from less than 3 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours, while also providing GHB plasma concentrations of at least 10 μg/mL over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours. In still other embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a Cmax to Cmin ratio of GHB selected from less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours, while also providing GHB plasma concentrations of at least 10 μg/mL over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours.

Drug delivery performance provided by the dosage forms described herein can be evaluated using a standard USP type 2 or USP type 7 dissolution apparatus set to 37° C.±2° C. under the conditions described, for example, in the experimental examples provided herein. The dissolution media may be selected from dissolution media known by those of skill in the art such as at least one of purified water, 0.1N HCl, simulated intestinal fluid, and others.

In particular embodiments, the controlled release formulations described herein work to reduce inter patient variability in delivery of GHB. In particular, controlled release formulations described herein provide time dependent release of GHB over a sustained period of time. Previous references have described targeted release dosage forms of GHB that function in a pH dependent manner. However, due to inter-subject variability in gastrointestinal pH conditions, delivery of GHB from such dosage forms can be inconsistent. Moreover, because relatively high doses of GHB are typically required for therapeutic effect, unit dosage forms of GHB are also relatively large and may be retained for a period of time in the stomach, which can lead to intra- and inter-patient variability in dose delivery of GHB from pH dependent delivery systems due to variability in gastric retention time. Further, patients with fibromyalgia have an increased chance of also suffering from irritable bowel syndrome (see, e.g., Fibromyalgia in patients with irritable bowel syndrome. An association with the severity of the intestinal disorder, Int J Colorectal Dis. 2001 August; 16(4): 211-5.) Irritable bowel syndrome is also associated with delayed gastric emptying and variable gastric emptying (see, e.g., Dyspepsia and its overlap with irritable bowel syndrome, Curr Gastroenterol Rep. 2006 August; 8(4):266-72.) Therefore many patients with fibromyalgia and suffering from irritable bowel syndrome may experience more variability in gastric transit or prolonged gastric transit. By operating in a time dependent manner once placed in an aqueous environment, controlled release formulations described herein offer consistent GHB delivery characteristics and reduce the likelihood of undesirable intra- and inter-patient inconsistencies in dose delivery that may result from variances in gastric retention time that can occur between different patients and different patient populations.

Controlled release formulations described herein may be formulated to completely release a drug within a desired time interval. As has been reported, the bioavailability of GHB decreases in the lower GI, with bioavailability decreasing the lower the drug is delivered in the GI (See, e.g., U.S. Patent Publication No. US2006/0210630). Therefore, in certain embodiments, the controlled release dosage forms are provided that deliver substantially all the GHB contained therein over a sustained period of time that is long enough to increase patient convenience, yet short enough to reduce dosing of GHB in the lower GI. In specific embodiments, controlled release GHB dosage forms are provided that deliver approximately 90% or more of the GHB contained within the controlled release formulation within about 4 to about 10 hours of administration. For example, dosage forms for the controlled release of GHB as described herein may be formulated to deliver approximately 90% or more of the drug included within the controlled release formulation within about 4, 5, 6, 7, 8, 9, 10, or 12 hours of administration. In one such embodiment, a dosage form for the sustained delivery of GHB according to the present description is formulated to deliver more than 90% of the GHB included within the controlled release formulation within 12 hours post-administration. Such embodiments serve to not only provide controlled release of GHB, but they also work to deliver GHB where bioavailability is highest, which can also provide increased dose consistency.

The controlled release dosage forms described herein may comprise a relatively high concentration of drug that can, in

some instances, harm a patient if the formulation releases the drug at a rate that is faster than the intended sustained rate. This rapid release of the drug is sometimes referred to as "dose dumping." To avoid this potential danger, certain embodiments of the controlled release dosage forms described herein may comprise formulations that are resistant to dose dumping. Some users may intentionally attempt to increase the drug release rate of the controlled release dosage form using alcohol (e.g., potential abusers may take the controlled release dosage form prior to, simultaneously with, or after consuming an alcoholic beverage or, alternatively, may seek to extract the drug from the controlled release dosage form by placing the dosage form in solution containing alcohol). Other users may take the dosage form with alcohol, not necessarily in a manner considered abuse of the drug or alcohol, but without regard for the potential risks of dose dumping or contraindication of the two substances. In one embodiment, a controlled release dosage form as disclosed herein may include a coating composition that is resistant to alcohol or that does not dissolve substantially faster in alcohol. In one such embodiment, the controlled release dosage form may comprise the drug sodium oxybate and include a coating composition including ethylcellulose that is resistant to dose dumping in alcohol. In another embodiment, the controlled release dosage form may include a coating composition that is resistant to dose dumping after administration. For example, the controlled release dosage form may include a coating composition that is resistant to dose dumping in the GI tract after being exposed to gastric fluid and intestinal fluid.

In certain embodiments, the controlled release formulations described herein are provided as a coated tablet composition having a controlled release core coated by a functional overcoat. The composition of the controlled release core provided in such embodiments facilitates high drug loading, thereby, rendering the coated tablet suitable for formulation and sustained delivery of drugs administered at high doses. The functional overcoat works to control delivery of drug from the controlled release core and maintain the structural integrity of the dosage form over time. In addition to the controlled release core and functional overcoat, the coated tablet composition as described herein may further include a moisture barrier or cosmetic coating disposed over the functional overcoat.

I. Controlled Release Component

Where the controlled release formulations described herein are formulated as a coated tablet having a controlled release core (CR core), the CR core includes at least one drug substance to be delivered from the controlled release dosage form. The drug included in the CR core may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. Examples of suitable salts of GHB include the calcium, lithium, potassium, sodium and magnesium salts. The CR core is formulated and configured to be suitable for oral administration. In one embodiment, coated tablets as described herein may be administered to provide a dose of GHB or a pharmaceutically acceptable salt, hydrate, tautomer, solvate or complex of GHB in a range of about 500 mg to about 12 g of drug in one or more tablets. In particular embodiments, a CR core included in a controlled release dosage form according to the present description may include an amount of drug selected from about 100 mg to about 2,000 mg. In some such embodiments, the amount of drug included in the CR core may be selected from up to about 250 mg, 400 mg, 500 mg, 600 mg, 700 mg, 750 mg, 800 mg, 900 mg, 1,000 mg, 1,100 mg, 1,200 mg, 1,400 mg, 1,500 mg, 1,600 mg, 1,700 mg, 1,800 mg, 1,900 mg, and 2,000 mg. In certain such embodiments, the amount of drug included in a CR core as described herein may range from about 500 mg to about 2,000 mg, such as, for example, about 500 mg to 1,000 mg, about 600 mg to 1,000 mg, about 600 mg to 900 mg, about 600 mg to 800 mg, about 700 mg to 1,000 mg, about 700 mg to 900 mg and about 700 mg to 850 mg. In other such embodiments, the amount of drug included in a CR core as described herein may range from about 700 mg to about 2,000 mg, such as, for example, about 700 mg to 1,500 mg, about 700 mg to 1,400 mg, about 700 mg to 1,300 mg, about 700 mg to 1,200 mg, about 700 mg to 1,100 mg, about 700 ring to 1,000 mg, about 700 mg to 900 mg, and about 700 mg to 850 mg.

In one embodiment, the controlled release dosage form comprises a CR core wherein the relative amount drug in the CR core is at least 90% or greater by weight. In another embodiment, the relative amount of drug in the CR core ranges from between about 90% and 98%, about 91% and 98%, about 92% and 98%, about 93% and 98%, about 94% and 98%, about 95% and 98%, about 96% and 98%, and between about 97% and 98% by weight of the CR core. In yet another embodiment, the relative amount of drug in a CR core may be present at an amount selected from about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, and 98% by weight of the CR core. In certain such embodiments, the amount of drug in the CR core may range from about 94 to 98%, 94 to 97%, 94 to 96%, 95 to 98%, 95 to 97%, and 95 to 96.5 by weight of the CR core.

In one embodiment, the controlled release dosage form comprises a CR core that includes drug substance in combination with one or more excipients, such as binders, fillers, diluents, disintegrants, colorants, buffering agents, coatings, surfactants, wetting agents, lubricants, glidants, or other suitable excipients. In one embodiment, a CR core as disclosed herein can include one or more binders that are known for use in tablet formulations. In one such embodiment, a CR core may include at least one binder selected from hydroxypropyl cellulose (HPC), ethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, carboxymethylcellulose sodium, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate. In specific embodiments, the CR core included in a controlled release dosage form as disclosed herein may comprise binder levels ranging from approximately 1% to 10% by weight. For example, the CR core may include a binder in an amount selected from about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, and 10% by weight. In certain such embodiments, the amount of binder included in the CR core may range from about 1 to 2%, 1 to 3%, 1 to 4%, 1 to 5%, 1 to 6%, 1 to 7%, 1 to 8%, 1 to 9% and 1 to 10% by weight.

The CR core may include one or more lubricants to improve desired processing characteristics. In one embodiment, the CR core may include one or more lubricants selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added to the CR core in a range of about 0.5% to 5% by weight. In particular embodiments, a CR core as disclosed herein may comprise a lubricant in a range of about 0.5% to 2% by weight, about

1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in the CR core in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight. Still lower lubricant levels may be achieved with use of a "puffer" system during tabletting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation.

The CR core may also include one or more surfactants. In certain embodiments, the CR core may include a tableted composition that may comprise one or more surfactants selected from, for example, ionic and non-ionic surfactants. In one such embodiment, CR core may include at least one anionic surfactant, including docusate sodium (dioctyl sulfosuccinate sodium salt) and sodium lauryl sulfate. In yet another embodiment, the CR core may include at least one non-ionic surfactant selected from including polyoxyethyelene alkyl ethers, polyoxyethylene stearates, poloxamers, polysorbate, sorbitan esters, and glyceryl monooleate. In specific embodiments, one or more surfactants included in a CR core as disclosed herein may be present, for example, in an amount of up to about 3.0% by weight of the CR core. For example, in certain embodiments, the CR core may include one or more surfactants present in a range selected from about 0.01% to 3%, about 0.01% to 2%, about 0.01% to 1%, about 0.5% to 3%, about 0.5% to 2%, and about 0.5% to 1% by weight of the CR core.

The CR core included in controlled release dosage form as disclosed herein may also include fillers or compression aids selected from at least one of lactose, calcium carbonate, calcium sulfate, compressible sugars, dextrates, dextrin, dextrose, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, powdered cellulose, and sucrose. In another embodiment, a CR core may be prepared by blending a drug and other excipients together, and the forming the blend into a tablet, caplet, pill, or other dosage form according to methods known by those of skill in the art. In certain embodiments, a controlled release formulation as described herein may comprise a solid oral dosage form of any desired shape and size including round, oval, oblong cylindrical, or triangular. In one such embodiment, the surfaces of the CR core may be flat, round, concave, or convex.

The CR core composition included in a controlled release formulation provided as a coated tablet dosage form as described herein may be manufactured using standard techniques, such as wet granulation, roller compaction, fluid bed granulation, and direct compression followed by compression on a conventional rotary tablet press as described in Remington, 20th edition, Chapter 45 (Oral Solid Dosage Forms).

II. Functional Coating Composition

Where the controlled release formulations as described herein are provided as a coated tablet composition, the CR core is coated with a functional coating. The coating composition works to preserve the integrity of the unit dosage form post administration and serves to facilitate controlled release of drug from the CR core. In certain embodiments, the coating composition is formulated to facilitate controlled release of a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. In one such embodiment, the coating composition is sufficiently robust to preserve the integrity of the coated tablet pre- and post-administration, yet is subject to disintegration or crushing as it passes through a patient's gastrointestinal tract and after all or substantially all the drug substance contained within the controlled release formulation has been delivered. Such a feature reduces the risk that bezoars formed from intact dosage form shells will form or be maintained within the GI tract of a patient, which may be of particular concern where the drug to be delivered must be administered at high doses using multiple unit dosage forms.

In one embodiment, a functional coating composition as disclosed herein may control, at least in part, the rate of release of the drug to be delivered from the CR core into the gastrointestinal tract. In one embodiment, the functional coating composition provides a functional coat that partly or fully covers the CR core included in the controlled release dosage form. In one embodiment, the functional coating composition as disclosed herein may include a polymer or blends of compatible polymers that are water soluble or that are water insoluble and selected to exhibit desired permeability characteristics. In one embodiment, the functional coating composition has a permeability that may be adjusted according the solubility of the drug used in the CR core. In one such embodiment, the functional coating composition may comprise one or more water insoluble polymers that may swell but do not substantially dissolve in the GI tract. For example, in particular embodiments, a functional coating composition as disclosed herein may comprise a rate-limiting film that includes at least one of ethylcellulose, cellulose acetate, such as CA-398. In other embodiments, the functional coating may include combinations of ethylcellulose with ammonio methacrylate copolymers, such as EUDRAGIT RS, EUDRAGIT RL, and combinations thereof. Suitable ethylcellulose materials are readily commercially available, and include, for example, ETHOCEL ethylcellulose polymers. Where ethylcellulose is used to form the functional coating, the physical characteristics of the coating composition and residual shell may be modified by adjusting the molecular weight of the ethylcellulose. For example, different grades of ethylcellulose, including, but not limited to, 4 cP, 7 cP, 10 cP, and 20 cP grades, may be used to achieve a coating composition having desired physical characteristics.

A functional coating composition as disclosed herein may include one or more base polymer and at least one pore-former. In one embodiment, the base polymer content may range from about 50% to about 80% by weight of the coating composition. In certain embodiments, the base polymer may be present in an amount ranging from about 50% to 75%, about 55% to 75%, about 60% to 75%, and about 65% to 75% by weight of the coating composition. In one such embodiment, the base polymer may be present in an amount selected from about 50%, 55%, 60%, 65%, 70%, 75%, and 80% by weight of the coating composition. In cases where a filler material is used (e.g., insoluble, non film-forming material such as magnesium stearate, talc, or fumed silica), these limits apply to the composition of the remaining non-filler components in the film.

The permeability of the base polymer included in a functional coating as described herein may be modified by including a pore former in the base polymer. In one such embodiment, the functional coating composition including the pore former may be obtained by combining the pore former with the base polymer material in solution according to conventional techniques. A pore former as disclosed herein may include at least one polymeric pore former, such as hydroxyalkyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycols, polyvinyl alcohol, povidone, copovidone, and poloxamers, such as 188 or 407. In one embodiment, a pore former as disclosed herein may include at least one small-molecule pore former,

such as a water soluble sugar or organic acid, including, for example, citric acid or sorbitol. In one such embodiment, a small-molecule pore former may be water soluble active agent, such as a pharmaceutically acceptable salt of GHB. In yet another embodiment, the pore former may comprise a polymer that expands in the presence of the drug included in the CR core, wherein expansion of the pore former may cause an increase in permeability of the functional coating composition. For example, in some embodiments, the functional coating composition may comprise a pore former that that expands or swells in the presence of sodium oxybate. In one such embodiment, the pore former includes a suitable carbomer.

Where used in the functional coating composition, a pore former or a pore-forming agent can be selected to modify the permeability of the coating composition provided over the CR core. For example, the permeability of the functional coating composition may be increased by including one or more pore formers or pore-forming agents in the coating composition. In one embodiment, the pore formers disclosed herein may be soluble in water. In one such embodiment, when a CR dosage form comprising a functional coating composition with at least one pore former is swallowed by a patient and contacted with gastric fluid, the water-soluble pore formers may dissolve and form pores or channels in the coating through which the drug is released. It is possible to use an enteric component as part or all of the pore former in the coating composition. Examples of such materials that may be used as a pore former in the context of the present description include cellulose acetate phthalate, methacrylic acid-methyl methacrylate copolymers, and polyvinyl acetate phthalate. However, incorporating enteric components in the film may result in delivery characteristics that exhibit some level of sensitivity to gastric and intestinal transit times.

Where included, the amount and nature of the pore former included in the functional coating composition can be adjusted to obtain desired release rate characteristics for a given drug substance. In one embodiment, the functional coating composition may include an amount of pore former that ranges from about 20% to about 50% by weight of the coating composition. For example, the pore former may be present in an amount ranging from about 20% to 45%, about 25% to 45%, about 30% to 45%, and about 35% to 45% by weight of the functional coating composition. In one such embodiment, the pore former may be present in an amount selected from about 20%, 25%, 30%, 35%, 40%, 45%, and 50% by weight of the functional coating composition.

The functional coating composition as disclosed herein may also comprise one or more plasticizers. In certain embodiments, the functional coating composition may include a plasticizer such as triethyl citrate or dibutyl sebacate. In one such embodiment, a plasticizer may be present in the functional coating composition in an amount ranging from about 5% to 15% by weight relative to the base polymer. In certain embodiments, the functional coating composition may include a plasticizer in an amount selected from about 5%, 8%, 10%, 12%, and 15% by weight relative to the base polymer.

The functional coating composition as disclosed herein may also include an anti-tack agent. For example, certain embodiments of the functional coating composition may include an anti-tack agent selected from one or more of talc, glyceryl monostearate, and magnesium stearate. Many of the anti-tack agents are also suitable fillers. Addition of fillers, especially magnesium stearate, is one way to make the film more brittle and the dosage form more prone to crushing as it transits through the GI. Depending on forces encountered in the GI, varying the filler level in the film may allow one to adjust the duration, or extent of drug delivered, at which breach of the film and abrupt release of remaining contents occurs.

The functional coating composition as disclosed herein may be applied to a CR core at a weight that facilitates a suitable combination of sustained drug release and dosage form structural integrity. In certain embodiments, the functional coating composition may be applied at a weight of about 10 to about 100 mg. In particular embodiments, for example, the functional coating may be applied at a weight selected from about 20 to 60 mg, about 20 to 50 mg, about 20 to 40 mg, about 20 to 30 mg, about 30 to 60 mg, about 30 to 50 mg, about 30 to 40 mg, about 40 to 60 mg, about 40 to 50 mg, and about 50 to 60 mg. These ranges are useful for oval tablets of about 500 mg to about 1000 mg in weight. Alternatively, for a given tablet size or weights, the functional coating composition as disclosed herein may be applied at between about 2.5% and 7.5% of the tablet weight. For example, in one such embodiment, where the tablet is a 2,000 mg oval tablet, a functional coating composition may be applied at a weight ranging from about 50 mg to about 150 mg.

In addition to adjusting the amount or nature of the pore former included in the functional coating composition, the release rate of drug provided by the controlled release dosage form disclosed herein may be adjusted by modifying the thickness or weight of the functional coating composition. For example, a more rapid release rate will generally be achieved as the amount of a given pore former included in the functional coating composition is increased or the thickness or weight of the coating composition applied over the CR core is decreased. Conversely, a slower or more controlled release may be achieved, generally, as relatively less of a given pore former is included in the functional coating composition or the thickness or weight of the coating composition applied to the CR core is increased. Additionally, in certain embodiments, the release rate of drug from the CR core may be adjusted by modifying the water content of the functional coating composition. For example, increasing the water content of the functional coating composition may increase the release rate of drug the CR core.

The functional coating compositions as disclosed herein may be applied to a CR core according to conventional coating methods and techniques. In one embodiment, the functional coating composition as disclosed herein may be applied using a conventional perforated pan coater. In another embodiment, the functional coating composition may be applied using an aqueous pan-coating process. In one such embodiment, the use of an aqueous pan-coating process may include the use of a latex dispersion. For example, a latex dispersion such as SURELEASE may be used for an ethylcellulose pan-coating process. In another example, a latex dispersion such as EUDRAGIT RS 30 D may be used in a pan-coating process for ammonio-methacrylates. In yet another embodiment, the functional coating composition may be applied using a solvent-based pan-coating process. In one such embodiment, a solvent-based pan-coating process may include the use of an alcohol solvent, such as ethanol. For example, an alcohol-solvent based pan-coating process may utilize a 95% ethanol and 5% water (w/w) solvent.

In one embodiment, the functional coating compositions as described herein may be applied using a fluid bed coating process such as a Wurster fluid bed film coating process. In another embodiment, the functional coating composition may be applied using a compression coating process. In yet

another embodiment, the functional coating composition may be applied using a phase inversion process. In certain embodiments, the functional coating composition as disclosed herein may be applied over a suitable subcoating.

III. Moisture Barrier/Cosmetic Coatings

When a controlled release formulation or dosage form is provided as a coated tablet, in some embodiments, it may be coated with a moisture barrier or a moisture-resistant coating composition. For example, a controlled release dosage form as disclosed herein comprising GHB as the drug substance may include a moisture barrier. In another example, a moisture barrier may be particularly useful where sodium oxybate is used as the drug substance. In one embodiment, the moisture barrier may be a polyvinyl alcohol-based coating, such as OPADRY AMB (Colorcon Inc., Harleysville, Pa.). In another embodiment, the moisture barrier may be a hydroxypropyl methylcellulose (HPMC)/wax-based coating, such as AQUARIUS MG (Ashland Aqualon, Wilmington, Del.). In yet another embodiment, the moisture barrier may be a HPMC/stearic acid-based coating. The moisture barrier as disclosed herein, in some embodiments, may be formed using a reverse enteric material, such as EUDRAGIT E, and may be coated from alcohol or alcohol/water solutions or from an aqueous latex dispersion. In embodiments where the controlled release dosage form is provided as a tablet of about 500 mg-1000 mg in weight, for example, the moisture barrier coating may be applied at a weight selected from about 10 mg to about 60 mg/tablet and about 25 mg to about 50 mg/tablet. In general, a minimum weight is needed to ensure complete coverage of the tablet in light of imperfections in the tablet surface, and a maximum weight is determined by practical considerations, such as coating time, or by the need for better moisture protection.

As will be readily appreciated, the controlled release dosage form can be further provided with a cosmetic top coat. In one embodiment, a top-coat may be applied to an existing coating composition such as a moisture barrier. In certain embodiments, a cosmetic top-coat may include at least one of HPMC and copovidone. For example, when the controlled release dosage form includes a coated tablet comprising sodium oxybate as the drug, a top-coat including HPMC, such as for example an HPMC material selected from one or more of HPMC E3, E5, or E15, may be applied over a moisture barrier to improve the effectiveness of the moisture barrier by reducing any seepage of sodium oxybate and water from the surface of the coated tablet.

B. Immediate Release Formulations

The controlled release formulations described herein can be dosed together with an immediate release (IR) formulation. In one embodiment, the IR formulation may be provided as a separate formulation or dosage form that may be dosed together with a dosage form provided by a controlled release dosage form as described herein. The IR formulation may be provided in any suitable form, such as a dry powder formulation, a tablet or capsule unit dosage form, or a liquid formulation such as a solution or suspension formulation. As used herein, "immediate release" refers to a drug formulation that releases more than about 95% of the drug contained therein within a period of less than one hour after administration. In particular embodiments, the IR component of the compositions described herein release more than about 95% of the drug contained therein within a period selected from less than 45 minutes, less than 30 minutes, and less than 15 minutes post-administration. In other embodiments, the IR component of the compositions described herein release more than about 80% of the drug contained therein within a period selected from less than 45 minutes, less than 30 minutes, and less than 15 minutes post-administration.

In certain embodiments, the IR formulation is provided as an immediate release component of a controlled release dosage form as described herein. In one such embodiment, the IR component is provided as a coating over a controlled release component or formulation as described herein. A unit dosage form that integrates both controlled release and immediate release components can increase the convenience and accuracy with which a drug such as GHB is dosed to patients by providing a unit dosage form that not only provides quick onset of action, but also sustained delivery of GHB to the patient over a prolonged period of time. Furthermore, where the drug to be delivered is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, dosing controlled release and immediate release formulations together may avoid the disadvantages of the current GHB dosing regimens, which can result in highly pulsatile plasma concentrations.

I. Immediate Release Component

When the immediate release formulation is provided as an integrated IR component of a controlled release dosage form, the amount of drug included in the IR component may range from about 10% to 50% by weight of the total drug included in the integrated dosage form. As used herein, "integrated dosage form" refers to a single unit dosage form that includes both immediate release and controlled release components as described herein. For example, where the drug to be delivered from the immediate release and controlled release formulations incorporated into an integrated dosage form is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB in some embodiments, the drug included in the IR component may comprise about 10% to about 50% by weight of the total drug included in the unit dosage form. In one such embodiment, the drug included in the IR component of an integrated dosage form may comprise about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% by weight of the total drug included in the unit dosage form. For example, an integrated dosage form as described herein may contain 1000 mg sodium oxybate, wherein 100 mg to 500 mg sodium oxybate (10% to 50% by weight) is contained within and delivered from the IR component and 500 mg to 900 mg sodium oxybate (50% to 90% by weight) is contained within and delivered from the CR component.

Where the IR component is provided as a coating over a controlled release dosage form, in certain embodiments, the drug included in the IR component may account for between about 75% and 98% by weight of the IR formulation. In the context of describing an IR component provided over a controlled release dosage form as described or disclosed herein, the controlled release dosage forms referred to include the controlled release formulations described herein, including, in specific embodiments, CR cores coated with a functional coating as described herein. Again, the drug included in such an embodiment may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. In certain embodiments, the IR component may comprise sodium oxybate in an amount of selected from a range of between about 75% and 98%, between about 80% and 98%, between about 85% and 98%, between about 90% and 98%, and between about 95% and 98% by weight.

An IR component formed as a coating over a controlled release dosage form as disclosed herein may be applied as a tableted overcoat according to conventional tablet coating

and binding methods. Alternatively, an IR component formed as a coating over a controlled release dosage form as disclosed herein may be applied as a film coating, such as, for example, from a solution containing a suitable amount of drug and film former. In one such embodiment, wherein sodium oxybate is the drug included in the IR component, the coating forming the IR component may be coated over a controlled release dosage form from a coating solution that utilizes an alcohol and water solvent. For example, a suitable immediate release coating may be formed using a 20% solution of sodium oxybate in a 60%/40% (w/w) alcohol/water solution that contains a suitable film-former.

Where the IR component is provided as a film coat and includes one or more film-formers, suitable film formers may be selected from, for example, copovidone, hydroxypropyl cellulose, HPMC, and hydroxymethyl cellulose materials. An IR component containing sodium oxybate as the drug can be applied as a suspension or as a solution by adjusting the water content of the coating mixture. For a suspension, little or no water is added to the alcohol, and the example film formers should be suitable. To prepare a solution, however, the water content of the solvent is increased, for example to 40%, and a smaller set of film formers would be suitable due to the precipitation of most common film formers in the presence of sodium oxybate solution. Hypromellose is one of several potential film formers that is suitable. It is further possible, with more difficulty, to apply the sodium oxybate from an aqueous solution; however, the same limitations on film former applies, and processing is complicated by the hygroscopic nature of the drug. In one embodiment, the IR component useful for use in a controlled release dosage form as described herein includes 91% sodium oxybate and 9% hypromellose (HPMC E-15) that is applied from a solution containing 20% sodium oxybate and 2% HPMC E-15 in a 60/40 w/w ethanol/water solvent.

Where the IR component of an integrated dosage form is provided as a coating over the controlled release dosage form, the coating forming the IR component may further include one or more of an anti-tack agent and a plasticizer to facilitate processing and to improve film properties. Furthermore, addition of one or more surfactants, such as sodium lauryl sulfate, may improve the dissolution of IR coatings that contain hydrophobic components (such as anti-tack agents or water-insoluble film formers).

In embodiments where the IR component is provided as a coating over a controlled release formulation as described herein, the IR component may be positioned directly over the functional coating of the controlled release formulation. Where desired or necessary based on the drug to be delivered from the IR component and controlled release formulation included in such an integrated dosage form, the outer surface of the IR component may then be coated with a moisture barrier layer. For example, where the drug delivered by the integrated dosage form is highly hygroscopic, such as, for example, sodium oxybate, a moisture barrier layer over the immediate release coating forming the IR component may be provided.

The formulation and structure of integrated dosage forms as described herein can be adjusted to provide a combination of immediate release and controlled release performance that suits a particular dosing need. In particular, the formulation and structure of integrated dosage forms as described herein can be adjusted to provide any combination of the immediate release and controlled release performance characteristics described herein. In particular embodiments, for example, the drug delivered from an integrated dosage form as described herein is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, and the integrated dosage form sustains delivery of GHB over a period of from about 4 to about 10 hours. In one such embodiment, the IR component of the integrated dosage form provides rapid onset of action, releasing more than about 90% of the drug contained therein within a period of time selected from less than one hour, less than 45 minutes, less than 30 minutes and less than 15 minutes after administration, while the controlled release composition included in the integrated dosage begins to deliver drug as the IR component is released and continues to deliver drug for a sustained period of between about 4 and about 10 hours. In another such embodiment, the IR component of the integrated dosage form provides rapid onset of action, releasing more than about 90% of the drug contained therein within a period of time selected from less than one hour, less than 45 minutes, less than 30 minutes and less than 15 minutes after administration, while the controlled release composition included in the integrated dosage begins to deliver drug after the IR component is released and continues to deliver drug for a sustained period of between about 4 and about 10 hours.

Moreover, the ratio of drug release from the IR component and CR component can be adjusted as needed to facilitate a desired dosing regimen or achieve targeted dosing. A dosage form as described herein that integrates both IR and CR components may be formulated to deliver as much as 2,000 mg of a desired drug, such as GHB or a pharmaceutically acceptable salt, hydrate, tautomer, solvates or complex of GHB. In particular embodiments, the total amount of drug contained within an integrated IR/CR dosage form according to the present description may be between about 500 mg and about 1,400 mg. For example, in certain such embodiments, the total amount of drug may be selected from between about 500 mg and 1,400 mg, about 500 mg and 1,200 mg, about 500 mg and 1,100 mg, about 600 mg and 1,200 mg, about 600 mg and 1,100 mg, about 600 mg and 1,000 mg, about 600 mg and 950 mg, about 600 mg and 850 mg, about 600 mg and 750 mg, about 750 mg and 1,200 mg, about 750 mg and 1,100 mg, about 750 mg and 1,000 mg, about 750 mg and 950 mg, and about 750 mg and 850 mg. In an integrated IR/CR dosage form, the relative amounts of drug delivered from the IR component and CR components may be adjusted as desired as well. In particular embodiments, the ratio of drug released from the IR component to drug released from the CR component is from about 1:2 to about 1:4. In certain embodiments, such ratio is selected from about 1:2, 1:2.5, 1:3, 1:3.5 and 1:4.

In particular embodiments, the integrated dosage form may be formulated such that the controlled release formulation begins release of drug substantially simultaneously with delivery of the drug from the IR component. Alternatively, the integrated dosage form may be formulated such that controlled release formulation exhibits a start-up time lag. In one such embodiment, for example, the integrated dosage form maybe formulated and configured such that start-up of delivery of drug from the controlled release composition occurs after delivery of drug from the IR component is substantially complete. Where a start-up lag time is desired, an enteric coating may be applied over the controlled release component (e.g., over a functional coating), but such a coating would necessarily limit the start-up lag to gastric residence and its associated variability. Use of enteric pore-formers would also impart a start-up lag, and such an embodiment would be more sensitive to food effects and gastric motility. Where a less pH-sensitive start-up lag

time is desired, the delay may be accomplished or adjusted by the use of one or more coatings and films, including the functional coating provided over a CR core and, where utilized, the moisture barrier or cosmetic overcoats. In particular, start-up lag time as disclosed herein may be adjusted by modifying the formulation, thickness, and/or weight of the functional coating provided over the CR core, the moisture barrier layer or one or more non-functional or cosmetic overcoats.

EXAMPLES

Example 1

Controlled Release Core

A granulation used to form CR cores as described herein was manufactured in a 25 L high shear granulator according to the formula in Table 1A. Klucel EXF was divided into two equal portions; half of the Klucel EXF was dissolved in the ethanol, and half was dry blended with sodium oxybate. The material was initially granulated with 10% w/w ethanol and then titrated with another 3.5% w/w ethanol solution to achieve desired granule growth. A suitable wet mass was obtained at a total ethanol concentration of 13.5% w/w. The wet granules were divided into two sub lots and then each sub lot was dried in a 5-liter Niro fluid bed dryer. The dried granules were combined and milled through a COMIL equipped with a 14 mesh screen. Granulation parameters and particle size distribution are shown in Tables 1B and 1C, respectively.

The granulation was then combined with 2% magnesium stearate lubricant, and tablets were compressed on a 16-station press fitted with chrome-plated 0.325"×0.705" modified oval tooling. The average tablet hardness was 10.7 kilo-ponds.

TABLE 1A

Controlled Release Core Tablet Formulation

	Ingredient(s)	% w/w	mg/tablet
1	Sodium Oxybate	96.0	750.0
2	Hydroxypropyl cellulose, NF (Klucel EXF)	2.0	15.6
3	Ethanol, USP (200 proof)*	13.5	
4	Magnesium Stearate, NF	2.0	15.6
	TOTAL	100.0	781.2

*Granulation solvent, removed during drying step

TABLE 1B

Granulation Parameters
WET GRANULATION

GRANULATION SOLUTION ADDITION RATE (G/MIN)	250	
TOTAL GRANULATION TIME (INCLUDING SOLUTION ADDITION AND WET MASSING TIME)	7 MINUTES	
IMPELLER SPEED (RPM)	300	
CHOPPER SPEED (RPM)	1800	
DRYING	SUBLOT 1	SUBLOT 2
DRYING INLET TEMPERATURE (° C.)	70	70
TOTAL DRYING TIME (MIN)	17	18
EXHAUST TEMPERATURE AT END OF DRYING (° C.)	47	48
LOD (% WT LOSS)	0.84	0.92

TABLE 1C

Screen Analysis of Milled Granulation

Screen size US Std mesh	Opening size microns	Wt Retained (%)
20	850	2.1
40	420	10.4
60	250	19.8
80	180	25.0
120	125	22.9
200	75	12.5
Pan	<45	7.3

Example 2

Functional Coating

Tablets from Example 1 were coated with a solution prepared according to the formulation in Table 2A. The ethylcellulose was first added to a 95/5 w/w mixture of ethanol and water and stirred until dissolved. Next, the hydroxypropyl cellulose and dibutyl sebacate were added and stirred until completely dissolved. 4.7 kg of tablets from Example 1 were then charged to an 8" pan Driam tablet coater and coated with the solution to 5.1 wt % gain (40 mg/tablet). The tablets were then dried for 5 minutes in the coater, and then finally cooled in the pan to an exhaust temperature below 30° C.

The dissolution profile was measured in de-ionized water using USP Apparatus 2 set to 37° C.±2° C. with paddles at 50 rpm. Samples were analyzed by HPLC. As shown in FIG. **1**, the coated tablets exhibited controlled release with duration of approximately 6 hours. The dosage form released 12% of its contents after 1 hour, 34% after 2 hours, 71% after 4 hours, 93% after 6 hours, and 99% after 8 hours.

TABLE 2A

Formulation of Sodium Oxybate Sustained-Release Tablets

	Ingredient(s)	% of coat solids	% w/w of tablet	mg/tablet
5	Sodium Oxybate tablet core		95.13	781.25
6	Hydroxypropyl cellulose, NF (Klucel EF)	37.0	1.80	14.80
7	Dibutyl sebacate	5.0	0.24	2.00
8	Ethylcellulose, NF (Ethocel Standard Premium 10)	58.0	2.82	23.20

TABLE 2A-continued

Formulation of Sodium Oxybate Sustained-Release Tablets

	Ingredient(s)	% of coat solids	% w/w of tablet	mg/tablet
9	Ethanol, USP (200 proof)*			
10	Purified water*			
	TOTAL	100.0	100.00	821.25

*Coating solvent, removed during processing

TABLE 2A

Coating Parameters for Driam 8" Pan Coater

CR COATING	AVERAGE	RANGE
INLET TEMPERATURE (° C.)	46	42-55
EXHAUST TEMPERATURE (° C.)	43	41-46
INLET AIRFLOW (PASCAL)	>300	>300
ATOMIZATION PRESSURE (BAR)	2	2.0
SPRAY RATE (G/MIN)	35	32-37
PAN SPEED (RPM)	6	5-7

Example 3

Immediate-Release Overcoat

A solution of 20% sodium oxybate as active and 2.0% hypromellose E-15 (HPMC E-15) as film-former was prepared in 60/40 (w/w) ethanol/water. The coating solution was manufactured by first dissolving the HPMC E15 in water, then adding the ethanol and sodium oxybate. 3 kg of 750-mg strength sustained-release tablets from Example 2 were charged to a Driam tablet coater equipped with an 8" pan and preheated to 40° C. The entire coating solution was applied according to the parameters listed in Table 3A. The tablet weight gain was monitored every 5 minutes, and the coating was stopped when the entire solution was sprayed (the theoretical weight gain is 33.5%). The tablets were dried for 15 minutes; the tablets did not lose any weight during the 15 minute drying time, and so it was assumed that the drying was complete. The tablets were then cooled in the pan to an exhaust temperature of <30° C.

Analysis by HPLC revealed an overall potency of 961 mg, and thus a drug overcoat potency of 211 mg. Dissolution testing using USP Apparatus 2 set to 37° C.±2° C. with paddles at 50 rpm, shown in FIG. **2**, demonstrates substantially the entire immediate-release overcoat is dissolved in 15 minutes and that controlled release is maintained for approximately 6 hours thereafter. Higher amounts of drug can be applied to the immediate release overcoat by using higher amounts of coating solution and extending the coating time accordingly.

TABLE 3A

Parameters for Immediate-Release Overcoating with 8" Driam Coater

DRUG OVER-COATING	AVERAGE	RANGE
INLET TEMPERATURE (° C.)	59	55-63
EXHAUST TEMPERATURE (° C.)	51	50-53
PRODUCT TEMPERATURE (° C.)	43	41-49
INLET AIRFLOW (PASCAL)	>300	>300
ATOMIZATION PRESSURE (BAR)	2	2
SPRAY RATE (G/MIN)	16	14-17
PAN SPEED (RPM)	8	7-8

TABLE 3A-continued

Parameters for Immediate-Release Overcoating with 8" Driam Coater

DRUG OVER-COATING	AVERAGE	RANGE
TOTAL RUN TIME (HRS)	4 HRS 47 MIN (COATING) 15 MIN (DRYING)	

The following examples illustrate aspects of the sustained-release coating formulation with several evaluations using tablets from Example 1.

Example 4

Effect of Membrane Weight with Poloxamer as Pore Former in Functional Coating

One means of controlling dissolution is by adjustment of the coating thickness, or amount of film applied to each tablet. This was illustrated with a film consisting of 33% poloxamer 188 (P188) and 67% ethylcellulose 10 cPs (EC-10). The coating solution was prepared by dissolving 3.59 grams of EC-10 and 1.77 grams of P188 in a mixture of 80 grams denatured alcohol ("alcohol") and 4 grams de-ionized water. (Denatured alcohol, S-L-X manufactured by W. M. Barr, is approximately a 50/50 w/w blend of methanol and ethanol.)

Twelve tablets from Example 1 were coated in a Caleva Mini-coater/Drier 2 under parameters listed in Table 4A. Periodically, the tablets were removed and weighed to determine film weight. Three tablets were removed at times corresponding to 21 mg, 30 mg, 40 mg, and finally 60 mg weight gain.

The dissolution profiles were measured with USP Apparatus 7 (Vankel Bio-dis) set to 37° C.±2° C. and using a dipping rate of 30/minute, tablets fixed in plastic holders and intervals corresponding to 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, and 14 h (each interval is 50 ml volume). The tubes were analyzed by conductivity, and results are calculated as percent of total amount. The results demonstrate that controlled release is achieved with membrane weights ranging from at least 21-60 mg/tablet, and that duration of delivery increases as the membrane weight increases.

TABLE 4A

Standard Parameters for Sustained-Release Coating in Caleva Mini-Coater/Drier 2

Parameter	Setting
Batch size	3-12 Tablets
Inlet temperature	40° C.
Air flow setting	70-85%
Solution flow rate	18 ml/hr
Agitator setting	32
Atomization pressure	0.5 bar
Gun position	Adjusted to achieve desired deposition

Example 5

Effect of Membrane Weight with Hydroxypropyl Cellulose as Pore Former in Functional Coating

Following procedures of Example 4, 12 tablets from Example 1 were coated with a film consisting of 36.5% HPC-EF, 5.0% dibutyl sebacate (DBS), and 58.5% EC-10 (all percentages by weight) coated from a solution consisting

of 7% solids in 95/5 alcohol/water. The results shown in FIG. **4** demonstrate that controlled release over a relevant time period is achieved with membrane weights ranging from at least 21-60 mg/tablet, and that duration of delivery increases as the membrane weight increases.

Example 6

Effect of Poloxamer Level in Functional Coating

In addition to adjustment of membrane weight, another useful means of controlling release rate or duration is by adjustment of the pore-former content of the formulation. Following procedures of Example 4, two additional solutions consisting of (a) 25% P188 by weight/75% EC-10 by weight and (b) 40% P188 by weight/60% EC-10 by weight were prepared as 7% (w/w) solutions in 95/5 alcohol/water. In each of the two separate coatings, four tablets from Example 1 were coated to 41 mg. The dissolution profiles are shown in FIG. **5**, along with that of the 40 mg set of Example 4 for comparison. The results demonstrate that poloxamer level can be adjusted at least over the range of 25%-40% by weight, while still providing controlled release of the drug.

Example 7

Effect of Hydroxypropyl Cellulose Level in Functional Coating

In a fashion similar to Example 6, the effect of HPC level in the functional coating was evaluated over the range of 30%-50% by weight. Three separate coating solutions were prepared with 30%, 40%, and 50% HPC-EF; 5% DBS; and the balance EC-10. All solutions were prepared with 7% total components in 95/5 alcohol/water. In each coating, 4 tablets from Example 1 were coated to 40-41 mg/tablet weight gain. The dissolution profiles shown in FIG. **6** demonstrate controlled release of the drug was achieved with HPC levels of at least 30-50% by weight.

Example 8

Effect of Hydroxypropyl Cellulose Molecular Weight when used in Functional Coating

Hydroxypropyl cellulose is supplied in several molecular weight grades, many of which may be suitable for use as pore-formers in ethylcellulose films. Two such grades (Klucel "EF" and "JF", supplied by Ashland) corresponding to 80,000 daltons and 140,000 daltons were evaluated with other components fixed. Following procedures of Example 4, solutions were prepared with 40% HPC, 5% DBS, and 55% EC-10 (all percentages by weight) using 7% total components in 95/5 alcohol/water. In each coating, 4 tablets from Example 1 were coated to 40-41 mg/tablet weight gain. The results shown in FIG. **7** demonstrate a modest effect of molecular weight and that the two grades tested provide for acceptable release profiles.

Example 9

Effect of Ethylcellulose Molecular Weight or Viscosity

Another consideration is the molecular weight, or viscosity, of ethylcellulose. Two grades were evaluated, corresponding to 4 cPs and 10 cPs viscosity for a 5% solution. Following procedures of Example 4, two solutions were prepared corresponding to 58.5 wt % ethylcellulose (EC-4 or EC-10), 36.5 wt % HPC-EF, and 5.0 wt % DBS having 7% w/w total components in 95/5 alcohol/water. Tablets from Example 1 were coated to 40 mg/tablet weight gain, and dissolution profiles are shown as FIG. **8**. The results indicate both grades of ethylcellulose provide for acceptable profiles, and suggest that other ethylcellulose grades (such as 20 cPs) may also be acceptable.

Example 10

Demonstration of Alcohol Ruggedness of Controlled Release Sodium Oxybate Tablets

Co-administration of sustained-release dosage forms with alcoholic beverages is a relevant concern, as ethanol is known to dissolve certain rate-controlling components that would not otherwise be dissolved. In some dosage forms, this may lead to dose-dumping. As ethanol is rapidly absorbed in the stomach, a relevant test involves dissolution of the dosage form in vodka (40% ethanol nominal) for 2 hours (representing gastric retention time), followed by normal dissolution in de-ionized water.

This test was performed on sustained-release tablets from Example 9 (36.5 wt % HPC EF, 5 wt % DBS, 58.5 wt % EC-4). The analysis of sodium oxybate by conductivity was corrected for the different response in vodka vs. de-ionized water. The results shown in FIG. **9**A indicate that dissolution is slower in Vodka, and that no dose-dumping occurred.

Likewise, a similar test was performed on sustained-release tablets with a film comprised of 33 wt % P188 and 67 wt % EC-10. Those results, shown in FIG. **9**B, also indicate slower release in vodka and no dose-dumping.

Example 11

Aqueous Coating of Controlled Release Film

Due to the hygroscopic nature of sodium oxybate, coating the rate-controlling film from an alcoholic solution is desirable. However, use of ethylcellulose aqueous dispersions is attractive for environmental and cost considerations. A film consisting of 30 wt % HPC EF and 70 wt % Surelease (aqueous ethylcellulose dispersion) was deposited on tablets from Example 1 as follows. First, 1.37 grams of HPC EF was dissolved in 22.6 grams de-ionized water. This was then poured into 32.5 grams of Surelease E-7-19040-clear while stirring. Eight tablets were coated in the Caleva Mini-coater/Drier 2 with flow rate of 15 ml/hr and 58° C. inlet temperature. Samples removed at 24 mg and 40 mg were then tested for dissolution, with no post-coating heat treatment. The results are shown in FIG. **10**.

Example 12

Calcium Oxybate Controlled Release

A controlled release dosage form for delivery of calcium oxybate was prepared by generally following procedures of Example 1 found in U.S. Pat. No. 4,393,296 (Klosa, Production of Nonhygroscopic Salts of 4-Hydroxybutyric Acid). The isolated calcium oxybate was milled to pass through a 16-mesh screen. For this study, a small sample comprising 9.3 grams of calcium oxybate was blended with 0.19 grams of sodium stearyl fumarate (Pruv, JRS Pharma,

Rosenberg, Germany). 800 mg aliquots of this 98% calcium oxybate and 2% sodium stearyl fumarate were then directly compressed into tablets using 0.325"×0.705" modified oval tooling and a Carver press with 1-ton applied force. Following procedures of Example 4, nine tablets were coated with a film having 33% poloxamer 188 and 67% EC-10 from a solution of 7% w/w solids in 95/5 alcohol/water. Two tablets were removed at each intermediate coating weight corresponding to 20 mg, 32 mg, 41 mg, and finally at 60 mg. The dissolution profiles are shown as FIG. **11**. These results using calcium oxybate follow the general behavior of sodium oxybate demonstrated in Example 4.

Example 13

Clinical Evaluation of Controlled Release Dosage Forms

An open-ended, randomized, crossover study was conducted to evaluate controlled release dosage forms as described herein. The controlled release dosage forms were formulated to deliver sodium oxybate and were compared to a sodium oxybate oral solution (commercially available as Xyrem® (sodium oxybate) oral solution). The study was conducted in healthy male and female volunteers.

Four different sodium oxybate formulations were administered to patients. The first, designated herein as Treatment A, was the sodium oxybate oral solution containing 375 mg/ml sodium oxybate. Treatments B through E, as designated herein, involved administration of three controlled release dosage forms (Treatments B through D), with one of the controlled release dosage forms being used to administer two different doses of sodium oxybate (Treatments D and E). The controlled release dosage forms administered as Treatment B included 750 mg sodium oxybate per dosage form and were produced with a CR core and functional overcoat as described in Example 1 and Example 2, the controlled release dosage forms administered as Treatment C included 750 mg sodium oxybate per dosage form and were produced as described in Example 1 and Example 4, and the controlled release dosage forms administered as Treatments D and E included 1,000 mg sodium oxybate per dosage form and were produced with a CR core (750 mg sodium oxybate), functional overcoat, and IR overcoat (250 mg sodium oxybate) as described in Examples 1 through 3.

Patients were divided into two groups. The first group received Treatment A, Treatment B, and Treatment C over the course of the clinical study, with a washout period between each treatment. Treatment A was administered to each patient as two 3 g doses given four hours apart (one dose at time zero and the second dose four hours later), for a total dose of 6 g sodium oxybate. Treatments B and C were administered to each patient only at time zero, with each treatment being administered as 8 tablets, providing a total dose of 6 g sodium oxybate. Blood samples from each patient were taken at various intervals and analyzed by LC/MS for total sodium oxybate content in the plasma. A total of 29 patients received Treatment A, a total of 19 patients received Treatment B, and a total of 19 patients received Treatment C. The mean plasma concentration of sodium oxybate over time achieved by each of the treatments is shown in FIG. **12** (Treatment A and Treatment B) and FIG. **13** (Treatment A and Treatment C), and a summary of pharmacokinetic parameters provided by Treatments A through C are provided in Table 5.

TABLE 5

Summary of PK Parameters for Treatments A, B, C

	λ_z (1/hr)	$T_{1/2}$ (hr)	Tmax (hr) [a]	Cmax (ug/ml)	AUClast (hr*ug/ml)	AUCinf (hr*ug/ml)
Treatment A						
N	29	29	29	29	29	29
Mean	1.22	0.60	4.50 (0.5, 4.75)	130.79	350.84	351.20
SD	0.27	0.13		31.52	116.74	116.74
CV %	21.93	22.61		24.10	33.27	33.24
Mean	1.19	0.58		127.37	333.33	333.72
Treatment B						
N	18	18	19	19	19	18
Mean	0.62	1.22	2.00 (1.50, 5.00)	41.78	188.23	196.25
SD	0.16	0.40		18.40	103.60	102.50
CV %	26.44	32.58		44.03	55.04	52.23
Mean	0.59	1.17		38.46	163.80	173.33
Treatment C						
N	19	19	19	19	19	19
Mean	0.74	0.99	2.50 (1.00, 5.00)	50.49	221.64	222.60
SD	0.16	0.23		15.83	106.85	106.80
CV %	22.25	22.93		31.35	48.21	47.98
Mean	0.72	0.96		48.10	200.08	201.12

The second group was administered Treatment A, Treatment D, and Treatment E during over the course of the clinical study, with a washout period between each treatment. Again, Treatment A was administered to each patient as two 3 g doses given four hours apart (one dose at time zero and the second dose four hours later), for a total dose of 6 g sodium oxybate. Treatments D and E were administered to each patient only at time zero. Patients receiving Treatment D were administered 4 tablets at time zero, providing a total dose of 4 g sodium oxybate, and patients receiving Treatment E were administered 8 tablets at time zero, providing a total dose of 8 g sodium oxybate. Blood samples from each patient were taken at various intervals and analyzed by LC/MS for total sodium oxybate content in the plasma. A total of 30 patients received Treatment A, and a total of 30 patients received Treatments D and E. The mean plasma concentration of sodium oxybate over time achieved by each of the treatments is shown in FIG. **14**, and a summary of pharmacokinetic parameters provided by Treatments A through C are provided in Table 6.

TABLE 6

Summary of PK Parameters for Treatments A, D, E

	λ_z (1/hr)	$T_{1/2}$ (hr)	Tmax (hr) [a]	Cmax (ug/ml)	AUClast (hr*ug/ml)	AUCinf (hr*ug/ml)
Treatment A						
N	30	30	30	30	30	30
Mean	1.08	0.71	4.50 (0.50, 5.50)	114.59	301.28	301.59
SD	0.31	0.27		27.91	100.85	100.87
CV %	29.00	37.90		24.36	33.47	33.45
Mean	1.03	0.67		111.20	285.47	285.79
Treatment D						
N	30	30	30	30	30	30
Mean	0.46	1.63	0.75 (0.50, 2.50)	25.10	64.44	65.58
SD	0.14	0.47		7.33	20.36	20.26
CV %	30.27	29.00		29.20	31.60	30.90
Mean	0.44	1.56		24.01	61.31	62.55

TABLE 6-continued

Summary of PK Parameters for Treatments A, D, E

	λ_z (1/hr)	$T_{1/2}$ (hr)	Tmax (hr) [a]	Cmax (ug/ml)	AUClast (hr*ug/ml)	AUCinf (hr*ug/ml)
Treatment E						
N	30	30	30	30	30	30
Mean	0.59	1.36	1.00 (0.50, 5.00)	59.52	242.30	243.80
SD	0.20	0.64		17.72	117.15	116.79
CV %	34.57	46.91		29.77	48.35	47.91
Mean	0.55	1.25		56.89	216.33	218.12

[a] Tmax is summarized as median (min, max).

It will be obvious to those having skill in the art that many changes may be made to the details of the above-described embodiments without departing from the underlying principles of the invention. The scope of the present invention should, therefore, be determined only by the following claims.

The invention claimed is:

1. A formulation comprising immediate release and sustained release portions, each portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, wherein:

a. the sustained release portion comprises a functional coating and a core, wherein the functional coating is deposited over the core, wherein the core comprises at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate wherein the functional coating comprises one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating; the sustained release portion comprises about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm;

b. the immediate release portion comprises about 75% and about 98% by weight of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, and the amount of gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the immediate release portion is about 10% to 50% by weight of the gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the formulation;

c. the formulation releases at least about 30% of its gamma-hydroxybutyrate by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm; and

d. the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

2. The formulation of claim **1** wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 7 hours when tested in a dissolution apparatus 2 when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

3. The formulation of claim **1** wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 6 hours when tested in a dissolution apparatus 2 when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

4. The formulation of claim **1** wherein the sustained release portion releases about 60% to about 90% of its gamma-hydroxybutyrate by about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

5. The formulation of claim **1** wherein the sustained release portion comprises hydrogenated vegetable oil, hydrogenated castor oil, or mixtures thereof.

6. The formulation of claim **1** comprising a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.

7. The formulation of claim **6** comprising a sodium salt of gamma-hydroxybutyrate.

8. The formulation of claim **1** wherein the immediate release portion comprises 50% by weight of the total gamma-hydroxybutyrate.

9. The formulation of claim **1**, wherein the one or more methacrylic acid-methyl methacrylate co-polymers comprise from about 30% to about 45% by weight of the functional coating.

10. An oral dosage form comprising the formulation of claim **1**.

11. The formulation of claim **1** wherein the sustained release portion releases about 10% or less of its gamma-hydroxybutyrate by about 1 hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

12. A formulation of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, comprising immediate release and a solid sustained release portions:

a. wherein the immediate release portion comprises about 55 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate;

b. wherein the sustained release portion comprises from about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate and a functional coating deposited over a core comprising the at least one pharmaceutically active ingredient, wherein the functional coating comprises one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm;

c. the formulation releases at least about 30% of its gamma-hydroxybutyrate or salt thereof by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm; and

d. the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours when tested in a

dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

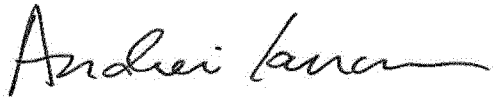
PATENT NO. : 10,758,488 B2
APPLICATION NO. : 16/025487
DATED : September 1, 2020
INVENTOR(S) : Allphin et al.

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

In the Claims

Claim 3, Column 28, Lines 5-6, replace "when tested in a dissolution apparatus 2 when tested in a dissolution apparatus 2 in deionized water" with --when tested in a dissolution apparatus 2 in deionized water--.

Signed and Sealed this
Twenty-seventh Day of October, 2020



Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT 2

Attorney Docket No. JAZZ-043/02US 306882-2331 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	ALLPHIN, Clark et al.	Confirmation No.:	3698
Application No.:	16/025,487	Group Art Unit:	1619
Filed:	July 2, 2018	Examiner:	Gotfredson, Garen

FOR: CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES

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

Response to Accompany a Request for Continued Examination

This paper is filed in response to the Final Office Action mailed May 2, 2019. A Request for Continued Examination is being concurrently filed, and a three month extension of time is hereby requested. Accordingly, in light of the Notice of Appeal filed on November 1, 2019, this paper is timely filed. Reconsideration of this application is respectfully requested in view of the following amendments and remarks.

AMENDMENTS TO THE CLAIMS

Set forth below in ascending order, with status identifiers, is a complete listing of all claims currently under examination. Changes to any amended claims are indicated by strikethrough or underlining. This listing also reflects any cancellation and/or addition of claims.

1-108. (Canceled)

109. (Currently Amended) A ~~solid dosage~~ formulation comprising immediate release and ~~controlled~~ sustained release portions, each portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate ~~or a pharmaceutically acceptable salt thereof~~, wherein:

a. the ~~controlled~~ sustained release portion comprises a functional coating and a [[CR]] core, wherein the functional coating is ~~coated onto~~ deposited over the [[CR]] core, wherein the [[CR]] core comprises at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate ~~or a pharmaceutically acceptable salt thereof~~;, ~~and~~ wherein the functional coating comprises one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating; the sustained release portion comprises about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm;

b. the immediate release portion comprises ~~an amount of gamma-hydroxybutyrate or pharmaceutically acceptable salt thereof that is between~~ about 75% and about 98% by weight of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-

hydroxybutyrate, and the amount of gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the immediate release portion is about 10% to 50% by weight of the gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the formulation;

~~c. wherein a total gamma hydroxybutyrate or pharmaceutically acceptable salt thereof in the solid dosage formulation is about 500 mg to about 12 g, and the amount of gamma-hydroxybutyrate or pharmaceutically acceptable salt thereof in the immediate release portion is about 10% to 50% by weight of the total gamma-hydroxybutyrate or pharmaceutically acceptable salt thereof in the solid dosage formulation;~~

~~d. the controlled release portion releases greater than about 40% of its gamma-hydroxybutyrate over about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm;~~

c[[e]]. the ~~solid dosage~~ formulation releases at least about 30% of its gamma-hydroxybutyrate by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm; and

d[[f]]. the ~~solid dosage~~ formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours ~~when tested in a dissolution apparatus 2~~ when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm.

110. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the ~~solid dosage~~ formulation releases greater than about 90% of its gamma-hydroxybutyrate by 7 hours when tested in a dissolution apparatus 2 when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm.

111. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the ~~solid dosage~~ formulation releases greater than about 90% of its gamma-hydroxybutyrate by 6

hours when tested in a dissolution apparatus 2 when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm.

112. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the ~~controlled~~ sustained release portion releases about 60% to about 90% of its gamma-hydroxybutyrate by about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm.

113. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the ~~controlled~~ sustained release portion comprises hydrogenated vegetable oil, hydrogenated castor oil, or mixtures thereof.

114. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 comprising a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.

115. (Currently Amended) The ~~solid dosage~~ formulation of claim 114 comprising a sodium salt of gamma-hydroxybutyrate.

116. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the immediate release portion comprises 50% by weight of the total gamma-hydroxybutyrate.

117. (Canceled)

118. (Currently Amended) The ~~solid dosage~~ formulation of claim 109, wherein the one or more methacrylic acid-methyl methacrylate co-polymers comprise from about 30% to about 45% by weight of the functional coating.

119. (Currently Amended) An oral ~~solid~~ dosage form comprising the ~~solid dosage~~ formulation of claim 109.

120. (New) The formulation of claim 109 wherein the sustained release portion releases about 10% or less of its gamma-hydroxybutyrate by about 1 hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm.

121 (New) A formulation of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, comprising immediate release and a solid sustained release portions:

a. wherein the immediate release portion comprises about 55 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate;

b. wherein the sustained release portion comprises from about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate and a functional coating deposited over a core comprising the at least one pharmaceutically active ingredient, wherein the functional coating comprises one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm;

c. the formulation releases at least about 30% of its gamma-hydroxybutyrate or salt thereof by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm; and

d. the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm.

REMARKS

I. Status of the Claims

Upon the entry of the amendments, claims 109-116 and 118-121 are pending. Claims 109-116, 118, and 119 have been amended. Claims 120 and 121 are new. Support for these amendments and new claims can be found throughout the specification and in the claims as originally filed, particularly in Paragraphs [0027], [0037], [0038], [0055], [0069], and Figures 3-5.

Entry and consideration of these amendments are respectfully requested. No new matter is believed to have been added by way of these amendments.

II. Interview

Applicant thanks the Examiner and his Supervisor for the productive interview on January 23, 2019, with the co-inventor, Clark Allphin, and Applicant's representatives, Philip McGarrigle, Michael Tuscan, and the undersigned. Applicant also thanks the Examiner for the withdrawn of the 35 U.S.C. §112 (pre-AIA), second paragraph rejection, as well as the obvious-type double patenting rejection.

III. Rejections

A. 35 U.S.C. §112 (pre-AIA)

The Office rejected claims 109-119 under 35 U.S.C. §112 (pre-AIA), first paragraph as allegedly failing to comply with the written description requirement. The Office asserts that the specification fails to describe in sufficient detail that one skilled in the art can reasonably conclude that the inventor had actual possession of the claimed invention at the time of the invention.

Applicant respectfully disagrees and submits that the instant specification provides ample guidance for one skilled in the art to recognize that Applicant was in possession of the claimed dosage formulation at the time of filing. To establish that the claims are adequately described, the specification must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, [Applicant] was in possession [of] . . . whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1564 (Fed. Cir. 1991). A genus is adequately described if the

specification permits one of skill in the art to "visualize or recognize members of the genus." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997).

The specification teaches that that the dosage forms of the present invention release gamma-hydroxybutyrate (GHB) over a sustained period of time.[1] Figures 3-5 describe the claimed *in vitro* release rates, and the detailed description provides a discussion of how formulations of the presently claimed invention can be made. The inventors teach that "(i)n addition to adjusting the amount or nature of the pore former included in the functional coating composition, the release rate of drug provided by the controlled release dosage form disclosed herein may be adjusted by modifying the thickness or weight of the functional coating composition." [2] The application teaches that a pore-former, such as a methacrylic acid-methyl methacrylate co-polymer can be present at about 20% to about 50% by weight of the functional coating.[3] According to the MPEP, "if the art has established a strong correlation between structure and function, one skilled in the art would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function." [4] The examples, in concert with the general disclosure, provide enough guidance for one of skill in the art to conclude that Applicant was in possession of the claimed dosage formulation.

The Examiner states that the examples do not show an embodiment within the scope of the present claims. Respectfully, it is not necessary to disclose such an example order to meet the written description requirement. As explained in the MPEP by the Federal Circuit "examples are not necessary to support the adequacy of a written description, … the written description standard may be met … even where actual reduction to practice of an invention is absent."[5] Further, the numerous examples in the specification demonstrate a correlation between structure and function. Applicant therefore asserts that the examples show elements of the present invention and that the other support throughout the application is sufficient to prove written description for the present claims.

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[1] As-filed specification [0037] and [0038].
[2] As-filed specification [0056].
[3] As-filed specification [0051] and [0052].
[4] MPEP 2163 IIA3(a), quoting Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613, quoting the Written Description Guidelines, 66 Fed. Reg. at 1106, n. 49.
[5] MPEP 2163 IIA3(a), quoting Falkner v. Inglis, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006).

Therefore, Applicant respectfully requests withdrawal of this rejection.

B. 35 U.S.C. §103(a)

The Office rejected claims 109-119 under 35 U.S.C. §103(a) as unpatentable over Liang *et al*. (U.S. Pat. Pub. No. 2006/0210630, hereinafter "Liang.") Applicant respectfully disagrees. As discussed in more detail below, as well as in the accompanying declaration, the release profile of the claimed invention is distinct from that taught in Liang.

The presently claimed invention is directed to an oxybate formulation with a ***sustained release*** component. Liang however, teaches a ***delayed release*** formulation. These formulations are quite different structurally and functionally, and it would not be obvious to modify a delayed release formulation to make a sustained release formulation. Liang not only fails to teach or suggest the claimed sustained release profile, it fails to provide any motivation for a skilled artisan to modify its teachings of a delayed release formulation and arrive at a sustained release formulation as presently claimed.

1. Liang cannot support a case of *prima facie* obviousness

As an initial matter, the office has failed to establish a *prima facie* case of obviousness. To establish a case of *prima facie* obviousness, the combination of references must teach each and every element in the claims. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). As previously discussed, and as the Office states in the Final Action dated May 2, 2019, Liang does not teach the amount of GHB and methacrylic polymer coating, nor the claimed functional limitations regarding the *in vitro* release of GHB. However, the Office alleges that one of skill in the art would be motivated to modify Liang to arrive at the claimed invention.

Specifically, the Office asserts that the delayed release coatings of Liang could be modified to make a sustained release formulation. However, a skilled artisan would not consider modifying a delayed release formulation to make a sustained release formulation as they produce very different pK profiles.[6] Delayed release formulations quickly release the majority of the drug a certain amount of time after dosing. Essentially, a patient is given a delayed bolus dose. Sustained release formulations, in contrast, provide for a more gradual, but extended release of

[6] The Allphin Declaration, paragraph 12.

the drug over a period of time. Such a formulation could start releasing the drug shortly after dosing, or there could be a lag before the drug starts to release. This sustained release of the drug can then take place over a longer period of time than would typically occur in a delayed release formulation.

Since Liang is directed to *delayed* release, not sustained release, formulations of GHB. Liang's delayed-release coatings comprise about 87% by weight pH-sensitive enteric polymers, specifically pH-sensitive methacrylic acid-methyl methacrylate co-polymers.[7] As the coatings comprise a large percentage of pH-sensitive polymer, these dosage forms would release the majority of the drug relatively rapidly upon exposure to intestinal pH (e.g., about 6 and above), i.e., delayed release. As shown in Example 7 and Figures 1 and 2 of Liang, these "delayed release prototypes" release about 70%-100% of the drug within an hour at intestinal pH.[8]

In contrast, the presently claimed invention is directed to dosage forms comprising an immediate release portion and a *sustained* release portion. The claimed sustained release portion releases less than 10% of the drug within an hour in DI water and at least about 40% of the drug by about four to six hours in DI water, and the sustained release coating comprises about 20-50% by weight methacrylic acid-methyl methacrylate co-polymers. As discussed in the accompanying declaration from inventor Clark Allphin, the inventors were aware of Liang's teachings.[9] The light of these teachings, they conducted a regional GHB absorption study in humans in order to create an improved model of GHB delivery and used pharmacokinetic modeling to predict an *in vitro* release profile that would provide improved bioavailability.

The Office alleges that there is motivation for the skilled artisan to modify the Liang composition. However, the Office has failed to point out with any particularity where Liang provides the motivation to drastically alter its delayed release profile to an entirely different type of release profile. Rather, the Office alleges that modifying coatings is "routine optimization." Applicant disagrees, as there is no such motivation in Liang to change from one type of release profile to a very different type by modifying its delayed release coating to achieve a sustained release formulation as presently claimed. As discussed above, and in the attached declaration,

[7] Liang, Example 6.
[8] Liang, Fig 1-3 and [015]-[017].
[9] The Allphin Declaration, paragraph 5.

delayed release and sustained release are distinctly different types of release, and altering a formulation from delayed release to sustained release is not routine. Further, there is no motivation to modify Liang's coatings to achieve the particular *in vitro* release rate that is presently claimed. By saying one of skill, guided by Liang, would settle on the claimed release rate, the Office is relying on impermissible hindsight. Therefore, the Office has failed to establish a *prima facie* case of obviousness. As such, Applicant maintains that the claimed invention is not obvious in light of the cited art and respectfully requests that the rejection be withdrawn.

2. The claimed sustained release formulations provide superior bioavailability over Liang

As discussed in the Allphin Declaration, and as evidenced by the data in Liang, the delayed release formulations disclosed in Liang did not provide the desired bioavailability. [10] The formulation targeting the colon (DR-1) had about a quarter of the bioavailability of the immediate release dosage form, while the duodenum targeting formulation (DR-2) had about half the bioavailability of the immediate release dosage form.[11] Such a formulation would not provide sufficient GHB, and therefore would not be a useful once-nightly formulation.

The inventors, aware of the poor bioavailability of the Liang formulations, designed experiments to study the regional absorption of GHB in humans. The results of this study showed that substantial GHB absorption occurred in the upper intestinal tract, specifically, the ileum and jejunum.[12] The inventors modeled plasma pharmacokinetic (PK) simulations based on the data from these regional absorption studies, which allowed the inventors to predict a PK profile based on an *in vitro* release profile. As discussed in the Allphin Declaration, this modeling indicated that a sustained release formulation, where at least about 40% of the GHB is released by 4 to 6 hours when tested at a neutral pH (i.e., in DI water) would target the ileum and jejunum, and thereby provide improved absorption and better bioavailability. Additionally, the modeling showed that lag time of 1 hour results in a flatter PK profile, which is preferred. Therefore, the inventors focused on sustained release GHB formulations wherein less than 10%

[10] The Allphin Declaration, paragraph 7.
[11] Liang, Example 7, paragraph [0115], ad Table 3.
[12] The Allphin Declaration, paragraph 8.

of the drug is released within the first hour and a substantial portion of the drug (i.e., at least about 40%) is released by about 4 to 6 hours.

As the cited art teaches neither the presently claimed structural limitations, nor the presently claimed release profile, and one of skill in the art would have no motivation, based on the cited art, to develop a GHB formulation with the claimed *in vitro* release profile, the Office has failed to establish a case of *prima facie* obviousness. Further, as shown in the declaration, the inventors had discovered that the claimed *in vitro* release profile provides superior bioavailability as compared to the formulations in the cited art. As such, the Applicant respectfully requests the withdrawal of this rejection.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that no further impediments exist to the allowance of this application and, therefore, requests an indication of allowability. However, the Examiner is requested to call the undersigned if any questions or comments arise.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

Dated: March 6, 2020

Respectfully submitted,
COOLEY LLP

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Reg. No. 65,841

EXHIBIT 3

Dictionary of Pharmacy

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RS51.D482 2004
615'.1'03—dc22

2004001894

surface active agent SEE *surfactant*

surface energy SEE *surface tension*

surface filtration pharmaceutical process of separating a usable solid material called a "cake" from a liquified dispersion medium by use of a flat filter and a support system

surface free energy SEE *surface tension*

surface tension a natural result of unequal attractive forces between molecules near the interface of a substance; used to express air-substance interfacial tension; force per unit length required to break a surface; energy required to expand a surface one area unit; synonym: surface energy

surface-shape factor quantitative expression relating the total surface area(s) of a given quantity of a drug powder to the sum of the products of the frequency (or number) of particles times their projected diameters squared; the more irregular the shape the larger the value of this factor; a measure of irregularity of shape

surfactant surface active agent; substance that reduces surface and interfacial tension in small concentrations; examples: emulsifiers, deflocculants, suspending oils, dispersants, soaps, detergents

surgeon a physician who specializes in surgical treatment of illnesses or malfunctions

surgi-center SEE *freestanding outpatient surgical center*

suspension a preparation of finely divided undissolved drugs dispersed in a liquid medium; used to provide insoluble drugs in a liquid dosage form

suspension, extended release liquid preparation consisting of solid particles dispersed throughout a liquid phase in which the particles are not soluble; formulated in a manner to allow at least a reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g., a solution or a prompt drug-releasing, conventional solid dosage form)

sustained action a dosage form designed so that the initial dose of a drug is absorbed rapidly followed by the maintenance of an effective plasma concentration through a continual release of the drug over a period of time

sustained release dosage form (usually a tablet or capsule) in which release of the drug is extended over a period of time; contrasted with a tablet that releases the entire dose at one time

suture **1:** act of stitching a wound together **2:** material used to stitch a wound together; strand or fiber used to hold wound edges in apposition

EXHIBIT 4

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²suspensory *n, pl* **-ries** : something that suspends or holds up; *esp* : a fabric supporter for the scrotum
suspensory ligament *n* : a ligament or fibrous membrane suspending an organ or part: as **a** : a ringlike fibrous membrane connecting the ciliary body and the lens of the eye and holding the lens in place **b** : FALCIFORM LIGAMENT
suspensory ligament of the ovary *n* : a fold of peritoneum that consists of a part of the broad ligament that is attached to the ovary near the end joining the fallopian tube and that contains blood and lymph vessels passing to and from the ovary — called also *infundibulopelvic ligament*; compare LIGAMENT OF THE OVARY
sustained–release *adj* : designed to slowly release a drug in the body over an extended period of time ⟨~ capsules⟩ — compare TIMED-RELEASE
sus•ten•tac•u•lar cell \ˌsəs-tən-ˈta-kyə-lər-\ *n* : a supporting epithelial cell (as of the olfactory epithelium) that lacks a specialized function
sustentacular fiber of Müller *n* : FIBER OF MÜLLER
sus•ten•tac•u•lum ta•li \ˌsəs-tən-ˈta-kyə-ləm-ˈtā-ˌlī\ *n* : a medial process of the calcaneus supporting part of the talus
su•ture \ˈsü-chər\ *n* **1 a** : a stitch made with a suture **b** : a strand or fiber used to sew parts of the living body **c** : the act or process of sewing with sutures **2 a** : the line of union in an immovable articulation (as between the bones of the skull); *also* : such an articulation **b** : a furrow at the junction of adjacent bodily parts — **su•tur•al** \ˈsü-chə-rəl\ *adj* — **suture** *vb*
suxa•me•tho•ni•um \ˌsúk-sə-mə-ˈthō-nē-əm\ *n, chiefly Brit* : SUCCINYLCHOLINE
Sv *abbr* sievert
sved•berg \ˈsfed-ˌbərg, -ˌber-ē\ *n* : a unit of time amounting to 10^{-13} second that is used to measure the sedimentation velocity of a colloidal solution (as of a protein) in an ultracentrifuge and to determine molecular weight by substitution in an equation — called also *svedberg unit*
Svedberg, Theodor (1884–1971), Swedish chemist.
SV40 \ˌes-ˌvē-ˈfȯr-tē\ *n* : SIMIAN VIRUS 40
SVT *abbr* supraventricular tachycardia
swab \ˈswäb\ *n* **1** : a wad of absorbent material usu. wound around one end of a small stick and used for applying medication or for removing material from an area **2** : a specimen taken with a swab ⟨a throat ~⟩ — **swab** *vb*
swamp fever *n* : EQUINE INFECTIOUS ANEMIA
Swan–Ganz catheter \ˈswän-ˈganz-\ *n* : a soft catheter with a balloon tip that is used for measuring blood pressure in the pulmonary artery
Swan, Harold James Charles (*b* **1922**), and **Ganz, William** (*b* **1919**), American cardiologists.
S wave \ˈes-ˌ\ *n* : the negative downward deflection in the QRS complex of an electrocardiogram that follows the R wave
sway•back \ˈswā-ˌbak\ *n* **1** : an abnormally hollow condition or sagging of the back found esp. in horses; *also* : a back so shaped **2** : LORDOSIS **3** : a copper-deficiency disease of young or newborn lambs that is marked by demyelination of the brain — **sway-backed** \-ˌbakt\ *adj*
¹sweat \ˈswet\ *vb* **sweat** *or* **sweat•ed; sweat•ing** : to excrete moisture in visible quantities through the opening of the sweat glands : PERSPIRE
²sweat *n* **1** : the fluid excreted from the sweat glands of the skin : PERSPIRATION **2** : abnormally profuse sweating — often used in pl. ⟨soaking ~s⟩ — **sweaty** \-ē\ *adj*
sweat duct *n* : the part of a sweat gland which extends through the dermis to the surface of the skin
sweat gland *n* : a simple tubular gland of the skin that secretes perspiration and in humans is widely distributed in nearly all parts of the skin — called also *sudoriferous gland*
sweat test *n* : a test for cystic fibrosis that involves measuring the subject's sweat for abnormally high sodium chloride content
swee•ny \ˈswē-nē\ *n, pl* **sweenies** : an atrophy of the shoulder muscles of a horse; *broadly* : any muscular atrophy of a horse
sweet \ˈswēt\ *adj* : being or inducing the one of the four basic taste sensations that is typically induced by disaccharides and is mediated esp. by receptors in taste buds at the front of the tongue — compare BITTER, SALT 2, SOUR — **sweet•ness** *n*
Sweet's syndrome \ˈswēts-\ *n* : a disease that occurs esp. in middle-aged women, that is characterized by red raised often painful patches on the skin, fever, and neutrophilia in the peripheral blood, that responds to treatment with corticosteroids but not antibiotics, and that is of unknown cause but is sometimes associated with an underlying malignant disorder — called also *acute febrile neutrophilic dermatosis*
Sweet, Robert Douglas (1917–2001), British dermatologist.
swell \ˈswel\ *vb* **swelled; swelled** *or* **swol•len** \ˈswō-lən\; **swell•ing** : to become distended or puffed up
swell•ing \ˈswel-iŋ\ *n* : an abnormal bodily protuberance or localized enlargement ⟨an inflammatory ~⟩
Swift's disease \ˈswifts-\ *n* : ACRODYNIA
Swift, H. (*fl* **1918**), Australian physician.
swimmer's ear *n* : inflammation of

EXHIBIT 5

US011077079B1

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

(10) **Patent No.: US 11,077,079 B1**
(45) **Date of Patent: Aug. 3, 2021**

(54) **GHB FORMULATION AND METHOD FOR ITS MANUFACTURE**

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(73) Assignee: **Jazz Pharmaceuticals Ireland Limited**, Dublin (IE)

(*) 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.: **17/118,041**

(22) Filed: **Dec. 10, 2020**

Related U.S. Application Data

(63) Continuation of application No. 16/448,598, filed on Jun. 21, 2019, now abandoned, which is a continuation of application No. 15/047,586, filed on Feb. 18, 2016, now Pat. No. 10,398,662.

(60) Provisional application No. 62/117,889, filed on Feb. 18, 2015.

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A61K 9/50	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/19*** (2013.01); ***A61K 9/5031*** (2013.01); ***A61K 31/785*** (2013.01); ***A61K 38/02*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/19; A61K 31/785; A61K 9/5031; A61K 38/02
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(57) **ABSTRACT**

The present application relates to GHB formulations and methods for manufacturing the same.

18 Claims, No Drawings

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GHB FORMULATION AND METHOD FOR ITS MANUFACTURE

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. application Ser. No. 16/448,598, filed Jun. 21, 2019, which is a continuation of U.S. application Ser. No. 15/047,586, filed Feb. 18, 2016, now U.S. Pat. No. 10,398,662, which claims priority to U.S. Provisional Application Ser. No. 62/117,889, filed Feb. 18, 2015, the disclosures of which are herein incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

Gamma-hydroxybutyrate (GHB), also known as "oxybate," 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 the brain, the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter (See Snead and Morley, 1981, Brain Res. 227(4): 579-89). 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 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, reduces sleep apnea, and improves general anesthesia (see, e.g., U.S. Pat. Nos. 6,472,431; 6,780,889; 7,262,219; 7,851,506; 8,263,650; and 8,324,275; each of which is incorporated herein by reference in its entirety).

Sodium oxybate (Na.GHB), commercially sold as Xyrem®, is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. It can be used for other sleep time disturbances. Na.GHB has also been reported to be effective for relieving pain and improving function in patients with fibromyalgia syndrome (See Scharf et al., 2003, J. Rheumatol. 30: 1070; Russell et al., 2009, Arthritis. Rheum. 60: 299), and in alleviating excessive daytime sleepiness and fatigue in patients with Parkinson's disease, improving myoclonus and essential tremor, and reducing tardive dyskinesia and bipolar disorder (See Ondo et al., 2008, Arch. Neural. 65: 1337; Frucht et al., 2005, Neurology 65: 1967; Berner, 2008, J. Clin. Psychiatry 69: 862).

SUMMARY OF THE INVENTION

GHB has a short in vivo half-life, so various embodiments of the invention include a formulation and a method for manufacturing a GHB formulation. One embodiment of the invention is a GHB formulation comprising polymeric beads and pharmaceuticals acceptable excipients. The formulation can be a solid or a liquid. Additional agents, such as surfactants, may be added to control the release of GHB from within the polymeric bead, such as sodium lauryl sulfate or stearic acid. The beads can be coated with a flexible film. Optionally, the formulation can contain supplemental anions separate from the coated or uncoated resin particles to facilitate exchange of the GHB when natural (e.g., physiologically produced) anions in the gut are depleted.

In another embodiment of the invention, a precursor to GHB, called gamma butyrolactone (GBL) is loaded onto a hydroxide form Type 1 strong base anion resin (or its equivalent) and the GBL is converted to GHB in the bead to form a GHB resinate product. One can achieve high loading efficiency of the GHB resinate product and a high reaction rate on the resin. Furthermore, organic non-anionic byproducts made in reaction or present in the GBL would not be captured on the resin.

In another embodiment of the invention, one can fully load GHB on the resin, then load a lipophilic agent on the resin with higher selectivity for the resin than GHB. The agent will slow the release of GHB.

In another embodiment, one can fully load an anionic hydrophobic agent, such as stearic acid, onto the resin with lower selectivity for the resin than GHB and then subsequently load GHB less completely, thereby retaining much of the hydrophobic agent and promoting a slower release of GHB.

In still another embodiment of the invention, the hydroxide-bearing resin beads are coated with a flexible film, then loaded with GBL which, in turn, will diffuse through the film and react with the hydroxyl anions of the resin and form the GHB resinate in-situ. The coating will provide further controlled release characteristics. Examples of such coatings include films comprising polyvinyl acetate (PVAcetate), Eudragit RS, ethylcellulose, cellulose acetate or an enteric coating such as acrylic acid-based Eudragit L100, FS100 or L55, cellulose acetate phthalate, and shellac. It is understood that these films can be modified with pore formers to adjust permeability or degree of enteric protection. The coating may also be combined with suitable plasticizer and anti-tack agents to facilitate coating. Finely ground resin beads may also be encapsulated within polysaccharide gel structures that confer enteric protection, through ionotropic gelation as with calcium alginate encapsulation.

Other embodiments include reducing the amount of water in the formulation. Oral administration may be achieved while reducing the amount of water by using agents that increase flow, such as slippants to reduce viscosity. Example slippants include polyethylene oxide (PEG) (and its equivalents) which is available in various grades of varying molecular weight and molecular weight distribution.

DETAILED DESCRIPTION OF THE INVENTION

One embodiment of the invention is a GHB formulation comprising polymeric beads and pharmaceuticals acceptable excipients. The formulation can be in the form of a solid or a liquid. Additional agents, such as surfactants, may be added to control the release of GHB from within the polymeric bead, such as sodium lauryl sulfate or stearic acid. The beads can be coated with a flexible film. Background information on GHB and its related compounds, use and methods for manufacture are listed below. Also, background information on ion exchange resins, their manufacture and uses can be found in the references listed below. The new formulations of the present invention described herein provide favourable sustained release profiles for GHB.

The following U.S. patents and applications relate to GHB and are hereby incorporated by reference in their entireties for all purposes: U.S. Pat. Nos. 6,472,431, 8,263,650, 8,324,275; 8,859,619; 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 8,461,197; 8,591,922; 8,731,963; 8,759,394; 8,771,735; 8,772,306; 8,778,301; 8,778,398; 8,901,173; and 2012/0076865. The following patents

are also incorporated by reference: U.S. Pat. Nos. 5,380,937; 4,393,236 German Patent DD 237,309 A1; and British Pat. No. 922,029.

Information on ion exchange resins, their manufacture and uses can be found in the following references which are hereby incorporated by reference in their entireties for all purposes. Mahore J. G, Wadher K. J, Umekar M. J, Bhoyar P. K., Ion Exchange Resins: Pharmaceutical Applications And Recent Advancement, International Journal of Pharmaceutical Sciences Review and Research, Volume 1, Issue 2, March-April 2010; Article 002; Munot, Neha M., et al. "Ion exchange resins in pharmaceuticals: A review." Journal of Pharmacy Research 3.12 (2010). Singh, Inderbir, et al. "Ion exchange resins: drug delivery and therapeutic applications." FABAD J. Pharm. Sci 32 (2007): 91-100; Srikanth, M. V., et al. "Ion-exchange resins as controlled drug delivery carriers." Journal of Scientific Research 2.3 (2010): 597; Singh, Inderbir, et al. "Ion exchange resins: drug delivery and therapeutic applications." FABAD J. Pharm. Sci 32 (2007): 91-100; Ohta et al., Development of a simple method for the preparation of a silica gel based controlled delivery system with a high drug content, European Journal of Pharmaceutical Sciences 26 (2005) 87-96; Akifuddin et al., Preparation, Characterization and In-vitro Evaluation of Microcapsules for Controlled Release of Diltiazem Hydrochloride by Ionotropic Gelation Technique, Journal of Applied Pharmaceutical Science Vol. 3 (04), pp. 035-042, April, 2013; Patil et al., A Review On Ionotropic Gelation Method: Novel Approach For Controlled Gastroretentive Gelispheres; International Journal of Pharmacy and Pharmaceutical Sciences, Vol 4, Suppl 4, 2012; Cabellero, et al., Characterization of alginate beads loaded with ibuprofen lysine salt and optimization of the preparation method, International Journal of Pharmaceutics 460 (2014) 181-188; J. M. C. Puguan, X. Yu, H. Kim, Diffusion characteristics of different molecular weight solutes in Ca-Alginate gel beads, Colloids and Surfaces A: Physicochemical and Engineering Aspects (2015), http://dx.doi.org/10.1016/j.colsurfa.2015.01.027; Takka and Gurel, Evaluation of Chitosan/Alginate Beads Using Experimental Design: Formulation and In Vitro Characterization, AAPS PharmSciTech, Vol. 11, No. 1, March 2010; Anand, et al., Ion-exchange resins: carrying drug delivery forward, DDT Vol. 6, No. 17 Sep. 2001. See also the Technical Information sheet for Dowex Ion Exchange Resins; the Product Data Sheet for Amberlite IRN78 Resin, both from Dow Chemicals. Also the Technical Sheet for Duolite AP143/1083 Pharmaceutical Grade Anion Exchange Resin (Cholestyramine Resin USP) from Rohm and Haas. The following U.S. Patents and applications are also incorporated by reference in their entireties for all purposes U.S. Pat. Nos. 4,221,778; 4,510,128; 6,322,819; 8,193,211, 8,202,537; 8,771,735; 8,778,398, 8,062,667, and 8,337,890; U.S. Patent Publication Nos. 2003/0180249; 2008/0003267; 2008/0118571; 2012/0076865; 2012/0148672; 2013/0273159; 2014/0004202; 2014/0093578; and 2014/0127306.

As used herein, the term gamma-hydroxybutyrate (GHB) or "oxybate" refers to the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid. The manufacture, use, known dosage forms and dosing can be shown in the above patents. An effective dosage range of Xyrem is 6 g to 9 g, given at night in divided doses approximately 2-4 hours apart. GHB is typically given twice nightly due to a short in vivo half-life. It is subject to a controlled drug distribution system. See U.S. Pat. Nos. 6,472,431, 8,263,650, 8,324,275; 8,859,619; 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 8,591,922; and 8,772,306 which are incorporated above.

One object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours. As described above, a single dose is eliminated within a shorter period of time. One object of the invention is to maintain the blood level of GHB from about 10 mg/L to about 20 mg/L for up to 8, 7, 6, or 5 hours. Additionally, it is an object of the invention to ensure that the sleep inducing effects of GHB do not remain for longer than the above periods as it would compromise a patient's ability to perform normal day to day activities, such as work or driving a car. One embodiment of the invention is a controlled release formulation of GHB designed to maintain a level of GHB in the blood that satisfies the above criteria. In addition to the controlled or extended release properties of one embodiment, there can be an immediate release GHB formulation that is present in or accompanies the controlled release formulation. A sufficient amount of GHB must be present in the blood to initiate the sleep function of GHB and then the controlled release component may engage to maintain the blood concentration above the threshold for a complete sleep of sufficient duration. It has been discovered that administration of food may extend the effects of GHB in some circumstances and care should be taken to consider this effect during administration. See U.S. Pat. Nos. 8,859,619; 8,778,398 and 8,591,922 as well as U.S. Pat. Publication 2012/0076865 among others.

The buffering capacity of GHB may affect gastric pH and compromise performance of enteric-coated dosage forms. Avoidance of the potential impact on gastric pH is another useful feature of the GHB resinate, since it has no effect on gastric pH.

In one embodiment, the present invention is directed to formulations of drugs that are carboxylic acids, as described herein, and are suited to the controlled release of high dose drugs that are highly water soluble. In addition, in certain embodiments, the formulations described herein provide controlled release of drugs that are highly hygroscopic, even where such drugs must be administered at relatively high doses. In particular embodiments, the controlled release formulations are provided as a unit dose or liquid dosage form.

The formulations and dosage forms of the present invention can also include an immediate release component. The immediate release component can form part of a solid controlled release unit dosage form or liquid dosage form (e.g., combined with a controlled release GHB resinate component) or may be a separate immediate release composition. Therefore, an immediate release component may be provided, for example, as a dry powder formulation, an immediate release tablet, an encapsulated formulation, or a liquid solution or suspension. However, the immediate release component may also be formulated as part of a single dosage form that integrates both the above components. The immediate release component can furthermore be an oxybate salt such as sodium, potassium, calcium, or magnesium, the immediate release component can also comprise the GHB resinate particles without modification to retard release, or a combination of these GHB forms.

In specific embodiments, controlled release and immediate release formulations can be dosed together to a subject to provide quick onset of action, followed by maintenance of therapeutic levels of the drug substance over a sustained period of time. However, because the controlled release component and immediate release component described

herein need not be present in a single dosage form, as it is used herein, the phrase "dosed together" refers to substantially simultaneous dosing of the controlled release and immediate release components, but not necessarily administration in the same dosage form. Dosing the controlled release and immediate release components together offers increased convenience, allowing patients to quickly achieve and maintain therapeutic levels of a drug over a sustained period of time, while reducing the frequency with which the drug must be dosed. Furthermore, dosing the controlled release and immediate release components together may avoid the disadvantages of dosing regimens and formulations that result in highly pulsatile plasma concentrations.

Gamma butyrolactone (GBL) is a prodrug for GHB. It can be produced by the dehydrogenation of 1, 4 butanediol. GBL can be hydrolyzed under basic conditions (the use of a metal ion hydroxide) to produce GHB. See Arena, C, et al., "Absorption of Sodium γ-Hydroxybutyrate and its Prodrug γ-butyrolactone: relationship between n vitro transport and in vivo absorption", Journal of Pharmaceutical Sciences, 69(3), (March 1980), 356-358; and Lettieri, J, et al., "Improved Pharmacological Activity via Pro-Drug Modification: Comparative Pharmacokinetics of Sodium Y-Hydroxybutyrate and Y-Butyrolactone", Research Communications in Chemical Pathology and Pharmacology, 22(1), (1978), 107-118.

The required dose of GHB, on a molar basis, is unusually high and quite different from most pharmaceutical agents normally considered for drug-resin complexes. A 9 g dose of sodium oxybate is 71 mMol of oxybate, a carboxylic acid. This stands in contrast to a typical moderately potent active pharmaceutical ingredient (API) having a molecular weight of about 400 daltons and a dose of 400 mg, which results in a molar dose of about 1 mMol. Thus, sodium oxybate dosing is about 70-fold higher (on a molar basis) than a more typical drug.

Much of the dose is required in immediate release form for initial therapeutic benefit. However, due to the buffering effect of oxybate (pKa of 4.5), the immediate-release portion of the dose would cause the gastric pH to increase to about 6. This complicates formulation design, as rate-controlling polymers often have pH-dependent dependent solubility. In particular, if delayed release via enteric coating is desired, then upon release of the immediate release portion of the dose, the concomitant rise in gastric pH could result in at least partial dissolution of the enteric coating, thereby compromising the delayed release function of the enteric coating.

The solubility of sodium oxybate is unusually high. For example, a Xyrem solution is provided as 500 mg/mL concentration in water, or 42 wt %, and its solubility limit is considerably higher. Furthermore, due to the small size and ionic nature of GHB at physiological pH, the drug is unusually mobile in solution. Those skilled in the art will appreciate that these factors complicate and, in many cases, limit conventional approaches for modified release, such as core/shell or matrix formulations, as the high solubility and mobility of GHB would tend to significantly reduce the number of viable approaches using such conventional solubility and diffusivity control technologies.

Furthermore, while extended release oxybate dosage forms are known, such extended release dosage forms are provided as solids, e.g. as tablets. Because the required dose of oxybate is high, such tablets can be quite large, and/or require the administration of multiple tablets. This can be problematic because some patient populations have difficulty swallowing solid dosage forms, or the need to swallow multiple tablets may reduce patient compliance. In addition, the sustained release matrix or coating compositions used to provide extended release are complex and expensive to produce. Accordingly, it would be desirable to provide oxybate (or analogous drugs which require administration in high doses) in an extended release, oral liquid dosage form (including suspensions of oxybate-containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user), using simply, readily controlled processing methods.

A drug-resin complex may address some of these limitations, as the drug is essentially insoluble as long as it remains bound to the resin. Instead, the drug release is regulated by exchange with other anions present in the gut, the most prevalent being chloride. Thus, the nature of the formulation challenge is to limit the diffusion of chloride anion into the dosage form rather than to limit the egress of the soluble drug, oxybate.

Drug-resin complexes including modified release drug-resin complexes are known. However, such complexes would typically be considered unsuitable for very high dose, low molecular weight drugs such as oxybate, because the molar amount of drug required is quite high, which would therefore necessitate correspondingly large amounts of ion exchange resin, particularly if the efficiency of binding is significantly less than 100%. Accordingly, for drugs such as oxybate that are dosed at much higher molar levels, e.g., approximately 100-fold higher compared to typical drug dosing, drug-resin complexes would not be considered acceptable.

In one embodiment, a particularly convenient means of administering drug resinates is as a suspension of individual drug resinate beads. The beads may be a plurality of individual resin beads, each loaded with drug and optionally coated with a rate-controlling polymer and additives to influence its properties (such as permeability, flexibility, etc.). Coating formulations exist to address processing challenges, such as the swelling of beads and retention of film integrity. One such example is methylphenidate resinate beads as shown in U.S. Patent No. U.S. Pat. No. 8,202,537.

In one embodiment, the present invention provides a GHB formulation which delivers a controlled release profile, for example a controlled release profile suitable for once-a-day dosing as described herein. Due to the prolongation of the drug release, compositions of the present invention are useful because the once-a-day dose provides a more consistent supply (release) of GHB to patients who otherwise may have to take multiple doses a day. In one embodiment, the invention provides a multi-particulate composition, for example a suspension (e.g., homogeneous suspension), or solid compositions such as a tablet, capsule, powder, wafer, or strip system comprised of a plurality of such particles and optionally other excipients.

As used herein, the term "controlled release" refers to compositions, for example GHB resinate compositions as described herein, which are characterized by having at least one of the active components having a release over a period of at least about 2 to about 8 hours, or about 4 to 6 hours, including about 2, about 2.5, about 3, about 3.5, about 4, about 4.5, about 5, about 5.5, about 6, about 6.5, about 7, about 7.5, or about 8 hours, inclusive of all ranges therebetween. The release profile may be assessed using in vitro dissolution assays known to those of skill in the art, e.g., USP apparatus 2 (paddle) or, more preferably, apparatus 4 (flow-through cell). Particularly when the molar dose of oxybate is large and approaches the amount of anion in the

dissolution media, a flow-through apparatus is desired so that the media composition and flow rate can better approximate the physiologic state. The release profile can be assessed for example (e.g., for bioavailability determinations), in pharmacokinetic studies using plasma concentrations to assess maximum concentration (C_{max}) and area under the curve (AUC). Such assays are well known to those of skill in the art.

In one embodiment, the present invention provides a drug-ion exchange resin composition for further use in a formulation with conventional pharmaceutically acceptable components to provide ingestible compositions. The finished dose compositions may take the form of liquid preparations, such as suspensions, or solid preparations such as tablets, capsules, liquigels, powders, wafers, strips, etc.

Ion-exchange matrices suitable for use in these preparations are water-insoluble and comprise in most embodiments a pharmacologically inert organic and/or inorganic matrix containing functional groups that are ionic or capable of being ionized under the appropriate conditions of pH. In one embodiment, the ion-exchange matrix is anionic. The organic matrix may be synthetic (e.g., polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene, etc.), or partially synthetic (e.g. modified cellulose and dextrans). The inorganic matrix, in various embodiments, can comprise silica gel modified by the addition of ionic groups, or other similar inorganic materials functionalized with ionic groups. Covalently bound ionic groups may be strongly acidic (e.g., sulfonic acid, phosphoric acid), weakly acidic (e.g., carboxylic acid), strongly basic (e.g., primary amine), weakly basic (e.g. quaternary ammonium), or a combination of acidic and basic groups. In general, the types of ion exchangers suitable for use in ion-exchange chromatography and for such applications as deionization of water are examples of materials suitable for use in the controlled release of drug preparations. Such ion-exchangers are described by H. F. Walton in "Principles of Ion Exchange" (pp: 312-343) and "Techniques and Applications of Ion-Exchange Chromatography" (pp: 344-361) in Chromatography. (E. Heftmann, editor), van Nostrand Reinhold Company, New York (1975). A high exchange capacity is desired to limit quantities of resin needed, and that typical values are about 4 mEQ/g

In one embodiment, the size of the ion-exchange particles is from about 5 microns to about 1,000 microns. In most embodiments the particle size is within the range of about 50 microns to about 750 microns (including about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 550, about 600, about 650, about 700, or about 740 microns, inclusive of all values and ranges therebetween) for liquid dosage forms, although particles up to about 1,000 micron (including the values and ranges herein, and in addition about 800, about 850, about 900, about 950, or about 1000 microns, inclusive of all values and ranges described herein) can be used for solid dosage forms, e.g., tablets and capsules. Particle sizes substantially below the lower limit are generally difficult to handle in all steps of the processing. Both uncoated and coated drug-ion exchange resin particles may be designed within this size range.

Both regularly and irregularly shaped particles may be used as resins. Regularly shaped particles are those particles that substantially conform to geometric shapes such as spherical, elliptical, cylindrical and the like, (e.g., three dimensional shapes readily described by a three dimensional space group) which are exemplified by (but not limited to) any of the ion exchange resins disclosed herein, for example Dow XYS-40010.00 and Dow XYS-40013.00 (The Dow Chemical Company). Irregularly shaped particles are all particles not considered to be regularly geometrically shaped (for example not readily described by a three dimensional space group), such as particles with amorphous shapes and particles with increased surface areas due to surface channels or distortions. Irregularly shaped ion-exchange resins of this type are exemplified by (but not limited to) any of the ion exchange resins disclosed herein, for example Amberlite IRP-69 (Rohm and Haas). Two of the resins of some of the embodiments of this invention are Amberlite IRP-69 and Dow XYS-40010.00. Both are sulfonated polymers composed of polystyrene cross-linked with about 8% of divinylbenzene, with an ion-exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H^+-form). Their essential difference is in physical form. Amberlite IRP-69 consists of irregularly shaped particles with a size range of about 5 microns to about 149 microns produced by milling the parent large size spheres of Amberlite IRP-120. The Dow XYS-40010.00 product consists of spherical particles with a size range of 45 microns to 150 microns.

In one embodiment, suitable ion-exchange resins include anion exchange resins, such as have been described in the art and are commercially available. These resins are particularly well suited for use with acidic drugs including GHB, as well as prodrugs such as GBL, salts, isomers, polymorphs, and solvates thereof, as well as other acidic drugs identified herein and/or known in the art such as salicylates, nicotinic acid, mefenamic acid, methotrexate, furosemide, phenolic drugs such as paracetamol, morphine, and levothyroxine, warfarin, phenylbutazone, indomethacin, barbiturates, phenytoin, sulphonamides, etc.

Any anion exchange suitable for pharmaceutical use can be employed in the compositions of the present invention, particularly strong anion exchange resins. An example of a suitable anion exchange resin is a cholestyramine resin, a strong base type 1 anion exchange resin powder with a polystyrene matrix and quaternary ammonium functional groups. The exchangeable anion is generally chloride which can be exchanged for, or replaced by, virtually any anionic species. Other examples include Type II resins, which contain dialkyl 2-hydroxyethyl ammonium chloride or hydroxide groups. Such Type I and Type II resins are available under the DOWEX® and Amberlite® trade names. A commercially available Cholestyramine resin is PUROLITE' A430MR resin. As described by its manufacturer, this resin has an average particle size range of less than 150 microns, a pH in the range of 4-6, and an exchange capacity of 1.8-2.2 eq/dry gm. Another pharmaceutical grade cholestyramine resin is available as DUOLITE' AP143/1094 (Rohm and Haas/Dow), described by the manufacturer as having a particle size in the range of 95%, less than 100 microns and 40%, less than 50 microns. The commercial literature from the suppliers of these and other resin is incorporated herein by reference (PUROLITE A-430 MR; DOW Cholestryramine USP, Form No. 177-01877-204, Dow Chemical Company; DUOLITE AP143/1083, Rohm and Haas Company, IE-566EDS—February 06). Other suitable anion exchange resins include POROS® XQ anion exchange resins available from ThermoFisher Scientific. Both regularly and irregularly shaped particles may be used as resins. Regularly shaped particles are those particles that substantially conform to geometric shapes such as spherical, elliptical, cylindrical and the like, (e.g., three dimensional shapes readily described by a three dimensional space group) Irregularly shaped particles are all particles not considered to be regularly geometrically shaped (for

example not readily described by a three dimensional space group), such as particles with amorphous shapes and particles with increased surface areas due to surface channels or distortions. The regular and irregularly shaped particles can comprise any of the anion exchange resins disclosed herein.

For the oxybate resinate compositions of the present invention, the amount of oxybate present in the resinate should be high to minimize the amount of resin required. Furthermore, in most embodiments, the amount of GHB resinate administered, expressed as GHB mEq (i.e., mmoles) is about 20 to about 120 mEq, including about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, or about 120 mEq, inclusive of all values and ranges therebetween.

The selected ion-exchange resins may be further treated by the manufacturer or the user to maximize the safety for pharmaceutical use or for improved performance of the compositions. Impurities present in the ion-exchange resins may be removed or neutralized by the use of common chelating agents, anti-oxidants, preservatives such as disodium edetate, sodium bisulfate, and so on by incorporating them at any stage of preparation either before complexation or during complexation or thereafter. These impurities along with their chelating agent to which they have bound may be removed before further treatment of the ion exchange resin with a compound to slow drug release and coating with a diffusion barrier.

Various analogous binding reactions can be carried out for binding an acidic drug to an anion exchange resin. These are (a) resin (Cl^- form) plus drug (salt form); (b) resin (Cl^- form) plus drug (as free acid); (c) resin (OH^- form) plus drug (salt form); (d) resin (OH^- form) plus drug (as free acid); (e) resin (OH^- form) plus prodrug (γ-butyrolactone). All of these reactions except (d) and (e) have ionic by-products and the anions generated when the reactions occur compete with the anionic drug for binding sites on the resin with the result that reduced levels of drug are bound at equilibrium. For acidic drugs, stoichiometric binding of drug to resin is accomplished only through reactions (d) and (e). The binding may be performed, for example as a batch or column process, as is known in the art.

Typically the drug-ion exchange resin complex thus formed is collected by filtration and washed with appropriate solvents to remove any unbound drug or by-products. The complexes can be air-dried in trays, in a fluid bed dryer, or other suitable dryer, at room temperature or at elevated temperatures which would not degrade the complex.

In one embodiment, the complexes of the present invention can be prepared by batch equilibration, in which a solution of the drug is contacted with finely divided ion-exchange resin powders. While ion exchange resins are typically provided in very fine particle sizes, which render conventional columnar ion-exchange processes inefficient, such methods can be used for ion exchange resins of suitable particle size. The total ion-exchange capacity represents the maximum achievable capacity for exchanging cations or anions measured under ideal laboratory conditions. The actual capacity which will be realized when loading a drug onto ion exchange resin will be influenced by such factors as the inherent selectivity of the ion exchange resin for the drug, the drug's concentration in the loading solution and the concentration of competing ions also present in the loading solution. The rate of loading will be affected by the activity of the drug and its molecular dimensions as well as the extent to which the polymer phase is swollen during loading.

In one embodiment, a batch or equilibrium process is used to load a drug onto an ion-exchange resin. It is usually desirable to load as much as possible of the drug, such as GHB or GBL, onto the ion exchange resin, as typical GHB doses required for treating excessive daytime sleepiness and cataplexy in patients with narcolepsy are quite high. Low loadings of GHB in the resinate would require quite large amounts of resin, resulting in unit dosages which would be too large to be conveniently administered and resin quantities that may give rise to more adverse effects such as gastrointestinal disturbance. Complete transfer of the drug from the loading solution into the ion-exchange resin is not likely in a single equilibrium stage. Accordingly, more than one equilibration may be required in order to achieve the desired loading onto the ion exchange resin. The use of two or more loading stages, separating the resin from the drug-containing liquid phase between stages, is a means of achieving maximum loading of the drug onto the ion exchange resin, although some loss of drug from the liquid phase of the final loading stage may occur.

The efficiency of loading the drug (e.g. GHB) onto the ion exchange resin can be influenced by the counter ion used in the ion exchange resin. Commercially supplied anionic resins for pharmaceutical use are almost exclusively in the chloride form. However, chloride ions have a much higher affinity for the exchange site in the resin relative to GHB. The affinity can be estimated based on the pK_a of GHB (4.44) relative to other short-chain fatty acids for which affinities are known. On that basis, GHB has approximately 18% affinity relative to chloride on the anion exchange resin. Bicarbonate, on the other hand, has an affinity of about 27% affinity relative to chloride. Therefore, when a bicarbonate-exchanged resin is contacted with GHB, a much higher efficiency of GHB incorporation may be achieved, because the affinity of GHB relative to bicarbonate is about 67% vs. about 18% relative to chloride. Other "intermediate" exchange anions can also be used, especially those with low affinity relative to chloride and much lower cost relative to oxybate. Thus in some embodiments, substantially all of the chloride counter ion of the e.g. commercially available pharmaceutical grade anion exchange resin is replaced with the intermediate anion (e.g. bicarbonate), in one or more batch equilibration steps as required. After rinsing with an appropriate solvent, the ion exchange resin exchanged with the lower affinity anion (relative to chloride) can then be then exchanged with oxybate.

Substantially complete incorporation (i.e., expressed as the percentage of theoretically available ion exchange sites) of oxybate in the anion exchange resin is desirable to minimize the amount of anion exchange resin required to provide a specified dose of drug (e.g. oxybate). In practice, 100% incorporation of the drug can be difficult and/or expensive to achieve, so somewhat less than substantially complete levels of incorporation of drug are also suitable. Typically, levels of incorporation of more than about 75% are acceptable, including about 75%, about 80%, about 85%, about 90%, about 92%, about 94%, about 96%, about 98%, about 99%, or about 100%, inclusive of all values and ranges therebetween.

When a multi-step batch equilibration is needed or desirable, the resinate slurry formed during equilibration can be decanted to remove the solution of oxybate. The decant can be collected for potential recovery of oxybate or waste disposal. The resinate is then rinsed with solvent, such as de-ionized water, and then charged to the batch equilibration tank where it is contacted with fresh or recovered oxybate to increase the level of incorporation of oxybate. Multiple

equilibration steps can be used with fresh or recycled oxybate solution until the desired level of incorporation, as described herein, is achieved.

Recovery of oxybate from a chloride-exchange process can be very challenging due to oxybate's high water solubility and relatively small size. If aqueous processing is used, all chloride salts are soluble. However, when an intermediate anion (e.g. bicarbonate) is used, the solubility can be manipulated with selection of the cationic form of oxybate. If full and complete exchange of oxybate is desired in one step, then the salt form of oxybate is selected such that the salt form of the exchanged anion is insoluble. For example, calcium salts of many exchangeable anions tend to have very low solubilities. Oxybate can be introduced as calcium oxybate, which is highly water-soluble and suitable for an aqueous exchange process. Precipitation drives the exchange process to near-completion, resulting in very high oxybate yield and incorporation. For example, bicarbonate would precipitate as calcium carbonate if the relatively insoluble calcium hydroxide is added in stoichiometric amount at the commencement of batch equilibration, as shown below. Other example intermediate examples include phosphate (precipitating as calcium phosphate), sulfate (precipitating as calcium sulfate), and hydroxide (precipitating as calcium hydroxide).

$$Ca^{++}(GHB^{-})_2+2R\text{—}HCO_3\rightarrow Ca^{++}+2HCO_3^{-}+2R\text{-GHB; R=resin}$$

$$Ca^{++}+2HCO_3^{-}+Ca(OH)_2\rightarrow CaCO_3(s)+H_2O$$

Use of precipitation as a means to drive batch equilibration can result in some difficulties in recovering the resin, as the resinate and precipitate can both be small particles. In some embodiments, the exchange process is carried out under conditions such that all species remain soluble, and therefore the resinate and solution are easily separated. Next, the oxybate is recovered from the solution in a separate vessel by performing a displacement precipitation by addition of another salt or base. For instance, in the above example, the calcium hydroxide can be added in a separate step, thereby avoiding a difficult separation problem. Although this process may provide a somewhat less efficient equilibration per batch cycle, recovery of the un-exchanged oxybate can be nearly 100%, and multiple batch equilibrations can be performed economically. The technique can be more generally applied if sodium oxybate is used in the exchange process, because most sodium salts of the exchanged anion would remain soluble. In the recovery step, a calcium salt or base is added in near-stoichiometric amount to precipitate the exchanged oxybate and enable full recovery of the sodium oxybate. In one embodiment, calcium hydroxide is added to facilitate recovery. Because it has low solubility, calcium hydroxide can be used in excess without appreciably contaminating the recovered sodium oxybate with calcium.

$$Na^{+}GHB^{-}+R\text{—}HCO_3\rightarrow Na^{+}+HCO_3^{-}+R\text{-GHB; R=resin}$$

$$2Na^{+}HCO_3^{-}+Ca(OH)_2\rightarrow CaCO_3(s)+2H_2O$$

In yet another embodiment of processes for forming the GHB resinate, the anion can be recovered by sub-stoichiometric addition of the soluble calcium oxybate to the sodium-exchanged intermediate anion in the recovery process. Most of the sodium oxybate can be recovered and recycled without causing precipitation during the batch equilibration.

In a particular embodiment, bicarbonate can be evolved as CO_2 gas and the sodium ions form sodium oxybate by adding GBL. This avoids a potentially difficult separation of precipitate during recovery. The sodium bicarbonate is first converted to sodium carbonate, and then the sodium carbonate is reacted with GBL to yield sodium oxybate and carbon dioxide as shown below.

$$NaOH+NaHCO_3\rightarrow Na_2CO_3+H_2O$$

$$2GBL+Na_2CO_3+H_2O\rightarrow 2Na\text{-GHB}+CO_2(g)$$

In yet another embodiment, the bicarbonate form of an anion exchange resin (e.g., and type 1 strong base anion exchange resin), prepared, for example by ion exchange of the chloride form with sodium or potassium bicarbonate (or other soluble bicarbonate salts), is equilibrated with a solution of sodium or potassium oxybate. The resulting oxybate resinate can be separated from the oxybate equilibration solution by known methods (decanting, filtering, etc.). The oxybate equilibration solution can then be treated with sodium or potassium hydroxide to increase the pH, and then contacted with GBL. At the elevated pH, the GBL reacts with exchanged bicarbonate to form additional GHB (oxybate) and carbon dioxide, thereby regenerating the oxybate equilibration solution so that it can be reused, as the bicarbonate ions produced during the initial ion exchange/equilibration step is lost as carbon dioxide gas. The regenerated oxybate equilibration solution can then be re-equilibrated with the oxybate resinate formed in the initial equilibration step, so as to further increase the degree of exchange of oxybate in the resinate. The regenerated equilibration solution can be further regenerated, and further equilibrated with the oxybate resinate as many times as is needed or desired to obtain the desired degree of incorporation of oxybate in the oxybate resinate. A further advantage of this method is the minimization of oxybate waste due to the ability to regenerate and recycle the oxybate equilibration solution.

High loading capacity will be favored by high charge density in the drug. A high loading rate is favored by lower molecular weight. Higher drug concentrations in the loading solution, with a minimum of competing ions, will also favor higher adsorption capacity.

Thus, in one aspect, the invention provides drug-ion exchange resin complexes comprising a drug loaded in an ion exchange resin as described herein. The drugs and ion exchange resins may be readily selected from amongst those drugs and resins described herein. In most embodiments, GHB and GBL are suitable drugs. The invention further provides drug-ion exchange resin matrixes defined as follows.

The drug-ion exchange resin complexes of the present invention can readily be formulated with pharmaceutically acceptable excipients according to methods well known to those of skill in the art, for example as described in Remington, The Science and Practice of Pharmacy, 22 Edition Philadelphia College of Pharmacy 2013 Pharmaceutical Press, herein incorporated by reference in its entirety for all purposes. In one embodiment, these formulations contain a substantially coated drug-ion exchange resin complex of the invention, optionally with a compound that will slow the release of the drug. In another embodiment, such formulations may also contain a selected amount of uncoated drug-ion exchange resin complex, optionally with a compound to slow the release as described herein. In certain formulations, mixtures of coated drug-ion exchange resin complexes and uncoated drug-ion exchange resin complexes

are present. These formulations may contain any suitable ratio of coated to uncoated product.

In one embodiment, the controlled release dosage form includes drug loaded onto beads (e.g., ion-exchange beads) in combination with one or more optional excipients, such as binders, fillers, diluents, disintegrants, colorants, buffering agents, coatings, surfactants, wetting agents, lubricants, glidants, or other suitable excipients. In one embodiment of the compositions of the present invention that can be fashioned into a tablet or other solid form, beads containing GHB or GBL can include one or more binders that are known for use in tablet formulations. In one such embodiment, the solid form may include at least one binder selected from hydroxypropyl cellulose (HPC), ethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers (crosslinked polyacrylates), polymethacrylates, carboxymethylcellulose sodium, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate. In specific embodiments, the solid form included in a controlled release dosage form as disclosed herein may comprise binder levels ranging from approximately 1% to 10% by weight. For example, the CR core may include a binder in an amount selected from about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, and 10% by weight, including all ranges therebetween. In certain such embodiments, the amount of binder included in the CR core may range from about 1 to 2%, 1 to 3%, 1 to 4%, 1 to 5%, 1 to 6%, 1 to 7%, 1 to 8%, 1 to 9% and 1 to 10% by weight.

One formulation of the present invention may include one or more lubricants to improve desired processing characteristics. One embodiment of the present invention may include one or more lubricants selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added in a range of about 0.5% to 5% by weight. Particular embodiments may comprise a lubricant in a range of about 0.5% to 2% by weight, about 1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight, inclusive of all ranges therebetween. Still lower lubricant levels may be achieved with use of a "puffer" system during tabletting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation. When "puffer" systems are used for tabletting, the compositions of the present invention can, but need not be, substantially free of lubricant (e.g., include only traces of lubricant deposited by contact with the lubricant coated tablet press).

In certain embodiments, where the compositions of the present invention are provided as liquid compositions, such as suspensions, the compositions of the present invention can further comprise colorants, flavoring agents (natural and artificial), stabilizing agents (EDTA salts, parabens, benzoates), thickeners (tragacanth, xanthan gum, bentonite, starch, acacia, cellulosics), humectants, sweeteners (sucralose, acesulfame K, saccharides, sorbitol, xylitol, mannitol, maltose), etc.

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 titrate, 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 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.

The drug-ion exchange resin composition thus prepared may be stored for future use or promptly formulated with conventional pharmaceutically acceptable carriers to prepare finished ingestible compositions for delivery orally, or via other means. In one embodiment, a tablet of the invention is formulated as an orally disintegrating tablet. Such orally dissolving tablets may disintegrate in the mouth in less than about 60 seconds. See U.S. Patent Publication. 2012/0076865.

In one embodiment, the oral liquid compositions of the present invention may also comprise one or more surfactants in amounts of up to about 5.0% w/v or from about 0.02 to about 3.0% w/v of the total formulation. The surfactants useful in the preparation of the finished compositions of the present invention are generally organic materials which aid in the stabilization and dispersion of the ingredients in aqueous systems for a suitable homogenous composition. In particular embodiments, suitable surfactants are non-ionic surfactants such as poloxamers, polyoxyethylene ethers (BRIJ), alkoxylated fatty acids (MYRJ), polysorbates (TWEENs), macrogol mixtures (Gelucire, Labrasol), and sorbitan esters (SPANs). These are produced in a wide variety of structures and molecular weights.

When present, the surfactant component may comprise from about 0.01 to about 2.0% w/v of the total composition (for example 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2.0% w/v, inclusive of all ranges therebetween) and in particular embodiments will comprise about 0.1% w/v of the total of the composition.

One or more additional emulsifiers or surfactants can also be employed in one embodiment of the invention.

The sustained-release profiles of drug can be obtained by using a mix of uncoated and semipermeable coated resinates and by selecting the degree of cross-linking and particle size of the resins without a coating process. Examples of ion exchange resins include simple resinates (i.e., uncoated drug-ion exchange resin complexes), microencapsulated or coated resinates (i.e., coated drug-ion exchange resin complexes), hollow fiber systems (i.e. hollow fibers with drug containing lumen), sigmoidal-release systems. Examples of such drugs are frusemide, cyclosporin, allopurinol and ciprofloxacin. See Mahore et al. Formulation of such drugs as resinates according to the present invention permits particle sizes that make such release characteristics (e.g., sigmoidal) feasible at reasonable coating weights.

Some embodiments of the present invention involve direct synthesis of oxybate resinate from one or more precursors. Using a hydroxide-form Type 1 strong base anion exchange resin, essentially 100% loading efficiency can be achieved with a simple aqueous reaction with GBL.

The ability to prepare an oxybate resinate, at high loading, in a one step process from GBL can be amenable to point-of-use synthesis (either in patient's hands or at clinical site), as it does not involve shipping or handling the regulated API (GHB). Such a direct synthesis can be carried out using a batch or equilibrium process as described herein, wherein a GBL loading solution is contacted with the particulate hydroxide-form strong base anion exchange resin. The GBL reacts in situ to form an ionic complex of oxybate with the ion-exchange resin, and releasing water as a by-product. It is possible to get 100% yield as well as 100% loading efficiency (i.e., oxybate ionically bound to 100% of the available binding sites) on the resin by such processes. For example, loading efficiencies higher than about 65% (e.g., 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, or about 100%, including ranges therebetween, can be achieved). Because GBL is uncharged and the reaction does not produce ionic byproducts, there are no anions to compete for reaction on the site. Such conditions can achieve 100% reaction on the resin, so the hydroxide-form resin can be used safely, whereas in other applications this may not be possible for patient safety reasons because any unexchanged hydroxide would leave the resin as sodium hydroxide, raising the pH at site of delivery and potentially causing gut wall irritation.

The one-step process is also advantageous because it simplifies purification of the GHB resinate. Because the reaction occurs on the resin and not in the bulk solution, any byproducts that would be made are rinsed off the product. These include any of the impurities in the GBL starting material, as well as unreacted GBL.

Because of the unusually large molar amount of GHB in the compositions of the present invention, relative to the molar quantity of anion present in the gut, the present inventors have found that the compositions of the present invention can provide sustained release without the use of diffusion controlling coatings on the resinate particles. The present inventors have recognized that because the volume and anion content of gastric juice in the fasted state is lower than the molar dose of GHB required for treating the conditions described herein, the rate of GHB release is strongly influenced by the rate of physiological production of anions, and therefore suitable GHB release profiles can be provided without the use of diffusion controlling coatings. For example, while the resinate beads are retained in the stomach, the release of GHB from the resinate beads provided by ion exchange with gastric ions (mainly Cl^-) can be limited by the rate of stomach acid secretion. Similarly, as the resinate beads transit the duodenum and small intestine, the remaining dose of bound GHB can exceed local anion capacity. Thus, the rate of GHB release can be limited by the rate of secretion or diffusion of anions into the gut.

The basal anion capacity of the GI tract is quite small. As summarized in McConnell (Int J Pharm 2008, 364: 213-226, Table 1), fasted state basal values of bile salts are so low that they may be ignored. The fasted state chloride balances are 4.6 mEq in the stomach and 13.1 mEq in the small intestine. Compared to an oxybate dose of about 100 mEq, there is almost an order of magnitude deficiency in resident anion capacity for exchange. Such a situation would not occur with the vast majority of drugs having doses in the <1 mMol range.

	Stomach	Small intestine
Volume, mL	45	105
Chloride, mM	102	125
Total mEq	4.6	13.1

Therefore, the present inventors have discovered that the release of the ion-exchange resin-bound oxybate can be limited by secretions of anions in the GI tract, of which chloride is dominant. In the stomach, basal acid output (as chloride) is about 3 mEq/h in the fasted state. Even in the event that fed-state behavior is induced upon dosing, the fed state maximum secretion is only about 25 mEq/h. Therefore, the stomach cannot support full exchange at rates required to impart a meaningful duration of effect.

Chloride is actively secreted in jejunum, at a rate of about 4 mEq/h/30 cm under conditions where 120 mM chloride is already present. (Davis G R, et al, Active chloride secretion in the normal human jejunum, J Clin Invest 66:1326-1333 (1980)) This translates to a basal rate of about 32 mEq/h in absence of a chloride gradient. In presence of a gradient, the present inventors have found that the contribution of passive diffusion can be sufficient, but may still provide a meaningful impediment to full and timely release of oxybate from the resin.

In the ileum, chloride secretions are substantially less, as characterized by Turnberg. (Turnberg L A et al, Interrelationships of chloride, bicarbonate, sodium, and hydrogen transport in human ileum, J. Clin Invest, 49: 557-567 (1970)). Most chloride secretion is associated with bicarbonate exchange when levels are high. One skilled in the art would appreciate that the perfusion studies by Turnberg indicate that chloride secretion in the ileum would almost certainly be insufficient to support the required exchange with GHB-resinate. For example, even in the extreme case where bicarbonate is almost 90 mM and chloride is only 40 mM, the chloride secretion—taking into account the whole length of ileum—would be expected to be at most 23 mEq/h. In the more typical case where bicarbonate is 40 mM, chloride is actually absorbed rather than secreted—even when chloride levels are set at 40 mM. Yet ileal fluid is maintained isotonic.

To further add to the limitations of biology, the reservoir of small intestinal fluid is small and not well distributed. Only about 10% of the physical volume of the small intestine is filled with fluid. The fluid is not continuously and evenly distributed, as reported by Schiller (Schiller C, et al, Intestinal fluid volumes and transit of dosage forms as

assessed by magnetic resonance imaging, Aliment Pharmacol Ther 2005; 22:971-979) but rather the majority of fluid exists in about 4 fluid pockets that access a relatively small amount of available surface area. This is not very limiting for non-resinate dosage forms, as long as drug dissolution can occur, as once the drug is dissolved, it can access most of the surface area of the small intestine for absorption. A resinate, on the other hand, requires exchange with dissolved anions in order to provide release of the drug. As exchange occurs, oxybate is released to, and chloride is depleted from, the surrounding fluid. Further exchange is limited until oxybate is absorbed and chloride is replenished in the surrounding fluid—both processes that require fluid contact with intestinal surface. Therefore, if only 10% of the intestinal surface is physically available at any given time, the rate of chloride replenishment must be 10-fold higher to reliably compensate. One skilled in the art considering these unusual aspects would conclude that, in the face of insufficient resident anion capacity in the small intestine, a resinate dosage form would not release its drug completely and, furthermore, what release occurs may not be well-regulated.

Given the above observations, permeability and amount of film may require adjustment to achieve the intended release profile.

Optionally, the release of GHB can be tailored by changing the bead size and/or degree of crosslinking of the beads to provide additional resistance to diffusion. For example, larger resinate beads have a lower surface area/volume ratio than smaller resinate beads, and therefore would release GHB more slowly than the smaller beads in the presence of a solution of the same ionic strength. Similarly, the degree of crosslinking of the beads relates to the degree of swelling of the beads, which in turn is related to the rate at which ion exchange, and this drug release can occur. Specifically, more highly crosslinked beads swell less, and thus have slower ion exchange kinetics, compared to less highly crosslinked beads, Thus, the kinetics of drug release can also be controlled by manipulating the degree of crosslinking of the beads. Effects of particle size, particularly 100 microns or greater, and crosslinking, particularly 4% or greater, that may be modest under normal circumstances may be more impactful in the absence of a rate-controlling coating and when gut anion concentrations are substantially diminished.

If no diffusion controlling coating is required, other processing schemes for making the resinate can be considered to improve manufacturing flexibility. For example, instead of using ~100 micron beads, the drug (e.g., GHB or GBL) can be loaded onto larger beads (e.g., 600 micron beads), and then ground to the desired particle size, particle size distribution, consistency, etc. to select or control the desired release characteristics. This could be carried out in an aqueous suspension, so that no isolation or drying of the resinate would be needed. Moreover, if there is no need to coat the particles (e.g., with a diffusion for coating), the irregular shape or dispersity in size distribution of ground particles, which is normally a complicating factor for coating processes, is not an issue.

In other embodiments, the compositions of the present invention can provide differential displacement of drug (e.g. oxybate) from the resinate. Core/shell release characteristics in the resinate beads can be provided by (a) loading oxybate onto an ion exchange resin such that complete loading is achieved, then (b) coating the beads with a portion of lipophilic agent (i.e. lipophilic anion) having much higher selectivity for the ion-exchange resin than GHB. The lipophilic agent will deposit in the outer shell, at the first sites it contacts, and will be relatively immobile resulting in reversible blockage of the bead pores. Suitable lipophilic agents would be, for example, sulfate salts of medium or long-chain fatty acids, such as sodium lauryl sulfate (SLS), or sulfonic esters, such as dioctyl sulfosuccinate (docusate). Other suitable agents may include alkylbenzene sulfonates, 2-naphthalene sulfonate, phenol, salicylic acid, or any other species that may bind more strongly to the resin than oxybate. In particular embodiments, the lipophilic agents are those which are bulky or present hydrophobic tails that may further hinder diffusion of chloride into the resin pore, or oxybate out of the pore after exchange. Although many effective agents may, in other contexts present toxicity concerns, because such agents are strongly bound to the resin, exposure of the agent to the patient is limited. In one embodiment, the lipophilic agent acts as a diffusion barrier both by blocking pores and by facilitating pore blockage by other hydrophobic agents, for example those added during manufacturing, or which may be present in the patient's digestive tract after administration. For example, if sufficient amounts of a surfactant such as SLS is employed, then a non-ionic hydrophobic agent may be more effectively introduced into the bead pore volume due to its compatibility with the hydrophobic "tail" of the SLS molecule. This provides retarded initial release of the drug (e.g., GHB). In other embodiments, further heat treating of the resinate beads can reduce the variability of release, or further retard release. In other embodiments the compositions of the present invention can comprise more than one population of beads, in which one or more of the bead populations is treated with a lipophilic agent, a combination of a lipophilic agent and a hydrophobic agent, or heat treated to as to provide the desired release characteristics. For example, untreated beads would provide more immediate or faster release, and treated beads would provide delayed or slower release.

If further control of release is needed, in a further embodiment the present invention provides a novel method for preparing GHB-containing resinate beads coated with a diffusion rate controlling coating. This embodiment takes advantage of the driving force supplied by reaction of GBL on the active (hydroxide-bearing) sites of hydroxide-form ion exchange resin beads, and the relatively high diffusion characteristics of the small and uncharged GBL molecule. Hydroxide-form ion-exchange resin beads (of any size) can be coated with a flexible film, such as PVAcetate, Eudragit RS, cellulose acetate 398, a mixture of Eudragit RS/RL or Eudragit NE, ethylcellulose, or an enteric such as Eudragit L100, L55 or FS100 with suitable plasticizer. The coated ion-exchange resin beads are then suspended in de-ionized water to equilibrate. GBL is introduced to the suspended beads, which then diffuses through the rate-controlling film, and reacts progressively with the OH-bearing sites within the resin. Sufficient batch equilibration time is provided to ensure complete reaction. The excess GBL is washed off, and the resulting wet resinate beads have a sustained release coating over GHB resinate, which were formed without starting with GHB resinate. This process may be useful for point-of-use preparation, or can improve the utilization of GBL in preparing the product: no GHB or GBL is lost due to processing during coating, as no GBL is present during the coating process.

In one embodiment of the present invention, the present formulation is administered to a patient once nightly. The patient is administered between 4 g and 10 g GHB/day, or 6 g and 9 g/day. Any of the compositions described herein can be used to provide retarded or delayed release of GHB. For example, the GHB resinate beads may be presented in

hydrated form as part of an aqueous suspension, or may be provided as dried beads for mixing with water immediately prior to ingestion or to be taken without water (e.g., as a powder, tablet, capsule etc.). As discussed herein, Type 1 strong base anion exchange resins swell in the presence of water, to an extent that depends on the degree of crosslinking and the nature of the anion bound to it. In the dried state, the sustained release resinate beads of the present invention can hydrate more slowly if release-retarding agents are used. As the beads hydrate, the diffusion of physiologically produced anions of the gastrointestinal tract (e.g. mainly chloride) into the beads can accelerate, thus producing a delayed or gradually increasing rate of release of oxybate.

In another embodiment, a water permeable but relatively insoluble coating is employed over the dry resinate beads such that, when the dry beads are suspended in water, water diffuses through the coating to hydrate and swell the resinate beads. The resulting expansion of the beads causes the coating to rupture, and allow release of the GHB. Suitable polymers for preparing such coatings include one or more of cellulosics such as ethyl cellulose, cellulose acetate, cellulose phthalate; polyvinyl acetate, acrylic polymers and copolymers such as those available under the Eudragit® trade name (e.g., Eudragit® NE30D, RL, and RS resins). Such coatings can be plasticized or unplasticized, and coated onto the beads using methods well-known in the art (pan coating, fluidized bed coating, etc.).

As discussed herein, the dose of GHB required for treating excessive daytime sleepiness and cataplexy in patients with narcolepsy is quite high, resulting in the administration not only of relatively large masses of GHB composition, but also water required for administration (particularly when the GHB composition is aqueous). However, since oxybate is administered at night, administering large quantities of water can cause bed-wetting. Accordingly, if administered as an aqueous suspension, the highest practical solids loading is desired. The factors which affect the solids loading (volume fraction) of the suspension include the medium used for dilution (water vs. alcohol) and its viscosity, the degree of swelling of the resinate, the sphericity and uniformity of the beads, and surface charge. See Seno and Yamabe, The Rheological Behavior of Suspensions of Ion—Exchange Resin Particles, Bulletin of the Chemical Society of Japan Vol 39, 776-778 (1966), herein incorporated by reference in its entirety for all purposes. In various embodiments, the compositions of the present invention can be administered as suspended resinate particles in a gel, suitable for ingestion by squeezing from a pouch. In other embodiments, the compositions of the present invention can be dosed in two stages: an initial loading dose followed by a chasing dose. Both the loading and chasing dose comprise suspended beads, but the chasing dose is less concentrated. In still other embodiments, the GHB resinate beads can be administered dry, e.g. by having the patient suck the dry beads through a tube or straw. In such embodiments, an added glidant, which is an excipient used in the art to facilitate powder flow by reducing interparticle friction and cohesion, can be used to facilitate administration. They are used in combination with lubricants as they have no ability to reduce die wall friction. Non-limiting examples include fumed silica, talc, and magnesium carbonate.

The oxybate resinate compositions of the present invention can include an immediate release and an extended release component of oxybate. Such compositions can include, for example, a combination of a population of uncoated resinate beads and a population of resinate beads with a diffusion rate controlling coating as described herein; a single resinate bead population that provides immediate release by ion exchange with physiological anions (e.g. chloride), followed by extended release of oxybate controlled by physiological production of e.g. chloride; combinations of populations of resinate beads having different particle sizes and/or crosslinking densities to control release; or any combination of immediate release and extended release resinate beads disclosed herein.

In one embodiment, the compositions of the present invention may be an immediate-release alternative to Xyrem®. Xyrem® has a steep dose-response curve, and inadvertently taking two doses at the same time would have an adverse effect on the patient. If sodium oxybate is instead provided in resinate form for immediate release, as described herein, the capacity of the stomach and small intestine to provide exchangeable anion would limit the consequences of an inadvertent overdose. A 4.5 g dose of Xyrem is 35.7 mEq oxybate. If the stomach has about 5 mEq chloride, then about 30 mEq of additional exchangeable anion must be provided with the resinate formulation of the present invention to ensure complete release of oxybate. This can be achieved by inclusion of exchangeable anion in the formulation, for example glycine or other amino acids, chloride, or in particular citrate. This embodiment would enable rapid release of the oxybate by providing supplementing exchangeable anions in the stomach.

In another embodiment, the supplemental anions are provided by digestion of proteins administered with or as part of the formulation. The resulting amino acids are then available for exchange with the resin and can provide a more convenient means of providing a large amount of supplemental anion.

In yet another embodiment, the supplemental anions are provided by digestion of a triglyceride administered with the formulation. When the triglyceride empties into the small intestine, lipolysis will generate anions available for exchange. In general, triglycerides of short-chain fatty acids (such as triacetin or tributyrin) can provide better oxybate release than medium- or long-chain triglycerides, because the binding affinity of the resulting anions are higher due to their pKa and size. Triglycerides with at least one short-chain fatty acid component are also suitable, particularly pharmaceutically acceptable short-chain triglycerides such as triacetin.

If the resinate particles are film-coated, then supplemental anions can be provided as separate coated particles, such that the supplemental anion is available when needed. The supplemental anion can be selected such that it is not absorbed rapidly yet has an affinity for the resinate that is much higher than that of oxybate. It can be particularly useful to target or enhance release of the supplemental anion in the ileum where chloride secretory deficit may be most pronounced, since absorption of organic acids might be considerably less in that location. Citric acid, glycine, and mesalazine (5-aminosalicylic acid) are examples of suitable supplemental anions. A non-limiting list of other suitable anions (or conjugate acids) includes pharmaceutically acceptable salts selected from the group consisting of chlorides, acetates, lactates, bicarbonates, sulfates, citrates, tartrates, malates, maleates, malonates, glutarates, succinates, fumarates, aspartates, glutamates, and combinations thereof.

These supplemental anions can be coadministered with the oxybate compositions of the present invention, for example within about an hour (before or after) of administering the drug resinate (e.g., oxybate resinate) compositions of the present invention, or simultaneously therewith. The amount of such supplemental anions can range from about

20 to about 200 mmoles, including about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, about 120, about 125, about 130, about 135, about 140, about 145, about 150, about 155, about 160, about 165, about 170, about 175, about 180, about 185, about 190, about 195, or about 200 mmoles, inclusive of all values and ranges therebetween. The supplemental anions can themselves be capable of anion exchange directly upon contact with the drug resinate (e.g., exchanging with the oxybate of the oxybate resinate), or can be "pro-anions"—that is, form anions upon biotransformation after administration to the patient. Non-limiting examples of such "pro-anions" are those described herein, such as triglycerides or proteins. The amount of such "pro-anions" suitable for use in treating patients according to the present invention are amounts that produce between about 20 and about 200 mmoles of anions, as described hereinabove.

If sustained release is desired, then extending gastric emptying can somewhat compensate for deficiencies in the jejunum and, particularly, the ileum. Reliably extending gastric emptying in the fasted state is very challenging. Although some investigators have found that administration of resinate particles can result in mucoadhesion, the unusually high molar doses of GHB of the resinate compositions of the present invention, approximately 100 mEq, will effectively cover the entire surface of the stomach many times over. Thus, observations made with conventional resinate formulations would not apply to GHB resinates. Therefore, a more effective means of promoting gastric retention would be administration of the compositions of the present invention with food or caloric liquid.

The oxybate compositions of the present invention, for example oxybate resinate compositions, provide therapeutically effective levels of oxybate over a period of at least about 3 to about 8 hours. In some embodiments, the composition can be considered to comprise a single population of resinate beads, wherein at least a portion of the resinate beads releases the oxybate quickly upon administration (essentially upon contacting physiologically produced anions such as chloride), and a remaining portion of the resinate beads releases oxybate more slowly, either controlled by the physiological rate of production of anions such as chloride, or by modification of the release characteristics of the resinate beads themselves (e.g., by providing a diffusion controlling coating, by control of bead diameter, or crosslinking density, or other method as described herein). If the compositions of the present invention comprise two or more distinct bead populations (distinguished by their oxybate release characteristics), the rapid (or immediate) release population provides therapeutically effective levels of oxybate for up to about 3 hours (including 1 or 2 hours) after administration, and the other population(s) provide therapeutically effective levels of oxybate for about 3 to about 8 hours (including 3, 4, 5, 6, 7, or 8 hours) after administration.

Xyrem for its approved indications is effective at between 6 g and 9 g administered twice nightly in equal amounts about 4 hours apart. A sustained release equivalent may require a matching AUC as compared to 9 g Xyrem. As disclosed in US2012076865, the overall relative bioavailability of an appropriately-timed sustained release would have at most about 75% relative to Xyrem. Therefore, about 12-13 grams of sodium oxybate would be required, or about 100 mMols.

Suitable blood levels of oxybate are at least about 10 mg/L, ranging up to about 70 m/L, maintained over a period of about 5-8 hours as described herein. For example suitable blood levels of oxybate can be about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, or about 70 mg/L, inclusive of all ranges therebetween.

The following examples are included to demonstrate particular 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 particularly suitable 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.

All documents cited herein, including patents, patent publications, and non-patent publications are herein incorporated by reference in their entirety for all purposes.

EXAMPLES

Example 1

A gel-type Type 1 strong base anion exchange resin, Dowex 1X2 (Dow Chemical), 100-200 mesh was loaded with GHB as follows. Calcium oxybate was loaded onto resin in a batch equilibration by combining 10 mL of 4 M calcium oxybate solution (approximately 490 mg/mL), 31.7 mL of de-ionized water, and 20.27 g of Dowex 1X2 wet resin as chloride form with 2% crosslinking. After mixing for 2 hours, the resin was filtered under mild vacuum using a Buchner funnel. It was then washed with 700 mL of de-ionized water in approximately 100-150 mL aliquots to remove any free oxybate. The wet beads were then dried in a 60° C. oven for 3.5 hours, and finally sized through a 36-mesh screen. The resinate beads were assayed by suspending 1.5 g of resinate in 12.5 g of 1 M calcium chloride and allowing them to equilibrate overnight at room temperature. The solution was analyzed by HPLC, and the measured oxybate released from the beads was 1.09 mEq per gram of dry resinate. The calculated loading efficiency was 1.14 mEq/gram dry resin, or 33% of the theoretical exchange capacity of the resin.

Example 2

GHB resinate beads were prepared by contacting GBL with another Type 1 strong base anion exchange resin (Amberlite IRN78, Dow Chemical) having a median particle size of about 0.63 mm, as the hydroxide form with 8% crosslinking. Batch B1 was prepared with a 2:1 molar ratio of GBL to hydroxide-bearing sites by suspending 26.78 g of wet resin in 41.2 g of de-ionized water. While stirring, 8.28 g of GBL was added, and the reaction was monitored by HPLC analysis of unreacted GBL. The reaction was largely complete after 30 minutes. After 90 minutes, the resin was filtered under mild vacuum, rinsed with de-ionized water to remove unreacted GBL, and then placed in a 60° C. oven overnight to dry.

Batch B2 was prepared by reacting GBL in only 16% molar excess over hydroxide-bearing sites on the same resin. 2.6 g of GBL was added to 20 g of wet resin (as supplied) while stirring by hand with a spatula. About 5.3 g of

additional water was added to facilitate blending. After about 1 hour, the mass was placed in the 60° C. oven overnight to complete the reaction, if necessary. The beads were then rinsed with de-ionized water (70 mL), filtered under mild vacuum, and transferred to the 60° C. oven for drying over 3 days.

The two batches were analyzed for oxybate content by first suspending 1.0 g of resinate in 20 mL of 2 M NaCl for 2 hours with stirring. 10 mL of the resulting solution was then titrated with 1 N HCl and the results were compared with a blank of 10 mL of 2 N NaCl. The initial pH values of B1 and B2 were 7.0 and 8.3, respectively, thus indicating that very little, if any, unreacted hydroxide was present in the resinate product. The oxybate titration indicated that GHB loadings of 4.2 and 4.3 mEq/g dry resin for B1 and B2, respectively. The result further indicates that complete reaction occurred, as the theoretical capacity of the resin is approximately 4 mEq/g.

Example 3

A larger batch of GHB resinate beads are prepared by reacting GBL with Amberlite IRN78 under conditions represented by Batch B2. GBL (36.9 g) is slowly added to a slurry of wet resin (Amberlite IRN78, 279 g) and water (about 200 g). The reaction is allowed to proceed for at least 1 hour at room temperature, with stirring. The product is vacuum filtered, then rinsed with several volumes of de-ionized water. The wet product is then placed in a 40° C. oven to dry overnight. 2.1 g of dried GHB resinate beads are then administered to each of 6 beagle dogs, fasted and weighing approximately 10-12 kg, by oral gavage. Blood is sampled at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 10 h for determination of plasma GHB content.

Example 4

Amberlite IRN78, a hydroxide form Type 1 anion exchange resin, is charged to a vessel and contacted with a 1M solution of sodium oxybate in a 2:1 stoichiometry to resin equivalents. After about 2 hours of equilibration, the mixture of sodium oxybate and sodium hydroxide is filtered from the resulting resinate. A sample of the solution is titrated to determine sodium hydroxide content, and then an equivalent amount of calcium oxybate is charged to the solution to precipitate calcium hydroxide. The calcium hydroxide is filtered from the solution of sodium oxybate, and the recovered sodium oxybate solution is returned to the equilibration tank and contacted with the wet resinate for 2 hours. The resinate is then filtered, and filtrate is recovered. The recovered filtrate is processed with calcium oxybate as in the first step, and set aside for future use. The resinate product is washed with several volumes of de-ionized water, and then dried.

Example 5

Cholestyramine (chloride form) is charged to a vessel and contacted with 1M sodium bicarbonate in a 2:1 stoichiometry (bicarbonate to resin). Five cycles of batch equilibration (2 h each) are conducted. The solutions in each cycle are not recycled, and resinate is rinsed with 2 volumes of de-ionized water between each cycle.

The wet, bicarbonate-exchanged resin is then contacted with 1M sodium oxybate in a single equilibration step in a 2:1 molar ratio of oxybate to resin. After 2 h, the resinate is filtered, and filtrate collected. Separately, the GHB-resinate is then washed with several volumes of de-ionized water. A sample of the first filtrate is titrated for bicarbonate content, and then a stoichiometric amount of calcium oxybate is added to the batch filtrate. The precipitated calcium carbonate is removed by filtration of the suspension, and the sodium oxybate solution is recovered and stored for future use.

Example 6

The above examples can involve difficult separation steps, as precipitated calcium carbonate is a thick slurry of fine particles at the concentrations used. In this example, filtration is avoided by use of a reaction in which the byproduct forms carbon dioxide rather than a precipitate.

The wet, bicarbonate-exchanged resin of Example 5 is contacted with 1M sodium oxybate in a single equilibration step in a 2:1 molar ratio of oxybate to resin. After 2 h, the resinate is filtered, and filtrate collected. Oxybate is recovered and bicarbonate is removed from the filtrate by addition of a stoichiometric amount of sodium hydroxide such that the bicarbonate is converted to carbonate by the reaction: $NaOH+NaHCO_3 \rightarrow Na_2CO_3+H_2O$. The pH drives this reaction to completion.

Next, GBL is added at a 1:1 stoichiometry. Sodium carbonate reacts with the GBL with the evolution of carbon dioxide gas, which drives the reaction to completion: $2\ GBL+Na_2CO_3+H_2O \rightarrow 2\ Na\text{-}GHB+CO_2(g)$. Optionally, a small excess of sodium hydroxide can be added to avoid conversion to bicarbonate during the reaction. This overall process avoids the filtration of carbonate, recovers all the sodium as unexchanged sodium oxybate, and replaces the exchanged sodium oxybate with new oxybate derived from GBL.

Example 7

Soy protein isolate is compressed into oblong or oval tablets of approximately 1000 mg, using compression aids such as fillers, microcrystalline cellulose, and lubricants as required. The tablets are enteric coated separately with two different polymers to achieve dissolution and release of the soy protein isolate in the jejunum and ileum. One batch is coated with Eudragit L30D-55 (jejunum-targeted), and the other is coated with Eudragit L100 (ileum-targeted). At least two of each kind of tablets are taken with one dose of GHB-resinate (35.7 mEq of resinate equivalent to 4.5 g oxybate) in a glass of water. This provides at least 36 mEq of amino acid content, as the protein is hydrolyzed. By releasing the protein in the small intestine rather than stomach, complete and rapid digestion is avoided. Instead, the protein is digested to amino acids more gradually as it transits the small intestine and as the tablet disintegrates. The amino acids are therefore available to facilitate exchange of the GHB-resinate taken concomitantly.

We claim:

1. A method of treating narcolepsy in a patient in need thereof, the method comprising:

administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises:

opening a sachet containing a solid oxybate formulation,

mixing the formulation with water, and

orally administering the mixture to the patient, wherein the oxybate formulation comprises an immediate release component and a controlled release component.

2. The method of claim 1, wherein the orally administering occurs at night.

3. The method of claim 1, wherein the oxybate formulation is mixed with water immediately prior to administration.

4. The method of claim 1, wherein the oxybate is administered with food.

5. The method of claim 1, wherein the administering promotes the patient to sleep for 6 to 8 hours.

6. The method of claim 1, wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate.

7. The method of claim 1, wherein the mixture is a suspension.

8. The method of claim 1, wherein the oxybate formulation further comprises an acid.

9. The method of claim 8, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

10. A method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof, the method comprising:

administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises:

opening a sachet containing a solid oxybate formulation,

mixing the formulation with water, and

orally administering the mixture to the patient, wherein the oxybate formulation comprises an immediate release component and a controlled release component.

11. The method of claim 10, wherein the orally administering occurs at night.

12. The method of claim 10, wherein the oxybate formulation is mixed with water immediately prior to administration.

13. The method of claim 10, wherein the oxybate is administered with food.

14. The method of claim 10, wherein the administering promotes the patient to sleep for 6 to 8 hours.

15. The method of claim 10, wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate.

16. The method of claim 10, wherein the mixture is a suspension.

17. The method of claim 16, wherein the oxybate formulation further comprises an acid.

18. The method of claim 17, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

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EXHIBIT 6

JSR Publications

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Review

Ion-Exchange Resins as Controlled Drug Delivery Carriers

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Abstract

Ion exchange resins (IER) are insoluble polymers that contain acidic or basic functional groups and have the ability to exchange counter-ions within aqueous solutions surrounding them. Based on the nature of the exchangeable ion of the resin as a cation or anion, it is classified as cationic or anionic exchange resins, respectively. The efficacy of ion exchange resins mainly depends upon their physical properties such as degree of cross-linking, porosity, acid base strength, stability, purity and particle size. Modified release of drugs from resinate (drug-resin complexes) is another potential application of ion exchange resins. Due to the versatile utility of ion exchange resins, they are being used for various drug delivery and therapeutic applications. Resins used are polymers that contain appropriately substituted acidic groups, such as carboxylic and sulfonic for cation exchangers; or basic groups, such as quaternary ammonium group for anion exchangers. This review addresses different types of ion exchange resin, their properties, the chemistry; role of IER in controlled drug delivery systems, its therapeutic applications, methods of preparation of IER along with their resonates.

Keywords: Anion exchange; Cation exchange; Resin; Controlled release; Resinates; Drug delivery.

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1. Introduction

Controlled drug delivery systems are gaining momentum in the recent two decades as these results in reduced frequency of dosing and patient compliance. Intensity and duration of action has been the subject of increasing multidisciplinary research. One of the attractive methods for modified drug delivery systems is the use of ion exchange resins (IER) as carriers for such systems [1]. Complexes between IER and drugs are known as

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ion exchange resonates, which have been used in pharmaceutical formulations for several decades.

IER are insoluble polymers that contain acidic or basic functional groups and have the ability to exchange counter-ions within aqueous solutions surrounding them. An ion exchange resin is exhibited like small bead with a diameter between 1-2 mm. It is usually white or yellowish and it is fabricated from an organic polymer substrate backbone [2]. Ion exchange is a reversible process in which ions of like sign are exchanged between liquid and solid when in contact with a highly insoluble body [3]. The drug is released from the resinate by exchanging with ions in the gastrointestinal fluid, followed by drug diffusion [4]. Due to the presence of high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. IER have specific properties like available capacity, acid base strength, particle size, porosity and swelling, on which the release characteristics of drug resinates are dependent [5]. Drug resinates are generally prepared with purified resins and appropriate drugs.

Ion-exchange systems are advantageous for drugs that are highly susceptible to degradation by enzymatic process. A major advantage of ion exchange system is low running cost. It requires little energy and the regenerated chemicals are cheap. Furthermore, if well maintained, resin beds can last for many years before replacement. However, the limitation is that the release rate is proportional to the concentration of the ions present in the area of administration. More so, the release rate of drug can be affected by variability in diet, water intake and individual intestinal content.

2. Structure and Chemistry of Ion Exchange Resin

IER are simply insoluble polyelectrolytes that are insoluble polymers which contain ionizable groups distributed regularly along the polymer backbone. The most common resins used in formulations are cross-linked polystyrene and polymethacrylate polymers [6]. When IER are mixed with a fluid such as water, ions in the fluid can exchange with the polyelectrolyte's counterions and be physically removed from the fluid.

An ion exchange resin is a polymer (normally styrene) with electrically charged sites at which one ion may replace another. There are numerous functional groups that have charge, only a few are commonly used for man-made IER. These are:

- -COOH, which is weakly ionized to $-COO^{-}$,
- $-SO_3H$, which is strongly ionized to $-SO_3^{-}$,
- $-NH_2$, which weakly attracts protons to form NH_3^{+},
- -secondary and tertiary amines that also attract protons weakly,
- $-NR_3^{+}$, which has a strong, permanent charge (R stands for some organic group).

These groups are sufficient to allow selection of a resin with either weak or strong positive or negative charge.

3. Types of Ion-exchange Resins

There are two major classes of ion-exchange polymers [7] (See Fig. 1): (a) Cation and (b) anion exchange resins. These are discussed in the following two sub-sections.

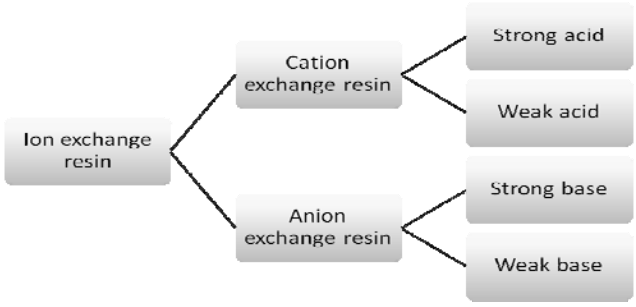

Fig. 1. Classification of IER.

3.1. *Cation exchange resins*

Cation exchange resins contain covalently bound negatively charged functional groups and exchanges positively charged ions. There are prepared by the copolymerization of styrene and divinyl benzene and have sulfonic acid groups (-SO_3H) introduced into most of the benzene rings (Fig. 2). The mechanism of cation exchange process can be represented by the following reaction in Eq. (1):

$$R\text{- - ex+} + C+ \rightarrow R\text{- - } C+ + ex+ \quad (1)$$

where, R is a resin polymer with SO_3-sites available for bonding with exchangeable cation (ex+), and C+ indicates a cation in the surrounding solution getting exchanged (Fig. 3).

Fig. 2. Chemical structure of (I) styrene (II) divinyl benzene.

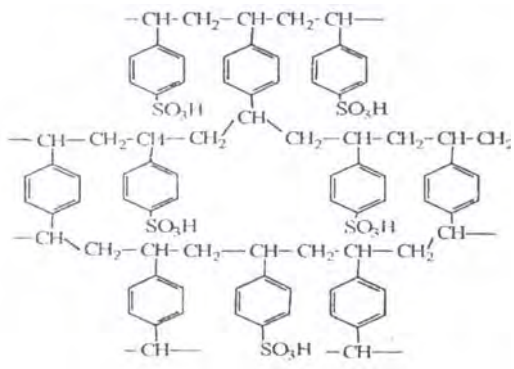

Fig. 3. Chemical structure of a cation exchange resin

Cation exchange resins can be further classified into (a) strong acid cation exchange resins and (b) weak acid cation exchange resins.

3.1.1. Strong acid cation exchange resins

The chemical behaviour of these resins is similar to that of a strong acid. These resins are highly ionized in both the acid ($R\text{-}SO_3H$) and salt (RSO_3Na) form of the sulfonic acid group ($\text{-}SO_3H$). They can convert a metal salt to the corresponding acid by the reaction in Eq. (2):

$$2(R\text{-}SO_3H) + NiCl_2 \rightarrow (R\text{-}SO_4)\,Ni + 2HCl \quad (2)$$

The hydrogen and sodium forms of strong acid resins are highly dissociated, and the exchangeable Na^+ and H^+ are readily available for exchange over the entire pH range. Consequently, the exchange capacity of strong acid resins is independent of the solution pH [8].

3.1.2. Weak acid cation exchange resins

These resins behave similarly to weak organic acids that are weakly dissociated. In a weak acid resin the ionisable group is a carboxylic acid (COOH) as opposed to the sulfonic acid group (SO_3H) used in strong acid resins. The degree of dissociation of a weak acid resin is strongly influenced by the solution pH. Consequently, resin capacity depends in part on the solution pH. A typical weak acid resin has limited capacity below a pH of 6.0, making it unsuitable for deionizing acidic metal finishing wastewater.

3.2. *Anion exchange resins*

Anion exchange resins have positively charged functional groups and there exchanges negatively charged ions. These are prepared by first chlormethylating the benzene rings of styrene-divinylbenzene copolymer to attach CH_2Cl groups and then causing these to react

with tertiary amines such as triethylamine. The chemical structure of an anion exchange resin is shown in Fig 4 while the mechanism of anion exchange process can be represented by the following reaction in Eq. (3):

$$R+ - ex - + A- \rightarrow R+ - A- + ex- \quad (3)$$

where, R+ indicates a resin polymer with number of sites available for bonding with exchangeable anion (ex-), and A- indicates cations in the surrounding solution getting exchanged.

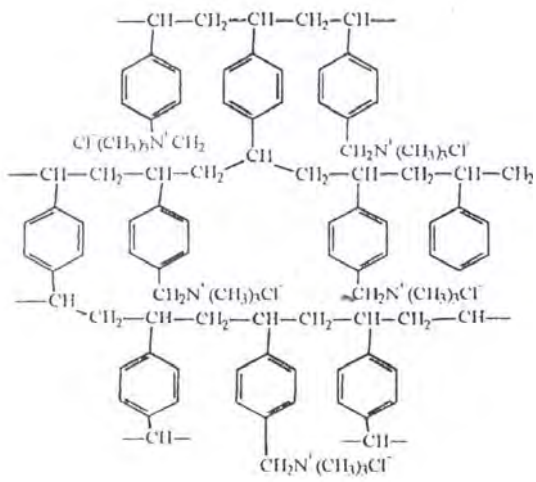

Fig 4. Chemical structure of an Anion exchange resin

Anion exchange resins can be further classified into [9] two which are as follows:

3.2.1. *Strong base anion exchange resins*

Strong base resins are highly ionized and can be used over the entire pH range. These resins are used in the hydroxide (OH) form for water deionization. They will react with anions in solution and can convert an acid solution to pure water Eq. (4):

$$R\text{-}NH_3OH + HCl \rightarrow R\text{-}NH_3Cl + H_2O \quad (4)$$

Regeneration with concentrated sodium hydroxide (NaOH) converts the exhausted resin to the OH form.

3.2.2. Weak base anion exchange resin

Weak base resins are like weak acid resins in that the degree of ionization is strongly influenced by pH. Hence, weak base resins exhibit minimum exchange capacity above a

pH of 7.0. The weak base resin does not have an OH ion form as does the strong base resin Eq. (5):

$$R\text{-}NH_2 + HCl \rightarrow R\text{-}NH_3Cl \quad (5)$$

Consequently, regeneration needs only to neutralize the absorbed acid; it need not provide OH ions. Less expensive weakly basic reagents such as ammonia (NH_3) or sodium carbonate can be employed.

A typical cation-exchange resin is prepared by the copolymerization of styrene and divinylbenze. During the polymerization, polystyrene formed as a linear chains and these become covalently bonded to each other by divinylbenze cross links. If sulphuric acid is then allowed to react with this copolymer, sulphonic acid groups are introduced into most of the benzene rings of the styrene-divinylbenze polymer, and the final substance formed is known as cation-exchange resin.

A typical anion exchange resin is prepared by first chloromethylating the benzene rings of the three dimensional styrene-divinylbenzene copolymers to attach – CH_2Cl groups and then causing these to react with a tertiary amine, such as trimethylamine. This gives the chloride salt of strong-base exchanges (Table 1).

Table. 1. Chemical constituents for IER.

Sl.	Resin type	Chemical constitution	Usual form
1.	Strongly acidic cation exchanger	Sulfonic acid groups attached to a system and divinyl benzene copolymer	$R\text{-}SO_3^-H^+$
2.	Weakly acidic cation exchanger	Carboxylic acid groups attached to an acrylic and divinyl benzene copolymers	$R\text{-}COO^-Na^+$
3.	Strongly basic anion exchanger	Quaternary ammonium groups attached to a styrene and divinylbenzene copolymer	$[\phi\text{-}CH_2N\text{-}(CH_3)_3^+]Cl^-$
4.	Weakly basic anion exchanger	Polyalkylamine groups attached to a styrene and divinyl benzene copolymer	$[\phi\text{-}NH\text{-}(R)]Cl^-$

4. Role of IER in Controlled Drug Delivery Systems

The major drawback of controlled release is dose dumping, resulting in increased risk of toxicity. The usage of IER during the development of controlled release formulations plays a significant role because of their drug retarding properties and prevention of dose dumping. The drug resinates can also be used as a drug reservoir, which has caused a change of the drug release in hydrophilic polymer tablets [10, 11].

The use of IER into drug delivery systems have been encouraged because of their physico-chemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in ionic environment [12]. The physical and chemical properties of the IER will release the drug more uniformly than that of

simple matrix formulations [13]. Drug molecules attached to the resins are released by appropriate charged ions in the gastrointestinal tract, followed by diffusion of free drug molecules out of the resins as shown below in Eqs. (6) and (7):

$$Resin^{-}\,Drug^{+} + X^{+} \rightarrow Resin^{-}....X^{+} + Drug^{+} \quad (6)$$

$$Resin^{+}\,Drug^{-} + X^{-} \rightarrow Resin+...X^{-} + Drug^{-} \quad (7)$$

where, X and Y are ions in the gastrointestinal tract.

IER have been used as drug carriers in pharmaceutical dosage forms for controlled release formulation [14-16]. The prolonged release of the active drug is accomplished by providing a semi-permeable coating around discrete, minute, ion exchange resin particles with which the drug component has been complexed to form an insoluble drug resin complex. The semi-permeable coating creates a diffusion barrier and the thickness of which can be adjusted to provide the desired level of retardation of drug availability in the gastrointestinal tract over a period of time [17]. Several preparations involving strong resonates of sulphuric acid (cation exchange resins) provided more moderate release than the weak resinates of carboxylic acid [18]. Hence, resinates of strong cationic drugs are formulated as sustained release suspension, tablets, capsules and micro particles.

5. Manufacture of IER and Resonates

Most IER are made by the process of suspension polymerization. In some cases the monomers are neutral (e.g. styrene, methyl acrylate and acrylonitrile) and the resulting polymer beads are then chemically modified to introduce the acid or base functionality; for example, sodium polystyrene sulfonate is prepared by suspension polymerization of a mixture of styrene and divinylbenzene to make small polymeric beads. The beads are then sulfonated using concentrated sulphuric acid and neutralized with sodium hydroxide to give the functionalized product - a sodium form of a strongly acidic cation exchange resin [19].

A few resins are made directly from acidic monomers; for example, polacrilex resin is made by suspension polymerization of a mixture of methacrylic acid and divinylbenzene with no further functionalization. For use in pharmaceutical formulations, the resins are usually dried and then ground to a fine powder, typically in the range of 40–150 μm in size [20].

Preparing resinates from the resins is a matter of mixing the resin with a solution and allowing sufficient time (typically a few hours) for loading. The resin/fluid slurry is then filtered and the filtrate washed. Depending on the application, resinate can then be dried in a vacuum oven at 60ºC. In cases where resinate is to be used in a liquid suspension drying may not be necessary, and in some cases the loading suspension can be used directly without filtration. The dried resinate will be a free flowing powder with physical properties similar to the original resin, which can be formulated into tablets, capsules, chewing gums, lozenges, suspensions and troches. It can also be coated in typical coating equipment such as fluid bed coaters.

The best approach for getting resinates is spray drying process in which fluidized bed processor can be used. In this process, the solution can be sprayed on the resin and

simultaneous drying takes place to get dried resinates which is free flowing powder mostly used in the solid dosage forms. The drug release mainly depending on the efficient complex formed between the drug and the resin. For further regulating drug release an alternative method is coating. In this technique the resin solution can be sprayed over the drug along with simultaneous drying. The advantage of this process is that it allows uniform distribution of the drug resinate mixture.

6. Mechanism and Principle

Anion exchange resins involve basic functional groups capable of removing anions from acidic solutions while Cation exchange resins contain acidic functional group, capable of removing cations from basic solutions.

The use of IER to prolong the effect of drug release is based on the principle that positively or negatively charged pharmaceuticals, combined with appropriate resins to yield insoluble polysalt resinates.

$$R\text{-}SO^-_3\,H^+ + H_2N\text{-}A \leftrightarrow R\text{-}SO^-_3 - H_3N\text{-}A \quad (8)$$

$$R\text{-}N^+H_3OH^- + HOOC\text{-}B \leftrightarrow R\text{-}N^+H_3 - OOC\text{-}B + H_2O \quad (9)$$

$H_2N\text{-}A \rightarrow$ basic drug, $R\text{-}SO^-_3H^+ \rightarrow$ cation exchanges, $HOOC\text{-}B \rightarrow$ acidic drug

$R\text{-}NH_3^+OH^- \rightarrow$ anion exchange resins.

Ion exchange resinates administered orally are likely to spend about two hours in the stomach in contact with an acidic fluid of pH 1.2, and then move into the intestine where they will be in contact for several hours with a fluid of slightly alkaline pH [21].

7. Important Properties of IER

During the process of developing formulations with IER, some of the important properties normally considered by researchers include the following:

Particle size and form: The rate of ion-exchange reactions depends on the size of the resin particles. Decreasing the size of resin particle significantly decreases the time required for the reaction to reach equilibrium with the surrounding medium [22].

Porosity and swelling: Porosity is defined as the ratio of the volume of the material to its mass. The size of the ions, which can penetrate into a resin matrix, depends strongly on the porosity. Porosity of the ion-exchangers depends upon polymerization procedures. The amount of swelling is directly proportional to the number of hydrophilic functional groups attached to the polymer matrix and is inversely proportional so the degree of divinyl benzene cross linking present in the resin [23].

Cross linkage: The percentage of cross linking affects the purely physical structure of the resin particles. The degree of cross linkage is controlled by the percent of divinylbenzene (DVB) used in the copolymerization. The fraction of DVB determines to what extent the ion exchange resin is free to swell and shrink. The swelling in turn affects the rate of

hydration, the volume expansion of resin to absorb large molecules. Even after absorption, some large molecules may be difficult to evaluate absorption, some large molecules may be difficult to elute unless the DVB percentage is low. The swelling capacity of the ion exchange resin when wetted has been put to practical use with the potassium form of the polymethacrylic acid resin, Amberlite IRP-88, as a tablet disintegrating agent [24]. Resins with low cross linking can take considerable amount of water and swell into a structure that is soft and gelatinous.

Available capacity: The capacity of an ion-exchanger is a quantitative measure of its ability to take up exchangeable counter-ions and is therefore a major importance. The exchange capacity refers to the number of ionic sites per unit weight or volume. The weight basis value is highly hydrated. The exchange capacity may limit the amount of drug that may be absorbed on a resin and hence the potency of a complex. Carboxylic acid resins derived from acrylic acid polymers have higher exchange capacities than sulphonic acid or amine resins because of bulkier ionic substituent's and the polystyrene matrix. Therefore, higher drug percentages may often be achieved with carboxylic acid resins.

Acid base strength: The acid or base strength of an exchanger is dependent on the various ionogenic groups, incorporated into the resin. The P_{ka} value of the resin will have a significant influence on the rate at which the drug will be released from resinate in the gastric fluids.

Stability: The resinous ion-exchangers are remarkably inert substances. At ordinary temperature and excluding the more potent oxidizing agents, vinylbenzene cross-linked oesins are resistant to decomposition through chemical attack.

Purity and toxicity: Since drug resin combinations contain 60% or more of the resin, it is necessary to establish toxicity of the ion-exchange resins. Commercial product cannot be used as such because they contain impurities that cause severe toxicity [25]. Therefore, careful purification of the resin prior to treatment with the drug is required.

8. General Preparation of Drug Resonates and Drug Loading

The foremost step in the preparation of drug resinates is to purify the resins carefully. Purification is generally done by cycling repeatedly between the sodium and hydrogen forms with a cation exchanger (or) between the chloride and hydroxide forms with anion exchanges [5]. After thoroughly washing with water and subsequent air drying, the resin is sieved to get a series of fractions. Drugs to be formulated into resinates should have in their chemical structure acidic or basic groups with its biological half life ($t_{1/2}$) between the range of 2 to 6 hrs. It should be well absorbed from all the areas of the gastrointestinal tract and also it should be stable in the gastric juice [5].

Loading of drugs is done by two ways: (a) column process, and (b) batch process:

(a) Column process – A highly concentrated drugs solution is eluted through a bed or column of the resin, until equilibrium is established.

(b) Batch process – The resin particles are stirred with a large volume of concentrated drug solution. Subsequently the resin is to be washed to remove adhering free and un-associated drug and thereafter it is air dried.

9. Evaluation of Drug Resonates

The *invitro* test demonstrates the release pattern of a drug from resinate preparation dosage form. It depends on size of resinate, degree of cross linkage of resin with drug, nature of the resins, nature of the drug and test conditions that is ionic strength of the dissolution medium [26].

In vivo procedures used for estimating drug activity of resinates include serum concentration level determination, urinary excretion, and toxicity studies. Bioavailability of drug from drug–resinate complexes depends on both transit of the particles through the gastrointestinal tract and drug release kinetics. The complex will release the active content only when it replaced by the ion which has the same charge. Since the exchange is an equilibrium process, it will depend on the ionic constitution and the fluid volume of the body fluid. In additional, release is not instantaneous, and the drug must diffuse through the resin from the internal exchange sites. Thus, agitation and time of exposure play a key role in drug release.

Stomach emptying with fine particles will likely follows a first order or distributional process. In the intestine, the neutral pH should keep all ionic sites ionized, and the exchange process should occur continuously. The absorption into the body of solubilised drug should drive the equilibrium further toward drug release. In the large intestine, desorption from resins and absorption into the body may be slowed considerably due to low fluid content, entrapment in faecal matter, and poor absorption in colon. The highly insoluble resin never dissolves, and should not be absorbed. It will simply be eliminated from the body with whatever counter-ions have replaced the drug.

10. Applications of IER

10.1. *Pharmaceutical applications*

Some pharmaceutical applications of IER include:

Taste masking

Masking of bitter taste in active principal ingredients in oral formulations poses a major challenge to pharmaceutical industry especially for paediatric and geriatric patients. Masking of the unpleasant taste of a drug improves compliance and product value. Amongst the numerous available taste-masking methods, ion exchange resins are inexpensive and can be used to develop. Previously some workers used carbomer to mask the nauseating and unpleasant taste of erythromycin and clarithromycin, by adsorption

into Carbopol and then encapsulating the resulting particles with hydroxylpropyl methylcellulose phthalate [27-30]

Eliminating polymorphism

Many pharmaceutical solids can exist in different physical forms. Polymorphism is often characterized as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice [31, 32]. This is a common problem in the pharmaceutical industry and huge sums of money are spent trying to identify polymorphs. and trying to make stable, suitably soluble forms. Failure to resolve such a problem can result in significant stability and stability problems for the final dosage form. Ion exchange resins present a unique way to deal with the problem because using resinates completely eliminates any problem with polymorphism.

Improving the dissolution of poorly soluble drugs

Ion exchange drug resinate complexes can be used to enhance the dissolution rate of a poorly soluble drug. Using micronization to increase the rate of dissolution can be problematic, because it frequent requires specialized equipment and often there can be agglomeration of the fine particles after grinding [33]. The grinding can also result in melting and conversion to other crystal forms. These problems are completely eliminated by using the ion exchange resin approach.

Improving stability

The drug resinate is frequently more stable than the original drug. For instance, vitamin B_{12} has a shelf-life of only a few months while its resinate has more than two years. Another example is nicotine which discolors on exposure to air and light, but the resinate used in manufacturing nicotine chewing gums and lozenges is much more stable.

Improving physical characteristics

Most drug substances are in solid form there are some that are liquids or difficult-to-handle solids. Because the physical properties of the resinates are similar to the resin not the drug, the resinates of these drugs will be free-flowing solids [34]. A very well established example of this is the nicotine resinate used in nicotine chewing gums and lozenges. Nicotine is in liquid form but its resinate is a stable, free- flowing solid.The resins have a uniform, macroreticular morphology, that provides excellent flowability to the formulation.

10.2. *Drug delivery applications*

Oral drug delivery

The major drawback of sustained release or extended release is dose dumping hence resulting in increased risk of toxicity. The use of IER has occupied an important place in the development of controlled or sustained-release systems due of their better drug retaining properties and prevention of dose dumping. The drug resinates can also be used as a drug reservoir, which has caused a change of the drug release in hydrophilic polymer tablets [35-37]. The use of ion exchange resins into drug delivery systems have been

encouraged because of their physico-chemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in ionic environment.

Nasal drug delivery

A novel nasal formulation, in the form of a nicotine-Amberlite resin complex powder, has been developed that provided an optimal combined pulsatile and sustained plasma nicotine profile for smoking cessation. Amberlite IRP69 and Amberlite IR120 are similar cationic exchange materials with the same ion exchange capacity but due to a smaller particle size range (10-150 µm). Amberlite IRP69 had a better flow property and a better adsorptive capacity than Amberlite IR120 [38]. The nicotine plasma profiles demonstrated that an initial rapid peak plasma level of nicotine followed by a sustained elevated level could be achieved by adjusting the ratio of free to bound nicotine in the Amberlite powder formulation [39, 40].

Transdermal drug delivery

IER are also involved in the formulation of transdermal drug delivery systems. The release rates of ketoprofen from the carbopol-based gel vehicles containing ion exchange fibers to which the ketoprofen had been bound were determined across 0.22 µm microporous membrane [40, 41]. The fluctuation of the release rate of ketoprofen from the vehicles was much lower compared with that of simple gels, though the cumulative amount of ketoprofen delivery was less. In addition ions could increase the rate and extent of ketoprofen delivery.

Ophthalmic drug delivery

IER also find application in opthalamic drug delivery systems. An example is Betoptic S which is a sterile ophthalmic suspension and it contains 0.25% betaxolol hydrochloride. It is a cardioselective beta-adrenergic receptor blocking agent manufactured by Alcon Laboratories in the US. It is an ocular resinate ophthalmic product designed to lower elevated intraocular pressure. The drug resinate complex is formed when the positively charged drug is bound to a cation ion-exchange resin (Amberlite[1] IRP 69). The 0.25% ophthalmic suspension of the drug showed an increased bioavailability [42].

10.3. *Diagnostic and therapeutic applications*

Synthetic as well as natural polysaccharides based on ion-exchange resins have been used with good results for diagnostic determinations. eg. In gastric acidity. They have also found applications as adsorbents of toxins, as antacids, and as bile acid binding agents. Ion-exchange resins have been successfully used therapeutic in the treatment of liver diseases, renal insufficiency, urolithic disease and occupational skin disease. For instance, sodium polystyrene sulfonate is a sulfonic cation-exchange resin used in the treatment of hyperkalemia and also used in acute renal failure. Phenteramine, a sympathomimetic amine is indicated for short term use in the management of exogeneous obesity in a regimen of weight reduction utilizing caloric restriction. It also has application in the control of cholesterol and potassium ion levels.

11. Some IER Available in the Market

The use of IER to form drug adsorbates for sustained release [43, 44] was closely associated with Strasenburgh Laboratories, an affiliate of Pennwalt Corporation, which was granted several patents in this area [45, 46]. Their first significant application involved amphetamine adsorbed onto a sulfonic acid cation exchange resin (Biphetamine) which is use in appetite suppression and for also for behavior control in children [47].The drug is administrated once or twice daily. Other products that have been introduced commercially since the initial work with amphetamine include Penntuss which is a combination of Codeine and Chlorpheniramine. This is a liquid suspension used as a cough suppressant and relief of cold. It is taken twice daily. Both drugs are bound to a sulfonic acid cation-exchange resin. The chlorpheniramine-resinates are uncoated due to much high affinity for the resin while the codeine-resinates are coated with ethylcellulose [48]. Other products used for cough and cold include phenylpropanolamine, chlorpheniramine, and dextromethorphan. Some other examples include Ionamin (phentermine) and Tussionex (hydrocodone polistirex and chlorpheniramine polistirex) both are marketed by Medeva Pharmaceuticals, Inc.) [49-54]. However, Table 2 gives a summary of some IER with their doses and suppliers.

Table 2. Some IER used in pharmaceutical formulations.

Component Name	Commercial Name	Suppliers	Daily Intake
Polacrilex resin	Amberlite IRP64	Roham andHaas, Philadelphia.	Estimated daily intake: 270 mg
Polacrilin potassium	Amberlite IRP88	Roham and Haas, Philadelphia.	Estimated daily intake: 270 mg
Sodium polystyrene Sulfonate	Amberlite IRP69	Roham and Haas, Philadelphia.	Maximum daily intake: 60 g
Cholestyramine resin	Duolite AP143	Roham and Haas, Philadelphia.	Maximum recommended dose for cholesterol reduction: 24 g in divided doses

12. Conclusion

IER play a major role in the modification of drug release by forming a complex with drug substances. This article has attempted to review the literature bring to light the chemistry, properties, method of preparation as well as its different applications with the hope that researchers will utilise the resins more effectively in formulating controlled drug delivery systems.

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EXHIBIT 7

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

(10) **Patent No.: US 11,147,782 B1**
(45) **Date of Patent: Oct. 19, 2021**

(54) **GHB FORMULATION AND METHOD FOR ITS MANUFACTURE**

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(21) Appl. No.: **17/210,064**

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(58) **Field of Classification Search**
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See application file for complete search history.

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(57) **ABSTRACT**

The present application relates to GHB formulations and methods for manufacturing the same.

24 Claims, No Drawings

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GHB FORMULATION AND METHOD FOR ITS MANUFACTURE

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. application Ser. No. 17/118,041, filed Dec. 10, 2020, which is a continuation of U.S. application Ser. No. 16/448,598, filed Jun. 21, 2019, which is a continuation of U.S. application Ser. No. 15/047,586, filed Feb. 18, 2016 (now U.S. Pat. No. 10,398,662), which claims priority to U.S. Provisional Application Ser. No. 62/117,889, filed Feb. 18, 2015, the disclosures of which are herein incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

Gamma-hydroxybutyrate (GHB), also known as "oxybate," 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 the brain, the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter (See Snead and Morley, 1981, Brain Res. 227(4): 579-89). 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 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, reduces sleep apnea, and improves general anesthesia (see, e.g., U.S. Pat. Nos. 6,472,431; 6,780,889; 7,262,219; 7,851,506; 8,263,650; and 8,324,275; each of which is incorporated herein by reference in its entirety).

Sodium oxybate (Na.GHB), commercially sold as Xyrem®, is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. It can be used for other sleep time disturbances. Na.GHB has also been reported to be effective for relieving pain and improving function in patients with fibromyalgia syndrome (See Scharf et al., 2003, J. Rheumatol. 30: 1070; Russell et al., 2009, Arthritis. Rheum. 60: 299), and in alleviating excessive daytime sleepiness and fatigue in patients with Parkinson's disease, improving myoclonus and essential tremor, and reducing tardive dyskinesia and bipolar disorder (See Ondo et al., 2008, Arch. Neural. 65: 1337; Frucht et al., 2005, Neurology 65: 1967; Berner, 2008, J. Clin. Psychiatry 69: 862).

SUMMARY OF THE INVENTION

GHB has a short in vivo half-life, so various embodiments of the invention include a formulation and a method for manufacturing a GHB formulation. One embodiment of the invention is a GHB formulation comprising polymeric beads and pharmaceuticals acceptable excipients. The formulation can be a solid or a liquid. Additional agents, such as surfactants, may be added to control the release of GHB from within the polymeric bead, such as sodium lauryl sulfate or stearic acid. The beads can be coated with a flexible film. Optionally, the formulation can contain supplemental anions separate from the coated or uncoated resin particles to facilitate exchange of the GHB when natural (e.g., physiologically produced) anions in the gut are depleted.

In another embodiment of the invention, a precursor to GHB, called gamma butyrolactone (GBL) is loaded onto a hydroxide form Type 1 strong base anion resin (or its equivalent) and the GBL is converted to GHB in the bead to form a GHB resinate product. One can achieve high loading efficiency of the GHB resinate product and a high reaction rate on the resin. Furthermore, organic non-anionic byproducts made in reaction or present in the GBL would not be captured on the resin.

In another embodiment of the invention, one can fully load GHB on the resin, then load a lipophilic agent on the resin with higher selectivity for the resin than GHB. The agent will slow the release of GHB.

In another embodiment, one can fully load an anionic hydrophobic agent, such as stearic acid, onto the resin with lower selectivity for the resin than GHB and then subsequently load GHB less completely, thereby retaining much of the hydrophobic agent and promoting a slower release of GHB.

In still another embodiment of the invention, the hydroxide-bearing resin beads are coated with a flexible film, then loaded with GBL which, in turn, will diffuse through the film and react with the hydroxyl anions of the resin and form the GHB resinate in-situ. The coating will provide further controlled release characteristics. Examples of such coatings include films comprising polyvinyl acetate (PVAcetate), Eudragit RS, ethylcellulose, cellulose acetate or an enteric coating such as acrylic acid-based Eudragit L100, FS100 or L55, cellulose acetate phthalate, and shellac. It is understood that these films can be modified with pore formers to adjust permeability or degree of enteric protection. The coating may also be combined with suitable plasticizer and anti-tack agents to facilitate coating. Finely ground resin beads may also be encapsulated within polysaccharide gel structures that confer enteric protection, through ionotropic gelation as with calcium alginate encapsulation.

Other embodiments include reducing the amount of water in the formulation. Oral administration may be achieved while reducing the amount of water by using agents that increase flow, such as slippants to reduce viscosity. Example slippants include polyethylene oxide (PEG) (and its equivalents) which is available in various grades of varying molecular weight and molecular weight distribution.

DETAILED DESCRIPTION OF THE INVENTION

One embodiment of the invention is a GHB formulation comprising polymeric beads and pharmaceuticals acceptable excipients. The formulation can be in the form of a solid or a liquid. Additional agents, such as surfactants, may be added to control the release of GHB from within the polymeric bead, such as sodium lauryl sulfate or stearic acid. The beads can be coated with a flexible film. Background information on GHB and its related compounds, use and methods for manufacture are listed below. Also, background information on ion exchange resins, their manufacture and uses can be found in the references listed below. The new formulations of the present invention described herein provide favourable sustained release profiles for GHB.

The following U.S. patents and applications relate to GHB and are hereby incorporated by reference in their entireties for all purposes: U.S. Pat. Nos. 6,472,431, 8,263,650, 8,324,275; 8,859,619; 7,895,059; 7,797,171; 7,668,

730; 7,765,106; 7,765,107; 8,461,197; 8,591,922; 8,731,963; 8,759,394; 8,771,735; 8,772,306; 8,778,301; 8,778,398; 8,901,173; and 2012/0076865. The following patents are also incorporated by reference: U.S. Pat. Nos. 5,380,937; 4,393,236 German Patent DD 237,309 A1; and British Pat. No. 922,029.

Information on ion exchange resins, their manufacture and uses can be found in the following references which are hereby incorporated by reference in their entireties for all purposes. Mahore J. G, Wadher K. J, Umekar M. J, Bhoyar P. K., Ion Exchange Resins: Pharmaceutical Applications And Recent Advancement, International Journal of Pharmaceutical Sciences Review and Research, Volume 1, Issue 2, March—April 2010; Article 002; Munot, Neha M., et al. "Ion exchange resins in pharmaceuticals: A review." Journal of Pharmacy Research 3.12 (2010). Singh, Inderbir, et al. "Ion exchange resins: drug delivery and therapeutic applications." FABAD J. Pharm. Sci 32 (2007): 91-100; Srikanth, M. V., et al. "Ion-exchange resins as controlled drug delivery carriers." Journal of Scientific Research 2.3 (2010): 597; Singh, Inderbir, et al. "Ion exchange resins: drug delivery and therapeutic applications." FABAD J. Pharm. Sci 32 (2007): 91-100; Ohta et al., Development of a simple method for the preparation of a silica gel based controlled delivery system with a high drug content, European Journal of Pharmaceutical Sciences 26 (2005) 87-96; Akifuddin et al., Preparation, Characterization and In-vitro Evaluation of Microcapsules for Controlled Release of Diltiazem Hydrochloride by Ionotropic Gelation Technique, Journal of Applied Pharmaceutical Science Vol. 3 (04), pp. 035-042, April, 2013; Patil et al., A Review On Ionotropic Gelation Method: Novel Approach For Controlled Gastroretentive Gelispheres; International Journal of Pharmacy and Pharmaceutical Sciences, Vol 4, Suppl 4, 2012; Cabellero, et al., Characterization of alginate beads loaded with ibuprofen lysine salt and optimization of the preparation method, International Journal of Pharmaceutics 460 (2014) 181-188; J.M.C. Puguan, X. Yu, H. Kim, Diffusion characteristics of different molecular weight solutes in Ca-Alginate gel beads, Colloids and Surfaces A: Physicochemical and Engineering Aspects (2015), http://dx.doi.org/10.1016/j.colsurfa.2015.01.027; Takka and Gurel, Evaluation of Chitosan/Alginate Beads Using Experimental Design: Formulation and In Vitro Characterization, AAPS PharmSciTech, Vol. 11, No. 1, March 2010; Anand, et al., Ion-exchange resins: carrying drug delivery forward, DDT Vol. 6, No. 17 Sep. 2001. See also the Technical Information sheet for Dowex Ion Exchange Resins; the Product Data Sheet for Amberlite IRN78 Resin, both from Dow Chemicals. Also the Technical Sheet for Duolite AP143/1083 Pharmaceutical Grade Anion Exchange Resin (Cholestyramine Resin USP) from Rohm and Haas. The following U.S. Patents and applications are also incorporated by reference in their entireties for all purposes U.S. Pat. Nos. 4,221,778; 4,510,128; 6,322,819; 8,193,211, 8,202,537; 8,771,735; 8,778,398, 8,062,667, and 8,337,890; U.S. Patent Publication Nos. 2003/0180249; 2008/0003267; 2008/0118571; 2012/0076865; 2012/0148672; 2013/0273159; 2014/0004202; 2014/0093578; and 2014/0127306.

As used herein, the term gamma-hydroxybutyrate (GHB) or "oxybate" refers to the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid. The manufacture, use, known dosage forms and dosing can be shown in the above patents. An effective dosage range of Xyrem is 6 g to 9 g, given at night in divided doses approximately 2-4 hours apart. GHB is typically given twice nightly due to a short in vivo half-life. It is subject to a controlled drug

distribution system. See U.S. Pat. Nos. 6,472,431, 8,263,650, 8,324,275; 8,859,619; 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 8,591,922; and 8,772,306 which are incorporated above.

One object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours. As described above, a single dose is eliminated within a shorter period of time. One object of the invention is to maintain the blood level of GHB from about 10 mg/L to about 20 mg/L for up to 8, 7, 6, or 5 hours. Additionally, it is an object of the invention to ensure that the sleep inducing effects of GHB do not remain for longer than the above periods as it would compromise a patient's ability to perform normal day to day activities, such as work or driving a car. One embodiment of the invention is a controlled release formulation of GHB designed to maintain a level of GHB in the blood that satisfies the above criteria. In addition to the controlled or extended release properties of one embodiment, there can be an immediate release GHB formulation that is present in or accompanies the controlled release formulation. A sufficient amount of GHB must be present in the blood to initiate the sleep function of GHB and then the controlled release component may engage to maintain the blood concentration above the threshold for a complete sleep of sufficient duration. It has been discovered that administration of food may extend the effects of GHB in some circumstances and care should be taken to consider this effect during administration. See U.S. Pat. Nos. 8,859,619; 8,778,398 and 8,591,922 as well as U.S. Pat. Publication 2012/0076865 among others.

The buffering capacity of GHB may affect gastric pH and compromise performance of enteric-coated dosage forms. Avoidance of the potential impact on gastric pH is another useful feature of the GHB resinate, since it has no effect on gastric pH.

In one embodiment, the present invention is directed to formulations of drugs that are carboxylic acids, as described herein, and are suited to the controlled release of high dose drugs that are highly water soluble. In addition, in certain embodiments, the formulations described herein provide controlled release of drugs that are highly hygroscopic, even where such drugs must be administered at relatively high doses. In particular embodiments, the controlled release formulations are provided as a unit dose or liquid dosage form.

The formulations and dosage forms of the present invention can also include an immediate release component. The immediate release component can form part of a solid controlled release unit dosage form or liquid dosage form (e.g., combined with a controlled release GHB resinate component) or may be a separate immediate release composition. Therefore, an immediate release component may be provided, for example, as a dry powder formulation, an immediate release tablet, an encapsulated formulation, or a liquid solution or suspension. However, the immediate release component may also be formulated as part of a single dosage form that integrates both the above components. The immediate release component can furthermore be an oxybate salt such as sodium, potassium, calcium, or magnesium, the immediate release component can also comprise the GHB resinate particles without modification to retard release, or a combination of these GHB forms.

In specific embodiments, controlled release and immediate release formulations can be dosed together to a subject to provide quick onset of action, followed by maintenance of therapeutic levels of the drug substance over a sustained period of time. However, because the controlled release

component and immediate release component described herein need not be present in a single dosage form, as it is used herein, the phrase "dosed together" refers to substantially simultaneous dosing of the controlled release and immediate release components, but not necessarily administration in the same dosage form. Dosing the controlled release and immediate release components together offers increased convenience, allowing patients to quickly achieve and maintain therapeutic levels of a drug over a sustained period of time, while reducing the frequency with which the drug must be dosed. Furthermore, dosing the controlled release and immediate release components together may avoid the disadvantages of dosing regimens and formulations that result in highly pulsatile plasma concentrations.

Gamma butyrolactone (GBL) is a prodrug for GHB. It can be produced by the dehydrogenation of 1, 4 butanediol. GBL can be hydrolyzed under basic conditions (the use of a metal ion hydroxide) to produce GHB. See Arena, C, et al., "Absorption of Sodium γ-Hydroxybutyrate and its Prodrug γ-butyrolactone: relationship between n vitro transport and in vivo absorption", Journal of Pharmaceutical Sciences, 69(3), (March 1980), 356-358; and Lettieri, J, et al., "Improved Pharmacological Activity via Pro-Drug Modification: Comparative Pharmacokinetics of Sodium Y-Hydroxybutyrate and Y-Butyrolactone", Research Communications in Chemical Pathology and Pharmacology, 22(1), (1978), 107-118.

The required dose of GHB, on a molar basis, is unusually high and quite different from most pharmaceutical agents normally considered for drug-resin complexes. A 9 g dose of sodium oxybate is 71 mMol of oxybate, a carboxylic acid. This stands in contrast to a typical moderately potent active pharmaceutical ingredient (API) having a molecular weight of about 400 daltons and a dose of 400 mg, which results in a molar dose of about 1 mMol. Thus, sodium oxybate dosing is about 70-fold higher (on a molar basis) than a more typical drug.

Much of the dose is required in immediate release form for initial therapeutic benefit. However, due to the buffering effect of oxybate (pKa of 4.5), the immediate-release portion of the dose would cause the gastric pH to increase to about 6. This complicates formulation design, as rate-controlling polymers often have pH-dependent dependent solubility. In particular, if delayed release via enteric coating is desired, then upon release of the immediate release portion of the dose, the concomitant rise in gastric pH could result in at least partial dissolution of the enteric coating, thereby compromising the delayed release function of the enteric coating.

The solubility of sodium oxybate is unusually high. For example, a Xyrem solution is provided as 500 mg/mL concentration in water, or 42 wt %, and its solubility limit is considerably higher. Furthermore, due to the small size and ionic nature of GHB at physiological pH, the drug is unusually mobile in solution. Those skilled in the art will appreciate that these factors complicate and, in many cases, limit conventional approaches for modified release, such as core/shell or matrix formulations, as the high solubility and mobility of GHB would tend to significantly reduce the number of viable approaches using such conventional solubility and diffusivity control technologies.

Furthermore, while extended release oxybate dosage forms are known, such extended release dosage forms are provided as solids, e.g. as tablets. Because the required dose of oxybate is high, such tablets can be quite large, and/or require the administration of multiple tablets. This can be problematic because some patient populations have difficulty swallowing solid dosage forms, or the need to swallow multiple tablets may reduce patient compliance. In addition, the sustained release matrix or coating compositions used to provide extended release are complex and expensive to produce. Accordingly, it would be desirable to provide oxybate (or analogous drugs which require administration in high doses) in an extended release, oral liquid dosage form (including suspensions of oxybate-containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user), using simply, readily controlled processing methods.

A drug-resin complex may address some of these limitations, as the drug is essentially insoluble as long as it remains bound to the resin. Instead, the drug release is regulated by exchange with other anions present in the gut, the most prevalent being chloride. Thus, the nature of the formulation challenge is to limit the diffusion of chloride anion into the dosage form rather than to limit the egress of the soluble drug, oxybate.

Drug-resin complexes including modified release drug-resin complexes are known. However, such complexes would typically be considered unsuitable for very high dose, low molecular weight drugs such as oxybate, because the molar amount of drug required is quite high, which would therefore necessitate correspondingly large amounts of ion exchange resin, particularly if the efficiency of binding is significantly less than 100%. Accordingly, for drugs such as oxybate that are dosed at much higher molar levels, e.g., approximately 100-fold higher compared to typical drug dosing, drug-resin complexes would not be considered acceptable.

In one embodiment, a particularly convenient means of administering drug resonates is as a suspension of individual drug resinate beads. The beads may be a plurality of individual resin beads, each loaded with drug and optionally coated with a rate-controlling polymer and additives to influence its properties (such as permeability, flexibility, etc.). Coating formulations exist to address processing challenges, such as the swelling of beads and retention of film integrity. One such example is methylphenidate resinate beads as shown in U.S. Pat. No. 8,202,537.

In one embodiment, the present invention provides a GHB formulation which delivers a controlled release profile, for example a controlled release profile suitable for once-a-day dosing as described herein. Due to the prolongation of the drug release, compositions of the present invention are useful because the once-a-day dose provides a more consistent supply (release) of GHB to patients who otherwise may have to take multiple doses a day. In one embodiment, the invention provides a multi-particulate composition, for example a suspension (e.g., homogeneous suspension), or solid compositions such as a tablet, capsule, powder, wafer, or strip system comprised of a plurality of such particles and optionally other excipients.

As used herein, the term "controlled release" refers to compositions, for example GHB resinate compositions as described herein, which are characterized by having at least one of the active components having a release over a period of at least about 2 to about 8 hours, or about 4 to 6 hours, including about 2, about 2.5, about 3, about 3.5, about 4, about 4.5, about 5, about 5.5, about 6, about 6.5, about 7, about 7.5, or about 8 hours, inclusive of all ranges therebetween. The release profile may be assessed using in vitro dissolution assays known to those of skill in the art, e.g., USP apparatus 2 (paddle) or, more preferably, apparatus 4 (flow-through cell). Particularly when the molar dose of

oxybate is large and approaches the amount of anion in the dissolution media, a flow-through apparatus is desired so that the media composition and flow rate can better approximate the physiologic state. The release profile can be assessed for example (e.g., for bioavailability determinations), in pharmacokinetic studies using plasma concentrations to assess maximum concentration (C_{max}) and area under the curve (AUC). Such assays are well known to those of skill in the art.

In one embodiment, the present invention provides a drug-ion exchange resin composition for further use in a formulation with conventional pharmaceutically acceptable components to provide ingestible compositions. The finished dose compositions may take the form of liquid preparations, such as suspensions, or solid preparations such as tablets, capsules, liquigels, powders, wafers, strips, etc.

Ion-exchange matrices suitable for use in these preparations are water-insoluble and comprise in most embodiments a pharmacologically inert organic and/or inorganic matrix containing functional groups that are ionic or capable of being ionized under the appropriate conditions of pH. In one embodiment, the ion-exchange matrix is anionic. The organic matrix may be synthetic (e.g., polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene, etc.), or partially synthetic (e.g. modified cellulose and dextrans). The inorganic matrix, in various embodiments, can comprise silica gel modified by the addition of ionic groups, or other similar inorganic materials functionalized with ionic groups. Covalently bound ionic groups may be strongly acidic (e.g., sulfonic acid, phosphoric acid), weakly acidic (e.g., carboxylic acid), strongly basic (e.g., primary amine), weakly basic (e.g. quaternary ammonium), or a combination of acidic and basic groups. In general, the types of ion exchangers suitable for use in ion-exchange chromatography and for such applications as deionization of water are examples of materials suitable for use in the controlled release of drug preparations. Such ion-exchangers are described by H. F. Walton in "Principles of Ion Exchange" (pp: 312-343) and "Techniques and Applications of Ion-Exchange Chromatography" (pp: 344-361) in Chromatography. (E. Heftmann, editor), van Nostrand Reinhold Company, New York (1975). A high exchange capacity is desired to limit quantities of resin needed, and that typical values are about 4 mEQ/g

In one embodiment, the size of the ion-exchange particles is from about 5 microns to about 1,000 microns. In most embodiments the particle size is within the range of about 50 microns to about 750 microns (including about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 550, about 600, about 650, about 700, or about 740 microns, inclusive of all values and ranges therebetween) for liquid dosage forms, although particles up to about 1,000 micron (including the values and ranges herein, and in addition about 800, about 850, about 900, about 950, or about 1000 microns, inclusive of all values and ranges described herein) can be used for solid dosage forms, e.g., tablets and capsules. Particle sizes substantially below the lower limit are generally difficult to handle in all steps of the processing. Both uncoated and coated drug-ion exchange resin particles may be designed within this size range.

Both regularly and irregularly shaped particles may be used as resins. Regularly shaped particles are those particles that substantially conform to geometric shapes such as spherical, elliptical, cylindrical and the like, (e.g., three dimensional shapes readily described by a three dimensional space group) which are exemplified by (but not limited to) any of the ion exchange resins disclosed herein, for example Dow XYS-40010.00 and Dow XYS-40013.00 (The Dow Chemical Company). Irregularly shaped particles are all particles not considered to be regularly geometrically shaped (for example not readily described by a three dimensional space group), such as particles with amorphous shapes and particles with increased surface areas due to surface channels or distortions. Irregularly shaped ion-exchange resins of this type are exemplified by (but not limited to) any of the ion exchange resins disclosed herein, for example Amberlite IRP-69 (Rohm and Haas). Two of the resins of some of the embodiments of this invention are Amberlite IRP-69 and Dow XYS-40010.00. Both are sulfonated polymers composed of polystyrene cross-linked with about 8% of divinylbenzene, with an ion-exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H^+-form). Their essential difference is in physical form. Amberlite IRP-69 consists of irregularly shaped particles with a size range of about 5 microns to about 149 microns produced by milling the parent large size spheres of Amberlite IRP-120. The Dow XYS-40010.00 product consists of spherical particles with a size range of 45 microns to 150 microns.

In one embodiment, suitable ion-exchange resins include anion exchange resins, such as have been described in the art and are commercially available. These resins are particularly well suited for use with acidic drugs including GHB, as well as prodrugs such as GBL, salts, isomers, polymorphs, and solvates thereof, as well as other acidic drugs identified herein and/or known in the art such as salicylates, nicotinic acid, mefanimic acid, methotrexate, furosemide, phenolic drugs such as paracetamol, morphine, and levothyroxine, warfarin, phenylbutazone, indomethacin, barbiturates, phenytoin, sulphonamides, etc.

Any anion exchange suitable for pharmaceutical use can be employed in the compositions of the present invention, particularly strong anion exchange resins. An example of a suitable anion exchange resin is a cholestyramine resin, a strong base type 1 anion exchange resin powder with a polystyrene matrix and quaternary ammonium functional groups. The exchangeable anion is generally chloride which can be exchanged for, or replaced by, virtually any anionic species. Other examples include Type II resins, which contain dialkyl 2-hydroxyethyl ammonium chloride or hydroxide groups. Such Type I and Type II resins are available under the DOWEX® and Amberlite® trade names. A commercially available Cholestyramine resin is PUROLITE™ A430MR resin. As described by its manufacturer, this resin has an average particle size range of less than 150 microns, a pH in the range of 4-6, and an exchange capacity of 1.8-2.2 eq/dry gm. Another pharmaceutical grade cholestyramine resin is available as DUOLITE™ AP143/1094 (Rohm and Haas/Dow), described by the manufacturer as having a particle size in the range of 95%, less than 100 microns and 40%, less than 50 microns. The commercial literature from the suppliers of these and other resin is incorporated herein by reference (PUROLITE A-430 MR; DOW Cholestryramine USP, Form No. 177-01877-204, Dow Chemical Company; DUOLITE AP143/1083, Rohm and Haas Company, IE-566EDS—February 06). Other suitable anion exchange resins include POROS® XQ anion exchange resins available from ThermoFisher Scientific. Both regularly and irregularly shaped particles may be used as resins. Regularly shaped particles are those particles that substantially conform to geometric shapes such as spherical, elliptical, cylindrical and the like, (e.g., three dimensional shapes readily described by a three dimensional space group) Irregularly shaped particles are all particles not

considered to be regularly geometrically shaped (for example not readily described by a three dimensional space group), such as particles with amorphous shapes and particles with increased surface areas due to surface channels or distortions. The regular and irregularly shaped particles can comprise any of the anion exchange resins disclosed herein.

For the oxybate resinate compositions of the present invention, the amount of oxybate present in the resinate should be high to minimize the amount of resin required. Furthermore, in most embodiments, the amount of GHB resinate administered, expressed as GHB mEq (i.e., mmoles) is about 20 to about 120 mEq, including about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, or about 120 mEq, inclusive of all values and ranges therebetween.

The selected ion-exchange resins may be further treated by the manufacturer or the user to maximize the safety for pharmaceutical use or for improved performance of the compositions. Impurities present in the ion-exchange resins may be removed or neutralized by the use of common chelating agents, anti-oxidants, preservatives such as disodium edetate, sodium bisulfate, and so on by incorporating them at any stage of preparation either before complexation or during complexation or thereafter. These impurities along with their chelating agent to which they have bound may be removed before further treatment of the ion exchange resin with a compound to slow drug release and coating with a diffusion barrier.

Various analogous binding reactions can be carried out for binding an acidic drug to an anion exchange resin. These are (a) resin (Cl^- form) plus drug (salt form); (b) resin (Cl^- form) plus drug (as free acid); (c) resin (OH^- form) plus drug (salt form); (d) resin (OH^- form) plus drug (as free acid); (e) resin (OH^- form) plus prodrug (γ-butyrolactone). All of these reactions except (d) and (e) have ionic by-products and the anions generated when the reactions occur compete with the anionic drug for binding sites on the resin with the result that reduced levels of drug are bound at equilibrium. For acidic drugs, stoichiometric binding of drug to resin is accomplished only through reactions (d) and (e). The binding may be performed, for example as a batch or column process, as is known in the art.

Typically the drug-ion exchange resin complex thus formed is collected by filtration and washed with appropriate solvents to remove any unbound drug or by-products. The complexes can be air-dried in trays, in a fluid bed dryer, or other suitable dryer, at room temperature or at elevated temperatures which would not degrade the complex.

In one embodiment, the complexes of the present invention can be prepared by batch equilibration, in which a solution of the drug is contacted with finely divided ion-exchange resin powders. While ion exchange resins are typically provided in very fine particle sizes, which render conventional columnar ion-exchange processes inefficient, such methods can be used for ion exchange resins of suitable particle size. The total ion-exchange capacity represents the maximum achievable capacity for exchanging cations or anions measured under ideal laboratory conditions. The actual capacity which will be realized when loading a drug onto ion exchange resin will be influenced by such factors as the inherent selectivity of the ion exchange resin for the drug, the drug's concentration in the loading solution and the concentration of competing ions also present in the loading solution. The rate of loading will be affected by the activity of the drug and its molecular dimensions as well as the extent to which the polymer phase is swollen during loading.

In one embodiment, a batch or equilibrium process is used to load a drug onto an ion-exchange resin. It is usually desirable to load as much as possible of the drug, such as GHB or GBL, onto the ion exchange resin, as typical GHB doses required for treating excessive daytime sleepiness and cataplexy in patients with narcolepsy are quite high. Low loadings of GHB in the resinate would require quite large amounts of resin, resulting in unit dosages which would be too large to be conveniently administered and resin quantities that may give rise to more adverse effects such as gastrointestinal disturbance. Complete transfer of the drug from the loading solution into the ion-exchange resin is not likely in a single equilibrium stage. Accordingly, more than one equilibration may be required in order to achieve the desired loading onto the ion exchange resin. The use of two or more loading stages, separating the resin from the drug-containing liquid phase between stages, is a means of achieving maximum loading of the drug onto the ion exchange resin, although some loss of drug from the liquid phase of the final loading stage may occur.

The efficiency of loading the drug (e.g. GHB) onto the ion exchange resin can be influenced by the counter ion used in the ion exchange resin. Commercially supplied anionic resins for pharmaceutical use are almost exclusively in the chloride form. However, chloride ions have a much higher affinity for the exchange site in the resin relative to GHB. The affinity can be estimated based on the pK_a of GHB (4.44) relative to other short-chain fatty acids for which affinities are known. On that basis, GHB has approximately 18% affinity relative to chloride on the anion exchange resin. Bicarbonate, on the other hand, has an affinity of about 27% affinity relative to chloride. Therefore, when a bicarbonate-exchanged resin is contacted with GHB, a much higher efficiency of GHB incorporation may be achieved, because the affinity of GHB relative to bicarbonate is about 67% vs. about 18% relative to chloride. Other "intermediate" exchange anions can also be used, especially those with low affinity relative to chloride and much lower cost relative to oxybate. Thus in some embodiments, substantially all of the chloride counter ion of the e.g. commercially available pharmaceutical grade anion exchange resin is replaced with the intermediate anion (e.g. bicarbonate), in one or more batch equilibration steps as required. After rinsing with an appropriate solvent, the ion exchange resin exchanged with the lower affinity anion (relative to chloride) can then be then exchanged with oxybate.

Substantially complete incorporation (i.e., expressed as the percentage of theoretically available ion exchange sites) of oxybate in the anion exchange resin is desirable to minimize the amount of anion exchange resin required to provide a specified dose of drug (e.g. oxybate). In practice, 100% incorporation of the drug can be difficult and/or expensive to achieve, so somewhat less than substantially complete levels of incorporation of drug are also suitable. Typically, levels of incorporation of more than about 75% are acceptable, including about 75%, about 80%, about 85%, about 90%, about 92%, about 94%, about 96%, about 98%, about 99%, or about 100%, inclusive of all values and ranges therebetween.

When a multi-step batch equilibration is needed or desirable, the resinate slurry formed during equilibration can be decanted to remove the solution of oxybate. The decant can be collected for potential recovery of oxybate or waste disposal. The resinate is then rinsed with solvent, such as de-ionized water, and then charged to the batch equilibration

tank where it is contacted with fresh or recovered oxybate to increase the level of incorporation of oxybate. Multiple equilibration steps can be used with fresh or recycled oxybate solution until the desired level of incorporation, as described herein, is achieved.

Recovery of oxybate from a chloride-exchange process can be very challenging due to oxybate's high water solubility and relatively small size. If aqueous processing is used, all chloride salts are soluble. However, when an intermediate anion (e.g. bicarbonate) is used, the solubility can be manipulated with selection of the cationic form of oxybate. If full and complete exchange of oxybate is desired in one step, then the salt form of oxybate is selected such that the salt form of the exchanged anion is insoluble. For example, calcium salts of many exchangeable anions tend to have very low solubilities. Oxybate can be introduced as calcium oxybate, which is highly water-soluble and suitable for an aqueous exchange process. Precipitation drives the exchange process to near-completion, resulting in very high oxybate yield and incorporation. For example, bicarbonate would precipitate as calcium carbonate if the relatively insoluble calcium hydroxide is added in stoichiometric amount at the commencement of batch equilibration, as shown below. Other example intermediate examples include phosphate (precipitating as calcium phosphate), sulfate (precipitating as calcium sulfate), and hydroxide (precipitating as calcium hydroxide).

$$Ca^{++}(GHB^{-})_2+2R—HCO_3 \rightarrow Ca^{++}+2HCO_3^{-}+2R—GHB;R=resin$$

$$Ca^{++}+2HCO_3^{-}+Ca(OH)_2 \rightarrow CaCO_3(s)+H_2O$$

Use of precipitation as a means to drive batch equilibration can result in some difficulties in recovering the resin, as the resinate and precipitate can both be small particles. In some embodiments, the exchange process is carried out under conditions such that all species remain soluble, and therefore the resinate and solution are easily separated. Next, the oxybate is recovered from the solution in a separate vessel by performing a displacement precipitation by addition of another salt or base. For instance, in the above example, the calcium hydroxide can be added in a separate step, thereby avoiding a difficult separation problem. Although this process may provide a somewhat less efficient equilibration per batch cycle, recovery of the un-exchanged oxybate can be nearly 100%, and multiple batch equilibrations can be performed economically. The technique can be more generally applied if sodium oxybate is used in the exchange process, because most sodium salts of the exchanged anion would remain soluble. In the recovery step, a calcium salt or base is added in near-stoichiometric amount to precipitate the exchanged oxybate and enable full recovery of the sodium oxybate. In one embodiment, calcium hydroxide is added to facilitate recovery. Because it has low solubility, calcium hydroxide can be used in excess without appreciably contaminating the recovered sodium oxybate with calcium.

$$Na^{+}GHB^{-}+R—HCO_3 \rightarrow Na^{+}+HCO_3^{-}+R—GHB;R=resin$$

$$2Na^{+}HCO_3^{-}+Ca(OH)_2 \rightarrow CaCO_3(s)+2H_2O$$

In yet another embodiment of processes for forming the GHB resinate, the anion can be recovered by sub-stoichiometric addition of the soluble calcium oxybate to the sodium-exchanged intermediate anion in the recovery process. Most of the sodium oxybate can be recovered and recycled without causing precipitation during the batch equilibration.

In a particular embodiment, bicarbonate can be evolved as CO_2 gas and the sodium ions form sodium oxybate by adding GBL. This avoids a potentially difficult separation of precipitate during recovery. The sodium bicarbonate is first converted to sodium carbonate, and then the sodium carbonate is reacted with GBL to yield sodium oxybate and carbon dioxide as shown below.

$$NaOH+NaHCO_3 \rightarrow Na_2CO_3+H_2O$$

$$2GBL+Na_2CO_3+H_2O \rightarrow 2Na—GHB+CO_2(g)$$

In yet another embodiment, the bicarbonate form of an anion exchange resin (e.g., and type 1 strong base anion exchange resin), prepared, for example by ion exchange of the chloride form with sodium or potassium bicarbonate (or other soluble bicarbonate salts), is equilibrated with a solution of sodium or potassium oxybate. The resulting oxybate resinate can be separated from the oxybate equilibration solution by known methods (decanting, filtering, etc.). The oxybate equilibration solution can then be treated with sodium or potassium hydroxide to increase the pH, and then contacted with GBL. At the elevated pH, the GBL reacts with exchanged bicarbonate to form additional GHB (oxybate) and carbon dioxide, thereby regenerating the oxybate equilibration solution so that it can be reused, as the bicarbonate ions produced during the initial ion exchange/equilibration step is lost as carbon dioxide gas. The regenerated oxybate equilibration solution can then be re-equilibrated with the oxybate resinate formed in the initial equilibration step, so as to further increase the degree of exchange of oxybate in the resinate. The regenerated equilibration solution can be further regenerated, and further equilibrated with the oxybate resinate as many times as is needed or desired to obtain the desired degree of incorporation of oxybate in the oxybate resinate. A further advantage of this method is the minimization of oxybate waste due to the ability to regenerate and recycle the oxybate equilibration solution.

High loading capacity will be favored by high charge density in the drug. A high loading rate is favored by lower molecular weight. Higher drug concentrations in the loading solution, with a minimum of competing ions, will also favor higher adsorption capacity.

Thus, in one aspect, the invention provides drug-ion exchange resin complexes comprising a drug loaded in an ion exchange resin as described herein. The drugs and ion exchange resins may be readily selected from amongst those drugs and resins described herein. In most embodiments, GHB and GBL are suitable drugs. The invention further provides drug-ion exchange resin matrixes defined as follows.

The drug-ion exchange resin complexes of the present invention can readily be formulated with pharmaceutically acceptable excipients according to methods well known to those of skill in the art, for example as described in Remington, The Science and Practice of Pharmacy, 22 Edition Philadelphia College of Pharmacy 2013 Pharmaceutical Press, herein incorporated by reference in its entirety for all purposes. In one embodiment, these formulations contain a substantially coated drug-ion exchange resin complex of the invention, optionally with a compound that will slow the release of the drug. In another embodiment, such formulations may also contain a selected amount of uncoated drug-ion exchange resin complex, optionally with a compound to slow the release as described herein. In certain

formulations, mixtures of coated drug-ion exchange resin complexes and uncoated drug-ion exchange resin complexes are present. These formulations may contain any suitable ratio of coated to uncoated product.

In one embodiment, the controlled release dosage form includes drug loaded onto beads (e.g., ion-exchange beads) in combination with one or more optional excipients, such as binders, fillers, diluents, disintegrants, colorants, buffering agents, coatings, surfactants, wetting agents, lubricants, glidants, or other suitable excipients. In one embodiment of the compositions of the present invention that can be fashioned into a tablet or other solid form, beads containing GHB or GBL can include one or more binders that are known for use in tablet formulations. In one such embodiment, the solid form may include at least one binder selected from hydroxypropyl cellulose (HPC), ethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, carboxymethylcellulose sodium, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate. In specific embodiments, the solid form included in a controlled release dosage form as disclosed herein may comprise binder levels ranging from approximately 1% to 10% by weight. For example, the CR core may include a binder in an amount selected from about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, and 10% by weight, including all ranges therebetween. In certain such embodiments, the amount of binder included in the CR core may range from about 1 to 2%, 1 to 3%, 1 to 4%, 1 to 5%, 1 to 6%, 1 to 7%, 1 to 8%, 1 to 9% and 1 to 10% by weight.

One formulation of the present invention may include one or more lubricants to improve desired processing characteristics. One embodiment of the present invention may include one or more lubricants selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added in a range of about 0.5% to 5% by weight. Particular embodiments may comprise a lubricant in a range of about 0.5% to 2% by weight, about 1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight, inclusive of all ranges therebetween. Still lower lubricant levels may be achieved with use of a "puffer" system during tabletting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation. When "puffer" systems are used for tabletting, the compositions of the present invention can, but need not be, substantially free of lubricant (e.g., include only traces of lubricant deposited by contact with the lubricant coated tablet press).

In certain embodiments, where the compositions of the present invention are provided as liquid compositions, such as suspensions, the compositions of the present invention can further comprise colorants, flavoring agents (natural and artificial), stabilizing agents (EDTA salts, parabens, benzoates), thickeners (tragacanth, xanthan gum, bentonite, starch, acacia, cellulosics), humectants, sweeteners (sucralose, acesulfame K, saccharides, sorbitol, xylitol, mannitol, maltose), etc.

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.

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.

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 some embodiments of the formulations of the present invention, the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof.

The drug-ion exchange resin composition thus prepared may be stored for future use or promptly formulated with conventional pharmaceutically acceptable carriers to prepare finished ingestible compositions for delivery orally, or via other means. In one embodiment, a tablet of the invention is formulated as an orally disintegrating tablet. Such

orally dissolving tablets may disintegrate in the mouth in less than about 60 seconds. See U.S. Patent Publication. 2012/0076865.

In one embodiment, the oral liquid compositions of the present invention may also comprise one or more surfactants in amounts of up to about 5.0% w/v or from about 0.02 to about 3.0% w/v of the total formulation. The surfactants useful in the preparation of the finished compositions of the present invention are generally organic materials which aid in the stabilization and dispersion of the ingredients in aqueous systems for a suitable homogenous composition. In particular embodiments, suitable surfactants are non-ionic surfactants such as poloxamers, polyoxyethylene ethers (BRIJ), alkoxylated fatty acids (MYRJ), polysorbates (TWEENs), macrogol mixtures (Gelucire, Labrasol), and sorbitan esters (SPANs). These are produced in a wide variety of structures and molecular weights.

When present, the surfactant component may comprise from about 0.01 to about 2.0% w/v of the total composition (for example 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2.0% w/v, inclusive of all ranges therebetween) and in particular embodiments will comprise about 0.1% w/v of the total of the composition. One or more additional emulsifiers or surfactants can also be employed in one embodiment of the invention.

The sustained-release profiles of drug can be obtained by using a mix of uncoated and semipermeable coated resonates and by selecting the degree of cross-linking and particle size of the resins without a coating process. Examples of ion exchange resins include simple resonates (i.e., uncoated drug-ion exchange resin complexes), microencapsulated or coated resonates (i.e., coated drug-ion exchange resin complexes), hollow fiber systems (i.e. hollow fibers with drug containing lumen), sigmoidal-release systems. Examples of such drugs are frusemide, cyclosporin, allopurinol and ciprofloxacin. See Mahore et al. Formulation of such drugs as resonates according to the present invention permits particle sizes that make such release characteristics (e.g., sigmoidal) feasible at reasonable coating weights.

Some embodiments of the present invention involve direct synthesis of oxybate resinate from one or more precursors. Using a hydroxide-form Type 1 strong base anion exchange resin, essentially 100% loading efficiency can be achieved with a simple aqueous reaction with GBL.

The ability to prepare an oxybate resinate, at high loading, in a one step process from GBL can be amenable to point-of-use synthesis (either in patient's hands or at clinical site), as it does not involve shipping or handling the regulated API (GHB). Such a direct synthesis can be carried out using a batch or equilibrium process as described herein, wherein a GBL loading solution is contacted with the particulate hydroxide-form strong base anion exchange resin. The GBL reacts in situ to form an ionic complex of oxybate with the ion-exchange resin, and releasing water as a by-product. It is possible to get 100% yield as well as 100% loading efficiency (i.e., oxybate ionically bound to 100% of the available binding sites) on the resin by such processes. For example, loading efficiencies higher than about 65% (e.g., 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, or about 100%, including ranges therebetween, can be achieved). Because GBL is uncharged and the reaction does not produce ionic byproducts, there are no anions to compete for reaction on the site. Such conditions can achieve 100% reaction on the resin, so the hydroxide-form resin can be used safely, whereas in other applications this may not be possible for patient safety reasons because any unexchanged hydroxide would leave the resin as sodium hydroxide, raising the pH at site of delivery and potentially causing gut wall irritation.

The one-step process is also advantageous because it simplifies purification of the GHB resinate. Because the reaction occurs on the resin and not in the bulk solution, any byproducts that would be made are rinsed off the product. These include any of the impurities in the GBL starting material, as well as unreacted GBL.

Because of the unusually large molar amount of GHB in the compositions of the present invention, relative to the molar quantity of anion present in the gut, the present inventors have found that the compositions of the present invention can provide sustained release without the use of diffusion controlling coatings on the resinate particles. The present inventors have recognized that because the volume and anion content of gastric juice in the fasted state is lower than the molar dose of GHB required for treating the conditions described herein, the rate of GHB release is strongly influenced by the rate of physiological production of anions, and therefore suitable GHB release profiles can be provided without the use of diffusion controlling coatings. For example, while the resinate beads are retained in the stomach, the release of GHB from the resinate beads provided by ion exchange with gastric ions (mainly Cl^-) can be limited by the rate of stomach acid secretion. Similarly, as the resinate beads transit the duodenum and small intestine, the remaining dose of bound GHB can exceed local anion capacity. Thus, the rate of GHB release can be limited by the rate of secretion or diffusion of anions into the gut.

The basal anion capacity of the GI tract is quite small. As summarized in McConnell (Int J Pharm 2008, 364: 213-226, Table 1), fasted state basal values of bile salts are so low that they may be ignored. The fasted state chloride balances are 4.6 mEq in the stomach and 13.1 mEq in the small intestine. Compared to an oxybate dose of about 100 mEq, there is almost an order of magnitude deficiency in resident anion capacity for exchange. Such a situation would not occur with the vast majority of drugs having doses in the <1 mMol range.

	Stomach	Small intestine
Volume, mL	45	105
Chloride, mM	102	125
Total mEq	4.6	13.1

Therefore, the present inventors have discovered that the release of the ion-exchange resin-bound oxybate can be limited by secretions of anions in the GI tract, of which chloride is dominant. In the stomach, basal acid output (as chloride) is about 3 mEq/h in the fasted state. Even in the event that fed-state behavior is induced upon dosing, the fed state maximum secretion is only about 25 mEq/h. Therefore, the stomach cannot support full exchange at rates required to impart a meaningful duration of effect.

Chloride is actively secreted in jejunum, at a rate of about 4 mEq/h/30 cm under conditions where 120 mM chloride is already present. (Davis GR, et al, Active chloride secretion in the normal human jejunum, J Clin Invest 66:1326-1333 (1980)) This translates to a basal rate of about 32 mEq/h in absence of a chloride gradient. In presence of a gradient, the present inventors have found that the contribution of passive

diffusion can be sufficient, but may still provide a meaningful impediment to full and timely release of oxybate from the resin.

In the ileum, chloride secretions are substantially less, as characterized by Turnberg. (Turnberg LA et al, Interrelationships of chloride, bicarbonate, sodium, and hydrogen transport in human ileum, J. Clin Invest, 49: 557-567 (1970)). Most chloride secretion is associated with bicarbonate exchange when levels are high. One skilled in the art would appreciate that the perfusion studies by Turnberg indicate that chloride secretion in the ileum would almost certainly be insufficient to support the required exchange with GHB-resinate. For example, even in the extreme case where bicarbonate is almost 90 mM and chloride is only 40 mM, the chloride secretion—taking into account the whole length of ileum—would be expected to be at most 23 mEq/h. In the more typical case where bicarbonate is 40 mM, chloride is actually absorbed rather than secreted—even when chloride levels are set at 40 mM. Yet ileal fluid is maintained isotonic.

To further add to the limitations of biology, the reservoir of small intestinal fluid is small and not well distributed. Only about 10% of the physical volume of the small intestine is filled with fluid. The fluid is not continuously and evenly distributed, as reported by Schiller (Schiller C, et al, Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging, Aliment Pharmacol Ther 2005; 22:971-979) but rather the majority of fluid exists in about 4 fluid pockets that access a relatively small amount of available surface area. This is not very limiting for non-resinate dosage forms, as long as drug dissolution can occur, as once the drug is dissolved, it can access most of the surface area of the small intestine for absorption. A resinate, on the other hand, requires exchange with dissolved anions in order to provide release of the drug. As exchange occurs, oxybate is released to, and chloride is depleted from, the surrounding fluid. Further exchange is limited until oxybate is absorbed and chloride is replenished in the surrounding fluid—both processes that require fluid contact with intestinal surface. Therefore, if only 10% of the intestinal surface is physically available at any given time, the rate of chloride replenishment must be 10-fold higher to reliably compensate. One skilled in the art considering these unusual aspects would conclude that, in the face of insufficient resident anion capacity in the small intestine, a resinate dosage form would not release its drug completely and, furthermore, what release occurs may not be well-regulated.

Given the above observations, permeability and amount of film may require adjustment to achieve the intended release profile.

Optionally, the release of GHB can be tailored by changing the bead size and/or degree of crosslinking of the beads to provide additional resistance to diffusion. For example, larger resinate beads have a lower surface area/volume ratio than smaller resinate beads, and therefore would release GHB more slowly than the smaller beads in the presence of a solution of the same ionic strength. Similarly, the degree of crosslinking of the beads relates to the degree of swelling of the beads, which in turn is related to the rate at which ion exchange, and this drug release can occur. Specifically, more highly crosslinked beads swell less, and thus have slower ion exchange kinetics, compared to less highly crosslinked beads, Thus, the kinetics of drug release can also be controlled by manipulating the degree of crosslinking of the beads. Effects of particle size, particularly 100 microns or greater, and crosslinking, particularly 4% or greater, that may be modest under normal circumstances may be more impactful in the absence of a rate-controlling coating and when gut anion concentrations are substantially diminished.

If no diffusion controlling coating is required, other processing schemes for making the resinate can be considered to improve manufacturing flexibility. For example, instead of using ~100 micron beads, the drug (e.g., GHB or GBL) can be loaded onto larger beads (e.g., 600 micron beads), and then ground to the desired particle size, particle size distribution, consistency, etc. to select or control the desired release characteristics. This could be carried out in an aqueous suspension, so that no isolation or drying of the resinate would be needed. Moreover, if there is no need to coat the particles (e.g., with a diffusion for coating), the irregular shape or dispersity in size distribution of ground particles, which is normally a complicating factor for coating processes, is not an issue.

In other embodiments, the compositions of the present invention can provide differential displacement of drug (e.g. oxybate) from the resinate. Core/shell release characteristics in the resinate beads can be provided by (a) loading oxybate onto an ion exchange resin such that complete loading is achieved, then (b) coating the beads with a portion of lipophilic agent (i.e. lipophilic anion) having much higher selectivity for the ion-exchange resin than GHB. The lipophilic agent will deposit in the outer shell, at the first sites it contacts, and will be relatively immobile resulting in reversible blockage of the bead pores. Suitable lipophilic agents would be, for example, sulfate salts of medium or long-chain fatty acids, such as sodium lauryl sulfate (SLS), or sulfonic esters, such as dioctyl sulfosuccinate (docusate). Other suitable agents may include alkylbenzene sulfonates, 2-naphthalene sulfonate, phenol, salicylic acid, or any other species that may bind more strongly to the resin than oxybate. In particular embodiments, the lipophilic agents are those which are bulky or present hydrophobic tails that may further hinder diffusion of chloride into the resin pore, or oxybate out of the pore after exchange. Although many effective agents may, in other contexts present toxicity concerns, because such agents are strongly bound to the resin, exposure of the agent to the patient is limited. In one embodiment, the lipophilic agent acts as a diffusion barrier both by blocking pores and by facilitating pore blockage by other hydrophobic agents, for example those added during manufacturing, or which may be present in the patient's digestive tract after administration. For example, if sufficient amounts of a surfactant such as SLS is employed, then a non-ionic hydrophobic agent may be more effectively introduced into the bead pore volume due to its compatibility with the hydrophobic "tail" of the SLS molecule. This provides retarded initial release of the drug (e.g., GHB). In other embodiments, further heat treating of the resinate beads can reduce the variability of release, or further retard release. In other embodiments the compositions of the present invention can comprise more than one population of beads, in which one or more of the bead populations is treated with a lipophilic agent, a combination of a lipophilic agent and a hydrophobic agent, or heat treated to as to provide the desired release characteristics. For example, untreated beads would provide more immediate or faster release, and treated beads would provide delayed or slower release.

If further control of release is needed, in a further embodiment the present invention provides a novel method for preparing GHB-containing resinate beads coated with a diffusion rate controlling coating. This embodiment takes advantage of the driving force supplied by reaction of GBL on the active (hydroxide-bearing) sites of hydroxide-form

ion exchange resin beads, and the relatively high diffusion characteristics of the small and uncharged GBL molecule. Hydroxide-form ion-exchange resin beads (of any size) can be coated with a flexible film, such as PVAcetate, Eudragit RS, cellulose acetate 398, a mixture of Eudragit RS/RL or Eudragit NE, ethylcellulose, or an enteric such as Eudragit L100, L55 or FS100 with suitable plasticizer. The coated ion-exchange resin beads are then suspended in de-ionized water to equilibrate. GBL is introduced to the suspended beads, which then diffuses through the rate-controlling film, and reacts progressively with the OH-bearing sites within the resin. Sufficient batch equilibration time is provided to ensure complete reaction. The excess GBL is washed off, and the resulting wet resinate beads have a sustained release coating over GHB resinate, which were formed without starting with GHB resinate. This process may be useful for point-of-use preparation, or can improve the utilization of GBL in preparing the product: no GHB or GBL is lost due to processing during coating, as no GBL is present during the coating process.

In one embodiment of the present invention, the present formulation is administered to a patient once nightly. The patient is administered between 4 g and 10 g GHB/day, or 6 g and 9 g/day. Any of the compositions described herein can be used to provide retarded or delayed release of GHB. For example, the GHB resinate beads may be presented in hydrated form as part of an aqueous suspension, or may be provided as dried beads for mixing with water immediately prior to ingestion or to be taken without water (e.g., as a powder, tablet, capsule etc.). As discussed herein, Type 1 strong base anion exchange resins swell in the presence of water, to an extent that depends on the degree of crosslinking and the nature of the anion bound to it. In the dried state, the sustained release resinate beads of the present invention can hydrate more slowly if release-retarding agents are used. As the beads hydrate, the diffusion of physiologically produced anions of the gastrointestinal tract (e.g. mainly chloride) into the beads can accelerate, thus producing a delayed or gradually increasing rate of release of oxybate.

In another embodiment, a water permeable but relatively insoluble coating is employed over the dry resinate beads such that, when the dry beads are suspended in water, water diffuses through the coating to hydrate and swell the resinate beads. The resulting expansion of the beads causes the coating to rupture, and allow release of the GHB. Suitable polymers for preparing such coatings include one or more of cellulosics such as ethyl cellulose, cellulose acetate, cellulose phthalate; polyvinyl acetate, acrylic polymers and copolymers such as those available under the Eudragit® trade name (e.g., Eudragit® NE30D, RL, and RS resins). Such coatings can be plasticized or unplasticized, and coated onto the beads using methods well-known in the art (pan coating, fluidized bed coating, etc.).

As discussed herein, the dose of GHB required for treating excessive daytime sleepiness and cataplexy in patients with narcolepsy is quite high, resulting in the administration not only of relatively large masses of GHB composition, but also water required for administration (particularly when the GHB composition is aqueous). However, since oxybate is administered at night, administering large quantities of water can cause bed-wetting. Accordingly, if administered as an aqueous suspension, the highest practical solids loading is desired. The factors which affect the solids loading (volume fraction) of the suspension include the medium used for dilution (water vs. alcohol) and its viscosity, the degree of swelling of the resinate, the sphericity and uniformity of the beads, and surface charge. See Seno and Yamabe, The Rheological Behavior of Suspensions of Ion-Exchange Resin Particles, Bulletin of the Chemical Society of Japan Vol 39, 776-778 (1966), herein incorporated by reference in its entirety for all purposes. In various embodiments, the compositions of the present invention can be administered as suspended resinate particles in a gel, suitable for ingestion by squeezing from a pouch. In other embodiments, the compositions of the present invention can be dosed in two stages: an initial loading dose followed by a chasing dose. Both the loading and chasing dose comprise suspended beads, but the chasing dose is less concentrated. In still other embodiments, the GHB resinate beads can be administered dry, e.g. by having the patient suck the dry beads through a tube or straw. In such embodiments, an added glidant, which is an excipient used in the art to facilitate powder flow by reducing interparticle friction and cohesion, can be used to facilitate administration. They are used in combination with lubricants as they have no ability to reduce die wall friction. Non-limiting examples include fumed silica, talc, and magnesium carbonate.

The oxybate resinate compositions of the present invention can include an immediate release and an extended release component of oxybate. Such compositions can include, for example, a combination of a population of uncoated resinate beads and a population of resinate beads with a diffusion rate controlling coating as described herein; a single resinate bead population that provides immediate release by ion exchange with physiological anions (e.g. chloride), followed by extended release of oxybate controlled by physiological production of e.g. chloride; combinations of populations of resinate beads having different particle sizes and/or crosslinking densities to control release; or any combination of immediate release and extended release resinate beads disclosed herein.

In one embodiment, the compositions of the present invention may be an immediate-release alternative to Xyrem®. Xyrem® has a steep dose-response curve, and inadvertently taking two doses at the same time would have an adverse effect on the patient. If sodium oxybate is instead provided in resinate form for immediate release, as described herein, the capacity of the stomach and small intestine to provide exchangeable anion would limit the consequences of an inadvertent overdose. A 4.5 g dose of Xyrem is 35.7 mEq oxybate. If the stomach has about 5 mEq chloride, then about 30 mEq of additional exchangeable anion must be provided with the resinate formulation of the present invention to ensure complete release of oxybate. This can be achieved by inclusion of exchangeable anion in the formulation, for example glycine or other amino acids, chloride, or in particular citrate. This embodiment would enable rapid release of the oxybate by providing supplementing exchangeable anions in the stomach.

In another embodiment, the supplemental anions are provided by digestion of proteins administered with or as part of the formulation. The resulting amino acids are then available for exchange with the resin and can provide a more convenient means of providing a large amount of supplemental anion.

In yet another embodiment, the supplemental anions are provided by digestion of a triglyceride administered with the formulation. When the triglyceride empties into the small intestine, lipolysis will generate anions available for exchange. In general, triglycerides of short-chain fatty acids (such as triacetin or tributyrin) can provide better oxybate release than medium- or long-chain triglycerides, because the binding affinity of the resulting anions are higher due to their pKa and size. Triglycerides with at least one short-

chain fatty acid component are also suitable, particularly pharmaceutically acceptable short-chain triglycerides such as triacetin.

If the resinate particles are film-coated, then supplemental anions can be provided as separate coated particles, such that the supplemental anion is available when needed. The supplemental anion can be selected such that it is not absorbed rapidly yet has an affinity for the resinate that is much higher than that of oxybate. It can be particularly useful to target or enhance release of the supplemental anion in the ileum where chloride secretory deficit may be most pronounced, since absorption of organic acids might be considerably less in that location. Citric acid, glycine, and mesalazine (5-aminosalicylic acid) are examples of suitable supplemental anions. A non-limiting list of other suitable anions (or conjugate acids) includes pharmaceutically acceptable salts selected from the group consisting of chlorides, acetates, lactates, bicarbonates, sulfates, citrates, tartrates, malates, maleates, malonates, glutarates, succinates, fumarates, aspartates, glutamates, and combinations thereof.

These supplemental anions can be coadministered with the oxybate compositions of the present invention, for example within about an hour (before or after) of administering the drug resinate (e.g., oxybate resinate) compositions of the present invention, or simultaneously therewith. The amount of such supplemental anions can range from about 20 to about 200 mmoles, including about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, about 120, about 125, about 130, about 135, about 140, about 145, about 150, about 155, about 160, about 165, about 170, about 175, about 180, about 185, about 190, about 195, or about 200 mmoles, inclusive of all values and ranges therebetween. The supplemental anions can themselves be capable of anion exchange directly upon contact with the drug resinate (e.g., exchanging with the oxybate of the oxybate resinate), or can be "pro-anions"—that is, form anions upon biotransformation after administration to the patient. Non-limiting examples of such "pro-anions" are those described herein, such as triglycerides or proteins. The amount of such "pro-anions" suitable for use in treating patients according to the present invention are amounts that produce between about 20 and about 200 mmoles of anions, as described hereinabove.

If sustained release is desired, then extending gastric emptying can somewhat compensate for deficiencies in the jejunum and, particularly, the ileum. Reliably extending gastric emptying in the fasted state is very challenging. Although some investigators have found that administration of resinate particles can result in mucoadhesion, the unusually high molar doses of GHB of the resinate compositions of the present invention, approximately 100 mEq, will effectively cover the entire surface of the stomach many times over. Thus, observations made with conventional resinate formulations would not apply to GHB resonates. Therefore, a more effective means of promoting gastric retention would be administration of the compositions of the present invention with food or caloric liquid.

The oxybate compositions of the present invention, for example oxybate resinate compositions, provide therapeutically effective levels of oxybate over a period of at least about 3 to about 8 hours. In some embodiments, the composition can be considered to comprise a single population of resinate beads, wherein at least a portion of the resinate beads releases the oxybate quickly upon administration (essentially upon contacting physiologically produced anions such as chloride), and a remaining portion of the resinate beads releases oxybate more slowly, either controlled by the physiological rate of production of anions such as chloride, or by modification of the release characteristics of the resinate beads themselves (e.g., by providing a diffusion controlling coating, by control of bead diameter, or crosslinking density, or other method as described herein). If the compositions of the present invention comprise two or more distinct bead populations (distinguished by their oxybate release characteristics), the rapid (or immediate) release population provides therapeutically effective levels of oxybate for up to about 3 hours (including 1 or 2 hours) after administration, and the other population(s) provide therapeutically effective levels of oxybate for about 3 to about 8 hours (including 3, 4, 5, 6, 7, or 8 hours) after administration.

Xyrem for its approved indications is effective at between 6 g and 9 g administered twice nightly in equal amounts about 4 hours apart. A sustained release equivalent may require a matching AUC as compared to 9 g Xyrem. As disclosed in US2012076865, the overall relative bioavailability of an appropriately-timed sustained release would have at most about 75% relative to Xyrem. Therefore, about 12-13 grams of sodium oxybate would be required, or about 100 mMols.

Suitable blood levels of oxybate are at least about 10 mg/L, ranging up to about 70 m/L, maintained over a period of about 5-8 hours as described herein. For example suitable blood levels of oxybate can be about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, or about 70 mg/L, inclusive of all ranges therebetween.

The following examples are included to demonstrate particular 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 particularly suitable 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.

All documents cited herein, including patents, patent publications, and non-patent publications are herein incorporated by reference in their entirety for all purposes.

EXAMPLES

Example 1

A gel-type Type 1 strong base anion exchange resin, Dowex 1X2 (Dow Chemical), 100-200 mesh was loaded with GHB as follows. Calcium oxybate was loaded onto resin in a batch equilibration by combining 10 mL of 4 M calcium oxybate solution (approximately 490 mg/mL), 31.7 mL of de-ionized water, and 20.27 g of Dowex 1X2 wet resin as chloride form with 2% crosslinking. After mixing for 2 hours, the resin was filtered under mild vacuum using a Buchner funnel. It was then washed with 700 mL of de-ionized water in approximately 100-150 mL aliquots to remove any free oxybate. The wet beads were then dried in a 60° C. oven for 3.5 hours, and finally sized through a 36-mesh screen. The resinate beads were assayed by suspending 1.5 g of resinate in 12.5 g of 1 M calcium chloride and allowing them to equilibrate overnight at room tem-

perature. The solution was analyzed by HPLC, and the measured oxybate released from the beads was 1.09 mEq per gram of dry resinate. The calculated loading efficiency was 1.14 mEq/gram dry resin, or 33% of the theoretical exchange capacity of the resin.

Example 2

GHB resinate beads were prepared by contacting GBL with another Type 1 strong base anion exchange resin (Amberlite IRN78, Dow Chemical) having a median particle size of about 0.63 mm, as the hydroxide form with 8% crosslinking. Batch B1 was prepared with a 2:1 molar ratio of GBL to hydroxide-bearing sites by suspending 26.78 g of wet resin in 41.2 g of de-ionized water. While stirring, 8.28 g of GBL was added, and the reaction was monitored by HPLC analysis of unreacted GBL. The reaction was largely complete after 30 minutes. After 90 minutes, the resin was filtered under mild vacuum, rinsed with de-ionized water to remove unreacted GBL, and then placed in a 60° C. oven overnight to dry.

Batch B2 was prepared by reacting GBL in only 16% molar excess over hydroxide-bearing sites on the same resin. 2.6 g of GBL was added to 20 g of wet resin (as supplied) while stirring by hand with a spatula. About 5.3 g of additional water was added to facilitate blending. After about 1 hour, the mass was placed in the 60° C. oven overnight to complete the reaction, if necessary. The beads were then rinsed with de-ionized water (70 mL), filtered under mild vacuum, and transferred to the 60° C. oven for drying over 3 days. The two batches were analyzed for oxybate content by first suspending 1.0 g of resinate in 20 mL of 2 M NaCl for 2 hours with stirring. 10 mL of the resulting solution was then titrated with 1 N HCl and the results were compared with a blank of 10 mL of 2 N NaCl. The initial pH values of B1 and B2 were 7.0 and 8.3, respectively, thus indicating that very little, if any, unreacted hydroxide was present in the resinate product. The oxybate titration indicated that GHB loadings of 4.2 and 4.3 mEq/g dry resin for B1 and B2, respectively. The result further indicates that complete reaction occurred, as the theoretical capacity of the resin is approximately 4 mEq/g.

Example 3

A larger batch of GHB resinate beads are prepared by reacting GBL with Amberlite IRN78 under conditions represented by Batch B2. GBL (36.9 g) is slowly added to a slurry of wet resin (Amberlite IRN78, 279 g) and water (about 200 g). The reaction is allowed to proceed for at least 1 hour at room temperature, with stirring. The product is vacuum filtered, then rinsed with several volumes of de-ionized water. The wet product is then placed in a 40° C. oven to dry overnight. 2.1 g of dried GHB resinate beads are then administered to each of 6 beagle dogs, fasted and weighing approximately 10-12 kg, by oral gavage. Blood is sampled at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 10 h for determination of plasma GHB content.

Example 4

Amberlite IRN78, a hydroxide form Type 1 anion exchange resin, is charged to a vessel and contacted with a 1M solution of sodium oxybate in a 2:1 stoichiometry to resin equivalents. After about 2 hours of equilibration, the mixture of sodium oxybate and sodium hydroxide is filtered from the resulting resinate. A sample of the solution is titrated to determine sodium hydroxide content, and then an equivalent amount of calcium oxybate is charged to the solution to precipitate calcium hydroxide. The calcium hydroxide is filtered from the solution of sodium oxybate, and the recovered sodium oxybate solution is returned to the equilibration tank and contacted with the wet resinate for 2 hours. The resinate is then filtered, and filtrate is recovered. The recovered filtrate is processed with calcium oxybate as in the first step, and set aside for future use. The resinate product is washed with several volumes of de-ionized water, and then dried.

Example 5

Cholestyramine (chloride form) is charged to a vessel and contacted with 1M sodium bicarbonate in a 2:1 stoichiometry (bicarbonate to resin). Five cycles of batch equilibration (2 h each) are conducted. The solutions in each cycle are not recycled, and resinate is rinsed with 2 volumes of de-ionized water between each cycle.

The wet, bicarbonate-exchanged resin is then contacted with 1M sodium oxybate in a single equilibration step in a 2:1 molar ratio of oxybate to resin. After 2 h, the resinate is filtered, and filtrate collected. Separately, the GHB-resinate is then washed with several volumes of de-ionized water. A sample of the first filtrate is titrated for bicarbonate content, and then a stoichiometric amount of calcium oxybate is added to the batch filtrate. The precipitated calcium carbonate is removed by filtration of the suspension, and the sodium oxybate solution is recovered and stored for future use.

Example 6

The above examples can involve difficult separation steps, as precipitated calcium carbonate is a thick slurry of fine particles at the concentrations used. In this example, filtration is avoided by use of a reaction in which the byproduct forms carbon dioxide rather than a precipitate.

The wet, bicarbonate-exchanged resin of Example 5 is contacted with 1M sodium oxybate in a single equilibration step in a 2:1 molar ratio of oxybate to resin. After 2 h, the resinate is filtered, and filtrate collected. Oxybate is recovered and bicarbonate is removed from the filtrate by addition of a stoichiometric amount of sodium hydroxide such that the bicarbonate is converted to carbonate by the reaction: $NaOH+NaHCO_3 \rightarrow Na_2CO_3+H_2O$. The pH drives this reaction to completion.

Next, GBL is added at a 1:1 stoichiometry. Sodium carbonate reacts with the GBL with the evolution of carbon dioxide gas, which drives the reaction to completion: $2\ GBL+Na_2CO_3+H_2O \rightarrow 2\ Na\text{-}GHB+CO_2(g)$. Optionally, a small excess of sodium hydroxide can be added to avoid conversion to bicarbonate during the reaction. This overall process avoids the filtration of carbonate, recovers all the sodium as unexchanged sodium oxybate, and replaces the exchanged sodium oxybate with new oxybate derived from GBL.

Example 7

Soy protein isolate is compressed into oblong or oval tablets of approximately 1000 mg, using compression aids such as fillers, microcrystalline cellulose, and lubricants as required. The tablets are enteric coated separately with two different polymers to achieve dissolution and release of the soy protein isolate in the jejunum and ileum. One batch is

coated with Eudragit L30D-55 (jejunum-targeted), and the other is coated with Eudragit L100 (ileum-targeted). At least two of each kind of tablets are taken with one dose of GHB-resinate (35.7 mEq of resinate equivalent to 4.5 g oxybate) in a glass of water. This provides at least 36 mEq of amino acid content, as the protein is hydrolyzed. By releasing the protein in the small intestine rather than stomach, complete and rapid digestion is avoided. Instead, the protein is digested to amino acids more gradually as it transits the small intestine and as the tablet disintegrates. The amino acids are therefore available to facilitate exchange of the GHB-resinate taken concomitantly.

We claim:

1. A formulation of gamma-hydroxybutyrate comprising:

a plurality of immediate release particles comprising gamma-hydroxybutyrate;

a plurality of modified release particles comprising gamma-hydroxybutyrate;

a viscosity enhancing agent; and

an acid;

wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.

2. The formulation of claim **1**, wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof.

3. The formulation of claim **1**, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

4. The formulation of claim **1**, wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate.

5. The formulation of claim **4**, wherein the lubricant is magnesium stearate.

6. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 4.0 g to 12.0 g of sodium gamma-hydroxybutyrate.

7. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 4.0 g, about 6 g, about 7.5 g or about 9 g of sodium gamma-hydroxybutyrate.

8. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 6 g of sodium gamma-hydroxybutyrate.

9. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 7.5 g of sodium gamma-hydroxybutyrate.

10. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 9 g of sodium gamma-hydroxybutyrate.

11. The formulation of claim **1**, wherein 8 h after administration of the formulation provides a blood concentration ranging from 10 mg/L to about 40 mg/mL.

12. The formulation of claim **1**, wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL.

13. The formulation of claim **1**, wherein the formulation is a multiparticulate composition.

14. A unit dose comprising a formulation of gamma-hydroxybutyrate,

wherein the formulation comprises:

a plurality of immediate release particles comprising gamma-hydroxybutyrate;

a plurality of modified release particles comprising gamma-hydroxybutyrate;

a viscosity enhancing agent; and

an acid;

wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.

15. The unit dose of claim **14**, wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof.

16. The unit dose of claim **14**, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

17. The unit dose of claim **14**, wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate.

18. The unit dose of claim **17**, wherein the lubricant is magnesium stearate.

19. The unit dose of claim **14**, wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL.

20. The unit dose of claim **14**, wherein the unit dose comprises an amount of gamma-hydroxybutyrate equivalent to from 4.0 g to 12.0 g of sodium gamma-hydroxybutyrate.

21. The unit dose of claim **14**, wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 6 g of sodium gamma-hydroxybutyrate.

22. The unit dose of claim **14**, wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 7.5 g of sodium gamma-hydroxybutyrate.

23. The unit dose of claim **14**, wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 9 g of sodium gamma-hydroxybutyrate.

24. The unit dose of claim **14**, wherein the unit dose is a sachet.

* * * * *

EXHIBIT 8

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/210,064	03/23/2021	Clark ALLPHIN	JAZZ-025/04US 306882-2491	6700

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Cooley LLP / Jazz Pharmaceuticals
1299 Pennsylvania Ave., NW, Suite 700
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EXAMINER	
ZHANG, YANZHI	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
06/18/2021	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):

zIPPatentDocketingMailboxUS@cooley.com

Office Action Summary

Application No.	Applicant(s)		
17/210,064	ALLPHIN et al.		
Examiner	**Art Unit**	**AIA (FITF) Status**	
YANZHI ZHANG	1617	Yes	

-- 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 MONTHS 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 03/23/21.

☐ 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) 1-24 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) 1-24 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/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Status

This action is a response to papers filed on December. 10, 2020. Claims 1-24 are pending in the application and under consideration on the merit.

Priority

Applicant claims that this application is a continuation of U.S. Application Ser. No. 17/118,041, filed December 10, 2020, which is a continuation of U.S. Application Ser. No. 16/448,598, filed June 21, 2019, which is a continuation of U.S. Application Ser. No. 15/047,586, filed February 18, 2016 (now U.S. Patent No. 10,398,662), which claims priority to U.S. Provisional Application Ser. No. 62/117,889, filed February 18, 2015 ((001) of the specification as filed). However, there is no support for the claimed subject matter in prov' 889. The word "modified" is found 4 times, two of them are related to modified cellulose and silica gel ((0028) of the specification as filed). The other 2-paragraph are reproduced below for clarity.

(008) In still another embodiment of the invention, the hydroxide-bearing resin beads are coated with a flexible film, then loaded with GBL which, in turn, will diffuse through the film and react with the resin and form the GHB resinate in-situ. Coating will achieve further controlled release. Example films include PVAcetate, Eudragit RS, ethylcellulose, cellulose acetate or an enteric coating such as acrylic acid-based Eudragit L100,FS100 or L55, cellulose acetate phthalate, and shellac. It is understood that these films can be modified with pore formers to adjust permeability or degree of enteric protection. The coating may also be combined with suitable plasticizer and anti-tack agents to facilitate coating. Finely ground resin beads may also

be encapsulated within polysaccharide gel structures that confer enteric protection, through ionotropic gelation as with calcium alginate encapsulation. It is understood that these films can be modified with pore formers to adjust permeability or degree of enteric protection (008) of the instant specification.

(0022) The solubility of sodium oxybate is unusually high. For example, a Xyrem solution is provided as 500mg/mL concentration in water, or 42 wt%, and its solubility limit is considerably higher. Furthermore, due to the small size and ionic nature at physiological pH, the drug is unusually mobile in solution. Those skilled in the art will appreciate that these factors complicate and, in many cases, limit conventional approaches for modified release, such as core/shell or matrix formulations.

Support for the claimed subject matter of "a formulation of gamma-hydroxybutyrate comprising: an immediate release portion comprising gamma-hydroxybutyrate; a modified release portion comprising gamma-hydroxybutyrate" can be found in paragraph (0014) for controlled or extended release) and (0016-7), particularly, for immediate release component on top of page 6.

Therefore, the earliest priority for the claimed subject matter is 02/18/2016, the effective filing date of 15/047,586.

Information Disclosure Statement

The Information Disclosure Statements filed 03/30/21 (21-page), 04/27/21 (2-page), and 06/07/21 (3-page) are in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. Accordingly, the information disclosure statements in English are fully considered by the examiner. The foreign language references, are only considered to the extent where an English translation available or examiner understands that language. A signed copy of form 1449 is enclosed herewith.

Claim Rejections - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-23 are rejected under 35 U.S.C. 103 as obvious over Allphin et al ("Allphin", US 20120076865 A1, and published March 29, 2012).

Claims 1-23 embrace a formulation or a unit dose comprising a formulation of gamma-hydroxybutyrate comprising: an immediate release portion comprising gamma-hydroxybutyrate; a modified release portion comprising gamma-hydroxybutyrate; a viscosity enhancing agent; and an acid; wherein the viscosity enhancing agent and the acid are separate from the immediate release portion and the modified release portion.

In addition, claims 1 and 14 use the open-ended transitional phrase “comprising”. Thus, they allow for the presence of additional unrecited steps or components.

Claim interpretation: modified release portion. INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

As evidenced by Jha, titled modified release formulations to achieve the quality target product profile (QTPP) (see attached non-patent literature, published 01 August, 2012), “The United States Pharmacopoeia definition of an MR (modified-release) system is that: “the drug release characteristics of time, course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms...” This includes technologies that modify the site of drug delivery. The successful formulation of an MR device requires a comprehensive understanding of the mechanisms of drug release from the macroscopic effects of size, shape and structure through to chemistry and molecular interactions. The benefits offered by MR systems include reduced dosing frequency with improved patient compliance, better and more uniform clinical effects with lower incidence of side effects and possible enhanced bioavailability.

'Modified release' means that the escape of the drug from the tablet has been modified in some way. Usually this is to slow the release of the drug so that the medicine doesn't have to be taken too often and therefore improves compliance. The other benefit from modifying release is

that the drug release is controlled and there are smaller peaks and troughs in blood levels therefore reducing the chance of peak effects and increasing the likelihood of therapeutic effectiveness for longer periods of time. Thus, modified release portion is broadly interpreted as being modified in some way. Therefore, controlled release in the prior art reads on the limitation of modified release in the instant claims.

A unit dose is the amount of a medication administered to a patient in a single dose (quote from https://www.collinsdictionary.com/us/dictionary/english/unit-dose).

Allphin is directed to controlled release dosage forms for high dose, water soluble and hygroscopic drug substances (title). Allphin teaches that controlled release dosage forms for delivery of a drug selected from GHB (gamma-hydroxy butyrate) and pharmaceutically acceptable salts, and complexes of GHB. The controlled release dosage forms described herein may incorporate **both controlled release and immediate release** (IR) **formulations** in a **single unit dosage** form (abstract and [0065], read on the limitation of immediate release portion and modified release portion in the intent claims 1 and 14). Allphin also teaches that, in one embodiment, the controlled release dosage form comprises a CR core that includes drug substance in combination with **one or more excipients**, including **binders** selected from **hydroxypropyl cellulose**, ethylcellulose, hydroxypropyl methylcellulose, fillers, diluents, disintegrants, colorants, buffering agents, coatings, surfactants, wetting agents, **lubricants** selected from at least one of **magnesium stearate**, stearic acid, calcium stearate, hydrogenated castor oil; glidants, or other suitable excipients ([0044] and Table 1A on page 10 of the specification, read on the limitation of the instant claim 2, 4-5, 15, and 17-18). Allphin further teaches that the IR formulation is provided as an **immediate release component of a controlled release dosage form** as described herein. A unit dosage form that integrates both controlled

release and immediate release components can increase the convenience and accuracy with which a drug such as GHB is dosed to patients by providing a unit dosage form that not only provides quick onset of action, but also sustained delivery of GHB to the patient over a prolonged period of time ([0066], advantage of integrating both). Allphin indicates that sodium oxybate oral solution, the FDA approved treatment for cataplexy and excessive daytime sleepiness associated with narcolepsy, contains 500 mg sodium oxybate/ml water, adjusted to pH = 7.5 with **malic acid** ([0009], read on the limitations of acid in the instant claims 1, 3, 14, and 16). In man, the plasma half-life of **sodium oxybate** given orally is about 45 minutes and doses of **2.25 grams to 4.5 grams** induce about 2 to 3 hours of sleep and the controlled release dosage forms deliver therapeutically effective amounts of drug over a period selected from a range of about 4 to about 10 hours, about 5 to about 10 hours, about 5 to about 12 hours ([0009] and [0032]). Based on the nature of the drug, Allphin additionally teaches that, in order to maintain therapeutic efficacy, **4.5 g to 9 g** of drug must be administered to the patient in two separate doses within 2 to 5 hours. In certain embodiments, for a given dose of GHB, administration of GHB using controlled release dosage forms can achieve a rapid rise in plasma concentrations of GHB, but with a prolonged duration of plasma levels above 10 μg/mL ([0035], read on the limitations of the amount in the instant claims 6-12 and 19-23). The total amount of drug contained within an integrated IR/CR dosage form according to the present description may be between about 500 mg and about 1,400 mg ([0075]). Furthermore, Allphin teaches that a granulation used to form CR cores and granulation parameters and **particle size** distribution are shown in Tables 1B and 1C, respectively ([0077], read on the limitation of multi-particulates in the instant claim 13).

Regarding wherein clause, the viscosity enhancing agent and the acid are separate from the immediate release portion and the modified release portion, in the instant claims 1 and 14, it is believed Allphin teaches or implies the limitation because the tablets from example 1 are coated with a solution containing ethylcellulose.

Regarding the amount of oxybate or oxybate equivalent of in the instant claims 6-10, and 20-23, the principal of law is "[Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). This rule is limited to cases in which the optimized variable is a "result-effective variable." In re Antonie, 559 F.2d 618, 620 (CCPA 1977). In this case, Alshaikh have taught various amount depending on the formulations. Thus, finding the optimum or workable ranges by routine experimentation is *prima facie* obvious.

Claim 24 is rejected under 35 U.S.C. 103 as obvious over Allphin et al ("Allphin", US 20120076865 A1, and published March 29, 2012) in view of Luhn (non-patent literature, Pharmaceutical Technology Europe, Volume 23, Issue 1, published January 7, 2011).

The teachings of Allphin have been discussed as applied to claims 1-23. Allphin does not expressly teach the formulation is a sachet. The deficiency is cured by Luhn.

Luhn is directed to using excipients in powder formulations (title). Luhn teaches that orally disintegration tablets (ODTs) have become very popular and are the starting point into a generation of drug products where patient friendliness is the decisive criteria to gain share in a saturated market environment; however, **sachets** can be faster and easier compared with ODTs (2nd para. on page 1/3 of the attached PDF, read on the limitation of sachet in the instant claim 24). Luhn also teaches that sachets may also beneficial when looking at compliance issues

within geriatric patient groups. Direct oral applications mean you don't need water to dissolve the powder or swallow the tablet. Sachets also do not look like a pill — it's important not to underestimate the psychological effects associated with a dosage form (bridging para. of pages 1-2/3 of the attached PDF).

It would have been obvious for one of ordinary skill in the art, as of the effective filing date of the claimed invention, to choose sachet form of sodium oxybate as taught by Luhn as the particular dose form to be incorporated into the method of Allphin o take advantage of sachet being faster and easier.

CONCLUSION

No claim is allowed.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to YANZHI ZHANG whose telephone number is (571)272-3117. The examiner can normally be reached on Monday-Friday 8am-5pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 5712720646. 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.

/YANZHI ZHANG/
Primary Examiner, Art Unit 1617

EXHIBIT 9

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
EMA/CHMP/EWP/280/96 Rev1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms

Draft Agreed by Pharmacokinetics Working Party	**October 2012**
Adoption by CHMP for release for consultation	21 February 2013
End of consultation (deadline for comments)	15 September 2013
Agreed by Working Party	23 October 2014
Adoption by Committee	20 November 2014
Date for coming into effect	1 June 2015

This guideline replaces the 'Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation)' (EMA/CPMP/EWP/280/96 Corr*)

Keywords	***Modified release, prolonged release, delayed release, transdermal drug delivery systems (TDDS), bioequivalence, pharmacokinetics, biowaiver, in vitro dissolution, generics, oral, intramuscular and subcutaneous***

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Executive summary

The primary purpose of this guideline is to define the studies necessary to investigate the efficacy, safety, biopharmaceutic and pharmacokinetic properties of modified release formulations following oral, intramuscular and subcutaneous administration and transdermal dosage forms in man and to set out general principles for designing, conducting and evaluating such studies. The revision of the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (EWP/QWP/1401/98) generated the necessity of consequential adjustments. Furthermore the guideline provides updated requirements for transdermal drug delivery systems (TDDS) and addresses recommendations for specific modified release formulations, e.g. for intramuscular/subcutaneous depot formulations.

1. Introduction (background)

1.1. Types of Modified release and dosage forms

Modified release dosage forms are formulations where the rate and/or site of release of the active ingredient(s) are different from that of the immediate release dosage form administered by the same route. This deliberate modification is achieved by special formulation design and/or manufacturing methods. Modified release dosage forms covered by this guideline include orally, intramuscularly, subcutaneously administered modified release and transdermal dosage forms.

- **Prolonged release dosage forms:** Prolonged release dosage forms are modified release dosage forms showing a sustained release compared to that of an immediate release dosage form administered by the same route.
- **Delayed release dosage form:** The release of the active substance from such modified release dosage forms is delayed for a certain period after administration or application of the dosage. The subsequent release is similar to that of an immediate release dosage form.
- **Multiphasic release dosage forms:**
    - **Biphasic Release:** The first phase of drug release is determined by a fast release dose fraction providing a therapeutic drug level shortly after administration. The second extended release phase provides the dose fraction required to maintain an effective therapeutic level for a prolonged period.
    - **Pulsatile Release:** Pulsatile drug release is intended to deliver a burst of drug release at specific time intervals.
- **Multiple-unit:** A multiple unit dosage form contains a plurality of units e.g. pellets or beads each containing release controlling excipients, e.g. in a gelatine capsule or compressed in a tablet
- **Single-unit**: The single-unit dosage forms consist of only one unit, e.g. osmotic tablet.
- **Intramuscular/subcutaneous depot formulations:** A depot injection is usually a subcutaneous or intramuscular product which releases its active compound continuously over a certain period of time. Subcutaneous depot formulations include implants.
- **Transdermal drug delivery systems (TDDS):** A TDDS or transdermal patch is a flexible pharmaceutical preparation of varying size containing one or more active substance(s) to be applied on the intact skin for systemic availability.

There are two main types of transdermal patch systems depending on how the drug substance is dispersed in other patch components:

- Matrix systems with drug release based on the diffusion of drug substance.
- Reservoir systems containing a specific liquid drug compartment and release is controlled by a membrane.

1.2. Rationale for Development

The development of a modified release formulation has to be based on a well-defined clinical need (e.g. improvement of patient compliance and/or safety) and on an integration of physiological, pharmacodynamic and pharmacokinetic considerations.

The dossier submitted in support of an application for a marketing authorisation must provide a complete justification of:

- The physical form of the modified release device and the mechanism of the release form;
- The choice of the dosage form, defining the in vitro and in vivo performance of the product;
- The choice of active substance contents per unit of the dosage form;
- The clinical rationale for the new dosage form, particularly in relation to the proposed indications and posology.

1.2.1. The clinical rationale

A *prolonged release dosage form* may be acceptable if the active substance can produce the desirable clinical effect with a different PK profile than that resulting from an immediate-release form. A prolonged release formulation may offer several advantages over an immediate-release form. For example:

- reduced fluctuations in drug plasma concentrations, which may result in more continuous effects and/or reduced incidence and/or intensity of adverse drug reactions,
- lower frequency of administration and thereby potentially improvement of patient compliance,
- non-oral route of administration (IM/SC and TDDS)

A *biphasic modified release form* may be considered if a rapid onset of action is required in addition to subsequent prolonged release characteristics.

Development of a *delayed release dosage form* may be considered to protect the active substance from the acid environment of the stomach, to protect the stomach from the active substance, or when the active substance is intended to be released in a defined segment of the intestine.

Development of a *pulsatile release dosage form* may be considered when treatment needs to be adjusted to a circadian rhythm of the underlying condition or when lower frequency of dosing is desirable, but the fluctuating plasma concentration profile of the immediate-release formulation is necessary for efficacy.

1.2.2. Considerations for use and posology

The conditions of administration of the modified release formulation and, where appropriate, its use in conjunction with an immediate release formulation should be clearly outlined in the following situations:

- At the initiation of treatment;
- When titration is required;
- For maintenance of therapeutic effect;
- In the management of acute conditions;
- In special populations such as the elderly, children, and patients with renal or hepatic insufficiency. Lack of dose strengths of the modified-release form to cover all required dose levels, e.g. a lower dose for special populations, should be justified.

When appropriate, recommendations should be given for switching between immediate release and modified release formulations. If applicable, specific recommendations should be provided to ensure optimum conditions of use (e.g. instructions not to chew or crush tablets, etc.).

2. Scope

The aim of this guideline is to define the studies necessary to investigate the characteristics of modified release drug delivery systems in humans and to set out general principles for designing, conducting and evaluating respective studies. However, the precise types and number of studies to be performed have to be defined on a case-by-case basis taking into consideration the intrinsic properties of the active substance, the route of administration, the type of the delivery system and the intended therapeutic indication(s). The guideline deals with oral formulations, intramuscular depot formulations, subcutaneous implants, and transdermal dosage forms containing chemically defined drug substances.

Separate guidance and standards are required for each of the circumstances in which a modified release (MR) formulation might be developed. These circumstances fall into three groups:

- Applications for modified release forms of new chemical entities (NCE)
- Application for a modified release formulation of a drug that is authorised in a formulation with a different release rate (e.g. immediate release formulation)
- Abridged applications for modified release forms referring to a marketed modified release form, e.g. applications according to Article 10(1) or 10(3)

For generic prolonged release or delayed release products this guideline provides guidance on bioequivalence studies that are not covered by the current guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98).

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with the Annex I of Directive 2001/83/EC as amended, as well as European and ICH guidelines for conducting clinical trials, including those on:

- General Considerations for Clinical Trials (ICH E8, CPMP/ICH/291/95)
- Guideline for Good Clinical Practice (ICH E6 (R1), CPMP/ICH/135/95)

- Statistical Principles for Clinical Trials (ICH E9, CPMP/ICH/363/96)
- Structure and Content of Clinical Study Reports (ICH E3, CPMP/ICH/137/95)
- CHMP Guidance for Users of the Centralised Procedure for Generics/Hybrid Applications (EMEA/CHMP/225411/2006)
- Pharmacokinetic Studies in Man (Eudralex, Volume 3, 3CC3a)
- Guideline on Quality of Oral Modified Release Products (EMA/492713/2012)
- Guideline on Quality of Transdermal Patches (EMA/CHMP/QWP/911254/2011)
- Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98)
- Fixed Combination Medicinal Products (CPMP/EWP/240/95)
- Note for Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95)
- Guideline on Reporting the Results of Population Pharmacokinetic Analyses (CHMP/EWP/185990/06)
- Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004)
- Studies in Support of Special Populations: Geriatrics (ICH E7, CPMP/ICH/379/95) and Questions and Answers - EMA/CHMP/ICH/604661/2009
- Guideline on Bioanalytical Method Validation EMEA/CHMP/EWP/192217/2009
- Guidance on photosafety evaluation of pharmaceuticals (ICH S10)

The guideline should also be read in conjunction with relevant guidelines on pharmaceutical quality. The test products used in the bioequivalence study must be prepared in accordance with GMP-regulations including Eudralex volume 4.

Clinical trials, including bioequivalence and pharmacokinetic studies, conducted in the EU/EEA have to be carried out in accordance with Directive 2001/20/EC. Trials conducted outside of the EU and intended for use in a Marketing Authorisation Application in the EU/EEA have to be conducted to the standards set out in Annex I of the community code, Directive 2001/83/EC as amended.

4. Applications for modified release dosage forms of new chemical entities

If a new chemical entity is developed first as a modified release formulation, the submitted dossier should contain the appropriate pharmaceutical and chemical data, necessary preclinical studies and a complete clinical data package as for any full application.

4.1. Pharmacokinetic studies required for oral MR formulation of a new chemical entity

A complete pharmacokinetic data package is required for a new chemical entity developed as MR formulation. Additional documentation specific to the MR dosage form include studies evaluating factors affecting the biopharmaceutic performance of the modified release formulation (see section 5.1.4 and 5.1.5).

In order to avoid a duplication of studies (e.g. time and dose dependency), it is advisable to conduct PK studies with the MR formulation as early as possible during clinical development. Initial phase I studies (e.g. first in man studies) are generally conducted with an oral solution or an immediate release formulation where basic pharmacokinetic characteristics of an active substance (Tmax, Vd, Cl, elimination half-life, route(s) of excretion) are obtained. Interaction studies and studies in special populations should preferably be conducted with the modified release formulation. In addition to general pharmacokinetic investigations relevant to any new formulation (e.g. single and multiple dose PK parameters, food effect when relevant and dose proportionality), the mechanism for the control of drug release should be described. This is generally done through bioequivalence/relative bioavailability studies conducted using different formulations where, for instance, the amount of a release controlling excipient varies if possible. The obtained pharmacokinetic profiles in vivo are recommended to be correlated with in vitro drug release profiles if possible (see Appendix II).

4.1.1. Food effect studies with oral modified release forms

Food interactions may be related to the drug substance itself and/or the formulation, the latter being most important in the case of modified release (MR) products.

The optimal experimental conditions to produce a food effect include the ingestion of a predefined high- fat meal immediately before dosing (see section 5.1.4.1).

Food effect studies for new MR formulations are recommended to be conducted early during drug development so that appropriate recommendations regarding intake in relation to food can be included in clinical efficacy and safety studies. This is also important from a safety perspective as the risk for dose dumping should be evaluated before initiation of efficacy and safety studies.

To evaluate the influence of food on the absorption of the drug substance from the new formulation a 2-way cross over study (MR formulation fasting and fed) may be sufficient. If there is a clinically relevant food effect on the MR formulation, additional study(ies) with an oral solution can be considered, to evaluate if the food effect is related to the formulation or to the drug substance. In this situation, a single dose 4 way crossover study; MR fed and fasted versus oral solution (or immediate release (IR) formulation if a solution is not feasible) fed and fasted can be conducted.

In case there is a clinically relevant food-effect, additional food-interaction studies might be needed to support dosing recommendations, i.e. studies of the effect of different kinds of food with respect to caloric and nutritional content of food, studies investigating the effect of a meal taken at certain time period before and after the drug, etc. (see Note for Guidance on the Investigation of drug interactions (CPMP/EWP/560/95)).

4.2. Pharmacokinetic Studies required for Transdermal Drug Delivery Systems (TDDS) of a new chemical entity

If a new chemical entity is developed to be administered as a TDDS formulation, the submitted dossier should contain the appropriate pharmaceutical and chemical data and a complete non-clinical and clinical data package as for any full application.

Generally, the kinetics of drug delivery from TDDS is determined by the interplay between the active substance, the formulation and the skin. In-vitro and in-vivo investigations should be conducted to evaluate drug diffusion characteristics and the rate limiting step that determines systemic availability i.e. drug release and/or skin reservoir and/or other formulation related particularities. Pharmacokinetic investigations should comprise single-dose and multiple-dose investigations considering particular

aspects like e.g. application site-dependent absorption, fluctuation, lag-times and concentration time profile after patch removal. Aiming to establish an IVIVC is advisable. In case of several dose strengths, dose proportionality issues should be adequately addressed (see section 5.1.3).

In addition to conventional phase I studies, skin irritation, sensitisation (see also appendix I), phototoxicity (see also ICH S10 Guidance on photosafety evaluation of pharmaceuticals) and patch adhesion (see also appendix IV) should be investigated. To evaluate patch adhesion, the influence of external factors (e.g. heat, sun cream) should be considered. TDDS usually deliver drugs intended for elderly people. Therefore tests should be performed in individuals with similar skin conditions as the expected patients (see also appendix IV). The Product Information Leaflet should provide clear instructions on the use in special situations (e.g. sauna). To avoid medication errors that arise from poor visibility, the development of invisible patches should be considered conservatively. In these cases the usage of prominent ink as printing on the patches to increase noticeability is encouraged.

4.3. Pharmacokinetic Studies required for intramuscular/subcutaneous Depot formulations of a new chemical entity

The kinetics of intramuscular depot formulations is determined by the interplay between the active substance, the formulation and the muscle tissue. In-vitro and in-vivo investigations should be conducted to evaluate drug diffusion characteristics from the IM/SC depot and the rate limiting step that determines systemic availability i.e. drug release and/or other formulation related particularities. Pharmacokinetic investigations should comprise single-dose and multiple-dose investigations considering particular aspects like e.g. application site-dependent absorption, fluctuation and lag-times. Aiming to establish an IVIVC is advisable. In case of several dose strengths, dose proportionality issues should be adequately addressed.

5. Application for a modified release formulation of a drug that is authorised in a formulation with a different release rate

Modified release forms are developed based on the rationale that there is a relationship between the pharmacological/toxicological response and the characteristics of systemic exposure to the active substance/metabolite(s). The aim of the modified release formulation is therefore, in most cases, to reach a similar total exposure (AUC) to active substance as for the immediate release formulation. This does not necessitate that the same nominal doses are given (the modified release formulation may have a different extent of absorption or metabolism).

In general modified-release formulations are not bioequivalent to their immediate release form. Consequently PK data alone may not be sufficient for evaluating whether the benefit/risk ratio of the modified release formulation is comparable to the corresponding doses of the immediate release form. Therefore additional clinical data will generally be required, unless otherwise justified as mentioned in section 5.2.

Whenever the strength of the new modified release formulation differs from those approved for the immediate release product this difference and the possible resulting different dosage regimen has to be highlighted very clearly in SmPC, PIL and labelling as most important routine risk minimisation measures to avoid medication errors. The applicant has to prove that the benefits of the new formulation outweigh the potential risks (e.g. medication error) linked with this product.

The new formulation should be characterised in appropriate single dose and multiple dose pharmacokinetic, pharmacodynamic and clinical efficacy/safety studies. Recommendations regarding pharmacokinetic studies to characterise the formulation are given in section 5.1 and the need for therapeutic studies in section 5.2. Additional studies may in certain cases be needed, e.g. pharmacokinetic studies to characterise the metabolic profile may be required in case the modified release product is administered by a new route of administration.

Toxicological, pharmacological or clinical tests to define the intrinsic properties of the active substance are not required assuming a similar total systemic exposure of active substance/metabolites for the modified and immediate release formulations.

The marketed immediate release product of the same active substance should serve as the reference product. The final market formulation should in general be used in the pharmacokinetic and therapeutic studies, unless it can be justified that differences between the study formulation and final market formulation do not affect release characteristics and bioavailability.

5.1. Pharmacokinetic studies

The purpose of these studies is to characterise the modified release formulation in vivo by investigating:

- the rate and extent of absorption
- fluctuations in drug concentrations at steady state
- inter-subject variability in pharmacokinetics arising from the drug formulation
- dose proportionality
- factors affecting the performance of the modified release formulation
- the risk of unexpected release characteristics (e.g. dose dumping)

The studies are based on concentration measurements of the active substance and/or metabolite(s) or, occasionally, in conjunction with determination of an acute pharmacodynamic effect. Due to the substantial formulation impact the requirements about metabolites given in the "Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98)" is not applicable in this case. Active metabolites should be measured since a change in absorption rate or route of administration may modify the extent and pattern of metabolism.

The studies can be performed either in healthy volunteers or in patients in case of safety concerns.

Whenever multiple dose studies are performed it should be demonstrated that steady state has been reached. Achievement of steady-state is assessed by comparing at least three pre-dose concentrations for each formulation, unless otherwise justified. In case of no accumulation (i.e. insignificant levels at the end of the dosing interval) based on the criteria outlined in section 6.1) multiple dose studies are not required.

In terms of concomitant food intake, the multiple dose bioavailability study should be performed under the SmPC labelled condition during dosing to steady state. If the SmPC states a certain timing of food intake in relation to drug administration, this timing should be used throughout the study, also on the day of pharmacokinetic profiling. If the SmPC recommends intake in the fasted state (without specifying time frame) or irrespective of food, a worst-case fasted condition (e.g. overnight fast before and continued 4 hours fast after dose) should in general be used on the day of profiling. If the SmPC

recommends intake under fed conditions normo-caloric meals should be used throughout the study including profiling days unless different meal conditions are requested by the SmPC.

5.1.1. Rate and extent of absorption, fluctuation

Rate and extent of absorption from a modified release formulation should be evaluated by comparison with an immediate release formulation following single dosing and if there is accumulation also following repeated dosing.

The pharmacokinetic parameters of interest for single dose studies may include $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, residual area, C_{max} , t_{max}, $t_{1/2}$ and t_{lag} and for multiple dose studies $AUC_{(0-\tau)}$, $t_{max,ss}$, $C_{max,ss}$, $C_{min,ss}$ and fluctuation. The pharmacokinetic parameter(s) chosen as primary for the comparison, i.e. the parameter(s) considered most likely to reflect efficacy and safety should be justified.

It should be demonstrated that the modified release formulation has the claimed release characteristics. It is encouraged to employ deconvolution of the concentration-time data for the modified release formulation against an appropriate immediate release formulation (see Appendix II for more detail) in order to obtain the cumulative absorption (or in vivo release) versus time profile for the modified release formulation. Both the cumulative amount absorbed and rate of absorption versus time should be used to support the claimed release characteristics.

Fluctuation in drug concentrations should be studied following repeated dosing. Unless otherwise justified, the modified release product should produce similar or less fluctuations as the immediate release product.

In those cases where the modified release formulation is to be administered to patients already treated with an immediate release dosage form (switching), the need for specific dosing instructions during the switch should be considered to maintain steady state concentrations.

Dose levels and strengths to be evaluated

If the active substance and the MR formulation (see section 5.1.3) exhibit linear pharmacokinetic properties it may be sufficient to compare the modified release formulation and the immediate release formulation after single and, in case of drug accumulation, after multiple dose administration at one dose level (see also recommendations given in section 6 general considerations).

If the active substance or the MR formulation (see section 5.1.3) exhibit nonlinear pharmacokinetics (in the therapeutic plasma-concentration range) it is necessary to compare the modified release formulation and the immediate release formulation at least at the highest and the lowest dose level. If the IR and MR formulation display different extent of non-linearity additional strengths may need to be compared.

5.1.2. Variability

The inter-individual variability of the pharmacokinetic parameters of interest should be determined in the single dose or multiple dose studies described in section 5.1.1 and should be compared between the modified and immediate release formulation. The variability for the modified release formulation should preferably not exceed that for the immediate release formulation unless it is adequately justified in terms of potential clinical consequences.

5.1.3. Dose proportionality

Whenever there are several strengths or when several single units can be taken simultaneously to achieve the desired dose, dose proportionality for different strengths / doses of the modified release formulations should be adequately addressed. Dose proportionality should be evaluated by means of a single dose and, in case of drug accumulation, a multiple dose study, where the PK parameters of interest of all the strengths/doses are compared after dose adjustment. The criteria described in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) for dose proportionality based on AUC only and 25% acceptance range are not applicable in this case since these criteria only apply for strength selection for bioequivalence studies.

5.1.4. Factors affecting the performance of a modified drug formulation

5.1.4.1. Food

The influence of food on the bioavailability of oral modified release formulations must be investigated in a single dose study.

The optimal experimental conditions to produce a food effect include the ingestion of a predefined high-fat high-calorie meal immediately before dosing. It is recommended that subjects should start the meal 30 minutes prior to administration of the drug product and finish this meal within 30 minutes. The meal should be a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal. This test meal should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate and fat, respectively. The composition of the meal should be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%)).

The design of the food effect study depends on which other studies are conducted comparing the new oral modified release formulation with the approved immediate release formulation and if there is a clinically significant food effect on the immediate release formulation.

If there is no clinically relevant food effect on the immediate-release formulation, a 2-way cross-over study comparing the modified release formulation in fasted and fed states could be sufficient (given that other studies compare the modified release and the immediate release formulations under fasting conditions).

In case of known clinically relevant food effects for the immediate release formulation, a 4-way cross-over study comparing the modified release formulation in fasted and fed states and the immediate release formulation in fasted and fed states could be useful to quantify the food effect on each formulation.

Whenever there are several strengths, the food effect can be investigated for one of the strengths only if the products are proportional in composition (e.g. multi-particulate dosage forms or proportional tablets), have the same manufacturing process, exhibit linear pharmacokinetics and their dissolution profiles are similar in a range of dissolution media. Generally, the highest strength should be tested, unless otherwise justified. In case the above conditions are not fulfilled, it is necessary to investigate the food effect at the highest and the lowest strengths or the extreme cases based on a bracketing approach.

For the assessment of food effect besides AUC and C_{max}, it may also be valuable to compare the modified release characteristics by verifying that the shape of the concentration – time profiles are not significantly altered.

The clinical relevance of the effect of food should be discussed both from an efficacy and a safety perspective. When needed, dose recommendations with respect to intake of the product in relation to meals should be given. Additional studies with other types of food or with intake of the product at certain time intervals before and after a meal may be needed to support the proposed dose recommendations (see also CPMP/EWP/560/95 Guideline on the Investigation of Drug Interactions)

If the formulation or the manufacturing process is changed during drug development in a way that potentially affects release characteristics, a new evaluation of the food effect for the final formulation may be needed.

Different type of administration: The labelling of certain multiple unit formulations can recommend that the product can be opened and the pellets/beads can e.g. be sprinkled on soft foods, dispersed in a glass of non-carbonated water and swallowed without chewing or administered through a gastric tube. For the labelling to indicate this additional type of administration, additional stability and in vitro dissolution testing showing equivalence between the closed and the opened formulation is necessary. The absence of BE studies imitating the additional options of administration should be justified.

5.1.4.2. Gastro-intestinal function

If an oral modified release formulation is to be usually co-administered with active substances affecting gastrointestinal physiology (e.g. opioids) it is necessary to investigate the performance of the oral modified release formulation under these conditions.

If the oral modified release formulation is intended for patients with markedly altered gastrointestinal function the modified release formulation may need to be studied also in those patients (see also section 5.1.5.1).

5.1.4.3. Unexpected release characteristics (e.g. dose dumping)

Unintended, rapid drug release of the entire amount or a significant fraction of the active substance contained in a modified release dosage form is often referred to as "dose dumping". Depending on the therapeutic indication and the therapeutic index of an active substance, dose-dumping can pose a significant risk to patients, either due to safety issues or diminished efficacy or both.

For modified release formulations the risk for unexpected release resulting in unforeseen exposure should be excluded. If dose dumping is observed (e.g. much higher peak exposure with an inadequate modified release profile) or suspected (e.g. absence of levels of a labile active substance in gastro-resistant formulation for some subjects) the product should be reformulated to avoid this deficiency of the biopharmaceutical quality.

Much higher peak exposure might also be observed in prolonged release products due to active substance release in the stomach for an extended period of time (i.e. at delayed gastric emptying) with a subsequent absorption of the released dose once the gastric content is emptied. As this unintended increased exposure is not related to a particular product failure causing uncontrolled release, dosing recommendations with regard to e.g. concomitant food intake should be implemented to avoid a prolonged residence in the stomach.

Effects of alcohol

Some modified-release oral dosage forms contain active substances and/or excipients that exhibit higher solubility in ethanolic solutions compared to water. Concomitant consumption of alcoholic beverages with such products may induce dose dumping.

For such formulations, *in vitro* studies of the release in alcohol solutions should be performed. Where accelerated active substance release is seen in vitro either at high or low alcohol concentrations over a short period of time or at lower alcohol concentrations over a longer period of time, the product should be reformulated. Only in those cases where it can be justified that an in vitro alcohol interaction cannot be avoided by reformulation, an in vivo study could be accepted, in order to substantiate that such an interaction is unlikely to occur in vivo.

The in vivo investigation of alcohol-induced dose-dumping should compare the systemic exposure when the modified release product is ingested with a reasonable amount of alcohol on an empty stomach. The results of the study should be assessed not only with respect to the clinical relevance of the group mean change but also to the clinical consequences of the observed individual ratios.

If a significant dose-dumping effect is likely in vivo and cannot be avoided by reformulation, the benefit/risk of the product needs to be carefully considered. Contraindicating alcohol as only measure is generally not considered an appropriate means to address a formulation interaction with alcohol. Information on relevant interactions with alcohol, in case of possible clinically relevant potentiation or a harmful additive effect should be given in the product information.

In addition other label warnings and risk management strategies need to be discussed.

5.1.5. Other points to consider

5.1.5.1. Special populations

Different physiological conditions (e.g. transit times, pH, food intake and type of food) in vegetarian, paediatric and elderly patients or in patients routinely taking antacids should be taken into consideration especially when designing oral once daily MR formulations.

5.1.5.2. Influence of site of application on plasma levels (SC/IM depot formulations, TDDS)

The effect of different sites of application of SC/IM depot formulations or TDDS on the absorption of the active substance should be investigated if the application site is not limited to one body area.

Safety and tolerability at the site of application should be assessed.

In case of SC/IM depot formulations or TDDS it should be investigated that not only the plasma levels are within the therapeutic concentrations at the end of the dosing interval but also how the plasma levels decrease after removal of the depot formulation or TDDS.

5.1.5.3. Multiphasic modified release products

There are modified release preparations that have been developed solely in order to mimic a TID or QID dosage schedule. In these cases the plasma concentration - time profile of the modified release preparation should be equivalent with the immediate release formulation given in the dose schedule that is imitated unless compareable efficacy and/or safety is supported by additional clinical data.

5.1.5.4. Prolonged residence time in the stomach

Gastric emptying of single unit dosage forms that do not disintegrate in the stomach may be prolonged and highly erratic. The consequences of this effect on the enteric coating of delayed release formulations are largely unpredictable. If for an acid labile active substance release occurs prior to stomach emptying degradation of the active substance can result and non-existing concentration profiles can be obtained.

Furthermore the release of the active substance may be considerably delayed due to a prolonged residence in the stomach. Therefore the sampling period should be designed such that measurable concentrations are obtained, taking into consideration not only the half-life of the active substance but also the possible occurrence of this effect to make sure that influence of delayed gastric emptying is adequately characterised.

5.2. Therapeutic studies

As a principle, comparative clinical efficacy and safety data are needed in addition to PK data for modified release products developed after the immediate release formulation, unless adequately justified. As the efficacy and safety of the immediate release product is known, the major issue would be to demonstrate that the new modified release formulation is as safe and effective as the existing formulation. Additional benefits of the new formulation should be shown or justified, if claimed.

However, in exceptional cases, if the assessment of concentration-effect relationship indicates that there is a well-defined relationship between plasma concentration(s) of the active substance /active metabolite(s) and clinical response, clinical trials may be considered unnecessary. In this case the same or a better level of efficacy and safety has to be concluded from PK/PD studies.

When assessing PK/PD relationships for modified-release products, the differential effects on efficacy and safety due to differences in rate of absorption and fluctuation should be determined since it is important not only to establish concentration - effect relationships, but also to determine the significance of differences in the shape of the steady state concentrations versus time profile for a modified release product regimen as compared to the approved immediate release product regimen. Tolerance to therapeutic effects and toxic effects related to drug exposure, concentration, absorption rate and fluctuation should also be examined.

5.2.1. Waiving of therapeutic studies

In principle therapeutic studies are necessary.

However, therapeutic studies might be waived in case at least one of the following conditions is met:

- bioequivalence between the reference and the test product is shown in terms of $C_{max,ss}$, $C_{min,ss}$ and $AUC_{(0-\tau)ss}$ because the new modified product is developed to actually mimic the performance of product with an different release mechanism and its dosage regimen e.g. a pulsatile multiphasic release dosage form containing pellets with different lag time.
- bioequivalence between the reference and the test product is shown in terms of $C_{max,ss}$, $C_{min,ss}$ and $AUC_{(0-\tau)ss}$ despite differences in the shape of the plasma concentration-time profile if it is possible to justify that the difference in shape has no relevance for efficacy and safety based on the exposure – response and profile shape - response relationships.

- there is a well-defined therapeutic window in terms of safety and efficacy, the rate of input is known not to influence the safety and efficacy profile or the risk for tolerance development and
    - bioequivalence between the reference and the test product is shown in terms of $AUC_{(0-\tau),ss}$ and
    - $C_{max,ss}$ for the new MR formulation is below or equivalent to the $C_{max,ss}$ for the appoved formulation and $C_{min,ss}$ for the MR formulation is above or equivalent to the $C_{min,ss}$ of the approved formulation.

5.2.2. How to design clinical studies

Comparative studies should be adequately designed and conducted to assess the intensity and duration of the therapeutic effect and undesirable effects of the modified release formulation in comparison with the authorised immediate release formulation. Studies should establish the clinical benefit of the new formulation relative to the authorised immediate release formulation, if such a claim is made. In addition to specific guidelines the following considerations should be taken into account:

In the assessment of the efficacy and safety of certain therapeutic classes it is necessary to measure the effects of the formulation throughout a 24-hour period and particularly at the end of dosage interval (e.g. assessment of breakthrough pain).

The different effects of medicinal products having different dose thresholds:

- Therapeutic activity is quantified with reference to the pharmacodynamic or clinical effects normally adopted as criteria for the assessment of efficacy in the concerned therapeutic class.
- In exceptional cases only, where the mechanism of action is the same between indications, an extrapolation can be made to indications other than those investigated in the trial, if it is appropriately justified by the applicant.
- In cases when the prolonged therapeutic activity may alter the safety profile of the drug during chronic dosing, safety studies may be required.

Clinical trials which compare the modified release form and the immediate release formulation on the basis of equal exposure may be planned to demonstrate non-inferiority of therapeutic efficacy or equivalence. In either situation, the design and analysis of the trials should consider the recommendations of ICH E9.

Whether these pharmacodynamic/clinical studies should show equivalence or non- inferiority as compared to the standard formulation depends on the direction of the effect or safety issue at stake. In case efficacy and safety are closely related equivalence studies are needed for showing that the effect studied remains within the equivalence margins. If it is acceptable to investigate only efficacy and it is not expected that formulations have different safety, a demonstration of non-inferiority might be sufficient.

The type of studies that are required depends on whether appropriate, pharmacodynamic endpoints can be defined, whether the relationship between the pharmacodynamic markers and clinical efficacy is known, whether assay sensitivity is guaranteed and whether a non-inferiority margin or equivalence margin can be defined.

Such equivalence and non-inferiority studies may include a placebo arm beside the immediate and modified release preparations. A placebo arm or an additional active arm with a lower dose is mandatory if assay sensitivity of the trial cannot be guaranteed (see ICH E10).

In addition, equivalence margins or non-inferiority margins have to be defined and justified irrespective of whether the endpoint is based on pharmacodynamic measurement or clinical variable.

A clinical development plan in accordance with existing guidelines or the state of the art is required if an indication is claimed that is different for a modified release product as compared to the immediate release formulation. In case the modified release product is either a patch or a depot formulation, local safety should also be addressed.

The remaining amount of active substance after patch removal should be considered in respect to safety concerns due to potential misuse or environmental risks.

When superiority is claimed it has to be proven with clinical trials. Applicants are referred to the scientific guidance documents relevant to the concerned therapeutic area.

If a claim is made for fewer systemic adverse reactions for the modified release form, this has to be substantiated.

6. Abridged application for modified release forms referring to a marketed modified release form

General considerations:

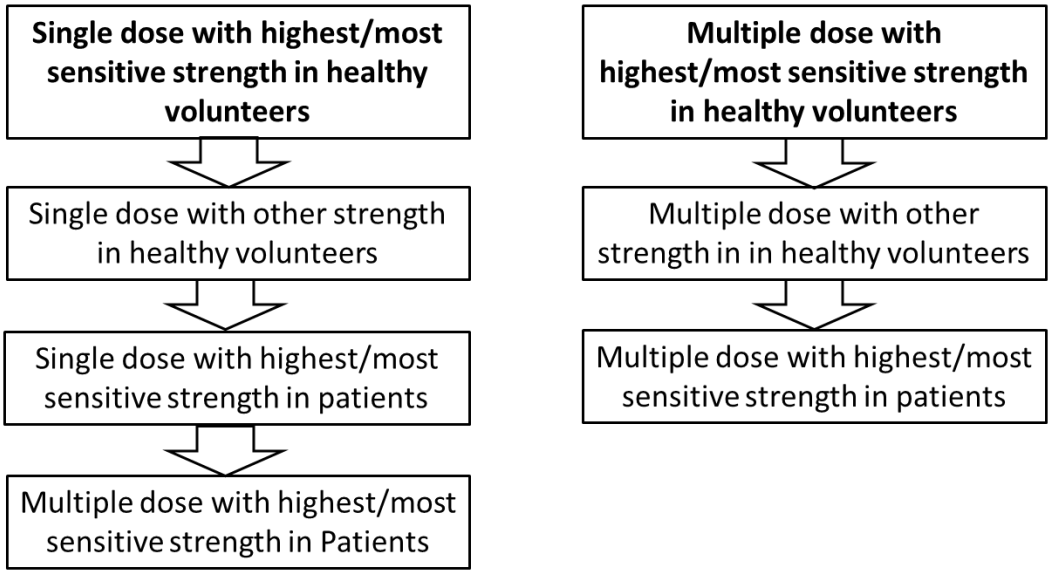
For orally administered products, bioequivalence studies of modified release formulations are recommended to be conducted by comparing two formulations (test versus reference) of the same pharmaceutical form. A generic MR formulation should be compared with the MR formulation that is either the originator or the line extension of an IR originator formulation, with which bioequivalence is claimed. The general recommendations regarding study design, conduct, evaluation and reporting of bioequivalence studies detailed in the Guideline on Bioequivalence (CPMP/EWP/QWP1401/98) are applicable also for bioequivalence studies for modified release products. Aspects specific to MR formulations are detailed in this section.

If two products with the same dosage form differ in their release controlling excipients or mechanism they can be considered generics if they are bioequivalent in vivo after single dose in the fasted and fed state (see section 6.1) as well as under multiple dose conditions, if needed.

In case criteria for a biowaiver for additional strength are fulfilled and the demonstration of BE is only requested for one strength the following recommendations are given:

If the pharmacokinetics of the originator modified release product are linear, single and multiple dose studies should be conducted at the highest strength. If the pharmacokinetic of the originator modified release product are nonlinear the studies must be conducted with the most sensitive strength. The choice of a lower dose has to be based on safety considerations.

Studies are in general recommended to be conducted in healthy volunteers. However, if it is not possible to conduct studies in healthy volunteers in any existing strength for safety reasons, studies can be conducted in patients, preferably after both single and multiple dose administration in line with recommendations below. If it is not feasible to conduct single dose studies in patients, these can be replaced by multiple dose studies.



In case criteria for bracketing approach are fulfilled and the demonstration of BE is requested for two strengths selected to represent the extremes the following recommendation is given:

A high strength study in patients together with a lower strength study in healthy volunteers is possible.

For evaluation of dissolution profiles, PK linearity and detecting the most sensitive strength see also the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98).

A difference regarding formulation-related food interactions indicates product differences thus contradicting the generic by definition. Accordingly, for products where bioequivalence can be shown in the SPC recommended condition but not in the non-recommended state due to less food effect, the product does not fulfil the requirements of a generic product, but could be eligible for an Article 10(3) application.

See also Appendix III "Summary of study recommendations for abridged applications"

6.1. Prolonged release formulations for oral administration

Bioequivalence between two prolonged release formulations should be evaluated on the basis of studies designed to demonstrate that:

- the test formulation exhibits the claimed prolonged release characteristics of the reference
- the active substance is not released unexpectedly from the test formulation (no dose dumping)
- performance of the test and the reference formulation is equivalent after single dose and at steady state
- the effect of food on the in vivo performance is comparable for both formulations when a single dose study is conducted.

6.1.1. Studies generally required to demonstrate bioequivalence:

- a single-dose fasting study comparing test and reference drug product
- a single-dose fed study using a high-fat meal (see 5.1.4.1) comparing test and reference drug product

- a multiple-dose study comparing test and reference drug product.

6.1.1.1. Single dose studies

One of the following schemes is recommended for single dose evaluation in fasting and fed state:

- A four-period cross-over trial with four complementary sequences of four treatment conditions. Both the test and reference products should be assessed in the fasting state as well as after the administration of a high-fat meal at a specified time before taking the drug.
- Two cross-over trials. The first trial should compare the test and reference products under fasting conditions. The study treatments should be administered during two periods and with two sequences of treatment conditions. The second trial should compare the test and reference formulations following the administration of a high-fat meal at a specified time before taking the study treatment, as well as the test formulation under fasting conditions to generate intra-individual data describing a possible food effect.
- Two cross-over trials, both with two periods and two sequences of test and reference product administration. One trial should be conducted in the fasting state. The other trial should be conducted after the administration of a high-fat meal at a specified time before taking the study treatment.

6.1.1.2. Multiple dose studies

A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that the mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference, and consequently a low extent of accumulation is expected. In this case bioequivalence needs to be demonstrated for additional parameters representing the shape of the plasma concentration versus time curve in the single dose study (see also section 6.8.2). An early $_{partial}AUC_{(0 - cut\text{-}off\ t)}$ and a terminal $_{partial}AUC_{(cut\text{-}off\ t - tlast)}$, separated by a predefined cut-off time point, e.g. the half of the dosage interval are recommended, unless otherwise scientifically justified.

In all other cases, where accumulation is likely ($AUC_{(0-\tau)}$ after the first dose covers less than 90% of mean $AUC_{(0-\infty)}$) a multiple dose study is required. Generally, steady-state studies should be performed under the conditions concerning concomitant food intake recommended in the SmPC for the originator product. If the SmPC states that the product has to be taken in fed condition only the study should be performed in fed conditions (standard meal) including the day of profiling. If the SmPC states that the product should be taken in fasted state or irrespective of food intake the studies should be performed in fasted conditions. Fasting conditions in a multiple dose study needs to be adapted to realistic situations, i.e. morning administration requires a 10 hour fasting interval whereas for all other administrations 4 hour fasting prior to administration is sufficient. Fasting after each administration should be defined as 2 hour minimum.

In steady-state studies, the washout period of the previous treatment can overlap with the build-up of the second treatment (direct switching), provided the build-up period is sufficiently long (at least 5 times the terminal half-life).

Whether the steady-state has been achieved is assessed by comparing at least three pre-dose concentrations for each formulation. The apparent half-life should also be taken into account.

6.1.2. Strength(s) to be evaluated

6.1.2.1. Single unit formulations

For single unit formulations with multiple strengths the following considerations apply:

A. Single dose studies

- If the reference SmPC recommends intake in the fasting state or irrespective of food intake:
  - Fasting state: a single dose study under fasting conditions is required for all strengths. However, a bracketing approach (see section 6.6) is also possible if justified. In case of safety concerns in healthy volunteers, studies should be conducted in patients, which may require steady state conditions.
  - Fed state: one single dose bioequivalence study at the highest/most sensitive strength conducted in fed state may be sufficient. The other strength(s) can be waived if the criteria described for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However, if the strengths of the test product do not fulfil these criteria or if the different strengths have different shape two strengths representing the most extreme difference should be tested in fed state.
- If the reference SmPC recommends intake under fed conditions:
  - Fed state: a single dose study under fed conditions is required for all strengths. However, a bracketing approach (see section 6.6) is also possible if justified.
  - Fasting state: one single dose bioequivalence study at the highest/most sensitive strength conducted in fasting state may be sufficient. The other strength(s) can be waived if the criteria described for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However, if the strengths of the test product do not fulfil these criteria or if the different strengths have different shape two strengths representing the most extreme difference should be tested in fasting state.

B. Multiple dose studies

- A multiple dose study should be performed with the highest strength (unless it is shown that there is no accumulation as detailed in section 6.1). In case of safety concerns the study should be conducted in patients. The other strength(s) can be waived if the criteria for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However, a bracketing approach (see section 6.6) is also possible if justified.

6.1.2.2. Multiple unit formulations

For multiple unit formulations of a medicinal product with several strengths, it is sufficient to conduct the studies listed in section 6.1.1 only at the highest/most sensitive strength if the compositions of the strengths are proportional, the formulations contain identical beads or pellets (and these are produced by the same manufacturing process) and the dissolution profiles are similar.

6.2. Delayed release formulations

Bioequivalence between two delayed release formulations should be evaluated on the basis of studies designed to demonstrate that:

- the test formulation exhibits the claimed delayed release characteristics of the reference
- the active substance is not released unexpectedly from the test formulation (to ensure the aimed location of release)
- performance of the test and the reference formulation is equivalent after a single dose
- the effect of food on the in vivo performance is comparable for both formulations when a single dose study is conducted.

6.2.1. Studies generally required to demonstrate bioequivalence:

- a single-dose fasting study comparing test and reference product
- a single-dose fed study using a high-fat meal (see 5.1.4.1) comparing test and reference product

A similar approach as detailed for prolonged release forms regarding study design of single dose studies can be used (see 6.1.1.1).

6.2.2. Strength(s) to be evaluated

6.2.2.1. Single unit formulations:

A. Single dose studies

- If the reference SmPC recommends intake under fasting state or irrespective of food intake:
  - Fasting state: a single dose study under fasting conditions is required for all strengths. However, a bracketing approach (see section 6.6) is also possible if justified.
  - Fed state: one single dose bioequivalence study at the highest/most sensitive strength conducted in fed state may be sufficient. The other strength(s) can be waived if the criteria described for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However, if the strengths of the test product do not fulfil these criteria or if the different strengths have different shape two strengths representing the most extreme difference should be tested in fed state.
- If the reference SmPC recommends intake under fed conditions only:
  - Fed state: a single dose study under fed conditions is required for all strengths. However, a bracketing approach (see section 6.6) is also possible if justified.
  - Fasting state: one single dose bioequivalence study at the highest strength conducted in fasting state may be sufficient. The other strength(s) can be waived if the criteria for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However, if the strengths of the test product do not fulfil these criteria or if the different strengths have different shape two strengths representing the most extreme difference should be tested in fasting state. When evaluating proportionality in composition, the similarity of gastro-resistant coating with respect to the surface area (not

to core weight) should be considered to have the same gastro-resistance (coating layer in mg/cm2 surface).

B. Multiple dose studies

In principle there is no need for multiple dose studies except when single dose studies cannot be performed because of safety concerns (see also section 6 "General considerations").

6.2.2.2. Multiple unit formulations:

For multiple unit formulations of a medicinal product with several strengths, it is sufficient to conduct the studies listed in section 6.2.1 only at the highest/most sensitive strength if the compositions of the strengths are proportional, the formulations contain identical beads or pellets (and these are produced by the same manufacturing process) and the dissolution profiles are similar.

6.2.3. Prolonged residence time in the stomach

Gastric emptying of modified release dosage forms that do not disintegrate in the stomach (e.g. enteric coated tablets) may be prolonged and highly erratic. The consequences of this effect on the enteric coating of delayed release formulations are largely unpredictable and can result in non-existing or aberrant concentration profiles. If the incidence of this outlier behaviour is observed with a comparable frequency (e.g. the number of cases is not numerically higher in the test product) in both, test and reference product, data of a period with non-existing or aberrant profile can be excluded from statistical analysis provided that it has been pre-specified in the study protocol. In a 2-period trial this will result in the subject being removed from the analysis. If the percentage of excluded subjects exceeds 20% for a particular study, the validity of the study may need to be discussed.

Furthermore the release of the active substance may be considerably delayed due to a prolonged residence in the stomach. Therefore the sampling period should be designed such that measurable concentrations are obtained, taking into consideration not only the half-life of the active substance but the possible occurrence of this effect as well.

6.3. Multiphasic modified release products

The regulatory criteria mentioned in this Guideline are also applicable in the assessment of bioequivalence for modified release products designed to achieve sequential release combining immediate and modified characteristics (e.g. biphasic-/ pulsatile-release).

6.3.1. Studies generally required to demonstrate bioequivalence:

If one of the release phases is modified, the type and number of studies required are those described above for this specific release mechanism.

However additional pharmacokinetic parameters are needed to demonstrate bioequivalence for all phases (see section 6.8.1).

6.4. Intramuscular/Subcutaneous Depot Formulations

6.4.1. Studies generally required to demonstrate bioequivalence:

- a single-dose study comparing test and reference products

- a multiple-dose study comparing test and reference products.

A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that:

- the mean $AUC_{(0-\tau)}$after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference, and consequently a low extent of accumulation is expected

6.4.2. Strength to be evaluated

Only one strength has to be investigated if the different strengths are proportional in composition and exhibit a similar in vitro dissolution profile. The strength should be selected based on the pharmacokinetic linearity and safety. If there are several non-proportional strengths a bracketing approach is possible, but the formulation strategy of the reference product should be taken into account.

If the originator product is marketed in only one concentration and the different doses are achieved by choosing the total volume to be injected any dose should be acceptable for a bioequivalence trial in case dose proportionality has been shown for the reference. In case therapeutic doses cannot be administered to healthy volunteers, non-therapeutic doses may be acceptable for safety reasons. In situations where it is not possible to perform single dose studies with an intramuscular/subcutaneous depot formulation in healthy volunteers for safety or ethical reasons, multiple dose studies in patients are acceptable to show bioequivalence.

6.5. Transdermal Drug Delivery Systems (TDDS)

A generic TDDS is defined by having the same amount of active substance released per unit time as compared to the reference TDDS. It is to note that this definition is different to the general definition of a generic since the overall amount of active substance could differ while the labelled amount of active substance released per unit time should be the same between a generic and the innovator TDDS.

Equivalence testing of TDDS should comprise both comparable or better adhesion properties (see appendix IV) and bioequivalence. It is advisable to ensure comparable or better adhesion properties prior to bioequivalence investigations in volunteers since inferior adhesion could invalidate the pharmacokinetic results and question the acceptability of the product. The skin of the population studied in adhesion equivalence testing should also be similar to the population using the drug, which implies that different studies may be necessary for the adhesion and the pharmacokinetic studies.

(see also Appendix IV)

6.5.1. Studies generally required to demonstrate bioequivalence:

- a single-dose study comparing test and reference products
- a multiple-dose study comparing test and reference products.

Bioequivalence of TDDS should generally be assessed after single dose as well as after multiple dose application. A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that the mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference, and consequently a low extent of accumulation is expected. The study design including the site of application should be justified in terms of its sensitivity to detect formulation differences. The application site should be standardized and be the same for both test and reference. Due to rotation of patches between several sites a different site in the same region

is typically used for the cross-over. The adhesion properties of the patch should not be altered by e.g. over-taping.

Bioequivalence should be assessed using the same pharmacokinetic parameters and statistical procedures as for prolonged release formulations.

The test product should demonstrate a similar or lower degree of local irritation, phototoxicity, sensitization, and similar or better adhesiveness to the skin as the reference product. In order to ensure equivalence in terms of safety, comparative state-of-the-art studies are required to investigate

- cutaneous tolerability, irritation and sensitisation (see appendix I)
- the potential to produce phototoxic reactions
- adhesion characteristics (for details regarding comparative adhesion tests see appendix IV)

unless otherwise justified by e.g. very similar quantitative and qualitative composition.

6.5.2. Strength to be evaluated

When the marketing authorisation of multiple strengths is required, a bioequivalence study can be performed with the highest/most sensitive strength provided that:

- the qualitative composition is the same for all strengths;
- the strengths are proportional to the effective surface area of the patch and the lower dose strengths can be considered as ''partial'' areas of the highest dose strength;
- there are similar dissolution/release profiles

In case of safety / tolerability limitations at the highest strength, the use of a lower strength is acceptable for size proportional formulations.

6.6. Bracketing approach

In case bioequivalence assessment at more than two strengths is needed, e.g. because of deviation from proportional composition and/or if dissolution profiles are not similar, or for single unit formulations with proportional composition, a bracketing approach may be used if the other waiver criteria (see Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98) are fulfilled. In this situation it can be acceptable to conduct two bioequivalence studies, if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition, dissolution or shape, so that any differences in composition or dissolution in the remaining strengths is covered by the two conducted studies.

However, for prolonged release formulations release-controlling excipients and mechanism should be the same for all strengths of the test product. The same is required for release controlling coatings for delayed release formulations.

6.7. New strength for an already approved MR product

Section 6 also applies to the development of a new strength within the existing dose range according to the SmPC of the reference product. For a new strength with proportional composition to approved strength(s) a bracketing approach may be applicable. For a new strength with non-proportional composition to approved strength(s), the new strength has to meet the requirements as described in relevant sections above (section 6.1-6.5). If a new strength is developed which is bracketed by other

strengths and meets the release-controlling and size/shape requirements and manufacturing requirements, then a new study should not be required because it falls in the category described in Section 6.6. "Bracketing approach".

A new dose strength outside the existing therapeutic range requires a clinical development. Certain parameters, e.g. skin safety profile for TDDS, may not need to be re-evaluated, if the new strength and the intended indication are not expected to alter the overall safety profile.

6.8. Evaluation

6.8.1. Parameters to be analysed

6.8.1.1. Single dose studies:

In studies to determine bioequivalence after a single dose, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, residual area, C_{max} , t_{max} should be determined and, when relevant, $_{partial}AUC$. A truncated $AUC_{(0-72h)}$ is not acceptable for MR products.

For multiphasic modified release products additional parameters to be determined include $_{partial}AUC$, C_{max} and t_{max} in all phases. The time point for truncating the $_{partial}AUC$ should be based on the PK profile for the e.g. IR and the MR parts respectively and should be justified and pre-specified in the study protocol.

6.8.1.2. Multiple dose studies:

In studies to determine bioequivalence after a multiple dose administration $AUC_{(0-\tau)}$, $t_{max,ss}$, $C_{max,ss}$, $C_{\tau,ss,}$ and fluctuation should be determined. In contrast to the need of characterisation of $C_{min,ss}$ for new MR formulations, a comparison of $C_{\tau,ss}$,which is easier to determine, should be sufficient. $C_{\tau,ss}$ is required to assess shape of the curve for generic applications and replaces the need to also evaluate $C_{min,ss}$ in those circumstances.

6.8.2. Evaluation characteristics and acceptance criteria

6.8.2.1. Parameters to be evaluated

Bioequivalence **for prolonged release products with accumulation** should be demonstrated by showing equivalence after statistical evaluation of the following parameters:

Single dose: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}
Multiple dose: $AUC_{(0-\tau)}$, $C_{max,ss}$, $C_{\tau,ss}$

	Single dose fasting study	Single dose fed Study	Multiple dose study
C_{max}	yes	yes	no
$AUC_{(0-t)}$	yes	yes	no
$AUC_{(0-\infty)}$	yes	yes	no
$_{partial}AUCs$	no	no	no

$C_{max,ss}$	no	no	yes
$C_{\tau,ss}$	no	no	yes
$AUC_{(0-\tau)ss}$	no	no	yes

For **prolonged release products with no risk of accumulation** (see section 6.1) or those intended exclusively for once only use, a statistical evaluation of the following parameters has to show bioequivalence:

Single dose: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max} and a representative metric of the shape of the curve (e.g. early and terminal $_{partial}$AUCs)

	Single dose fasting study	Single dose fed Study	Multiple dose study
C_{max}	yes	yes	no
$AUC_{(0-t)}$	yes	yes	no
$AUC_{(0-\infty)}$	yes	yes	no
$_{partial}$AUCs	yes	yes	no
$C_{max,ss}$	no	no	no
$C_{\tau,ss}$	no	no	no
$AUC_{(0-\tau)ss}$	no	no	no

Bioequivalence for **delayed release products** should be demonstrated by showing equivalence after statistical evaluation of the following parameters:

Single dose: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}

	Single dose fasting study	Single dose fed Study	Multiple dose study
C_{max}	yes	yes	no
$AUC_{(0-t)}$	yes	yes	no
$AUC_{(0-\infty)}$	yes	yes	no
$_{partial}$AUCs	no	no	no
$C_{max,ss}$	no	no	no
$C_{\tau,ss}$	no	no	no
$AUC_{(0-\tau)ss}$	no	no	no

For **multiphasic modified release products** a statistical evaluation of the following parameters has to show bioequivalence:

Single dose: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $_{partial}AUC$s and C_{max} in all phases.

*and in case of accumulation in
Multiple dose: $AUC_{(0-\tau)}$, $C_{max,ss}$, $C_{\tau,ss}$

	Single dose fasting study	Single dose fed Study	Multiple dose study*
$C_{max(x)}$	yes	yes	no
$C_{max(x+1)}$	yes	yes	no
$AUC_{(0-t)}$	yes	yes	no
$AUC_{(0-\infty)}$	yes	yes	no
$_{partial}AUC_{(x)}$	yes	yes	no
$_{partial}AUC_{(x+1)}$	yes	yes	no
$C_{max,ss}$	no	no	yes
$C_{\tau,ss}$	no	no	yes
$AUC_{(0-\tau)ss}$	no	no	yes

6.8.2.2. Statistical evaluation and acceptance criteria

The bioequivalence approach considering usual acceptance limits (80.00 – 125.00 %) is applicable for generic MR products (see CPMP/EWP/QWP/1401/98). Any widening of the acceptance criteria for C_{max} should follow the recommendations on highly variable drug products in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98).

A similar approach can be used for widening the acceptance criteria for $C_{max,ss}$, $C_{\tau,ss}$, and $_{partial}AUC$. Calculation of the intra-subject variability in multiple dose studies can be based on two consecutive administrations of the same product after reaching steady state.

For delayed and multiphasic release formulations differences in t_{max} is also recommended to be assessed, especially for products where a fast onset of action is important. A formal statistical evaluation of t_{max} is not required. However, there should be no apparent difference in median t_{max} and its range between test and reference product.

6.9. Effects of alcohol

For generic oral formulations, *in vitro* studies of the release in alcohol solutions should be performed. Where accelerated active substance release is seen in vitro either at high or low alcohol concentrations over a short period of time or at lower alcohol concentrations over a longer period of time, the product should be reformulated.

If the alcohol effect cannot be avoided and it is present also in the reference product, the applicant should justify / demonstrate that it lacks of clinical relevance or discuss the possible clinical relevance in comparison to the reference product.

6.10. Further points to consider for bioequivalence studies

The following issues should be handled in line with the recommendations for immediate release formulations stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98)

- Test and reference product
- Subjects
- Study conduct
- Statistical evaluation of primary endpoints
- Parent compound or metabolites
- Enantiomers
- Endogenous substances
- Narrow therapeutic index drugs (in addition narrowing of the acceptance criteria of C_τ might be necessary)
- Highly variable drugs or drug products
- Linearity

Definitions

$AUC_{(0-t)}$:	Area under the plasma concentration curve from administration to last observed concentration at time t;
$AUC_{(0-\infty)}$:	Area under the plasma concentration curve extrapolated to infinite time;
$AUC_{(0-72h)}$	Area under the plasma concentration curve from administration to 72h;
$_{partial}AUC$:	Partial AUC separated by predefined cut off points
$_{partial}AUC_{(x)}$	Partial AUC in phase x for multiphasic products
C_{max}:	Maximum plasma concentration;
residual area	Extrapolated area ($AUC_{(0-\infty)}$ - $AUC_{(0-t)}$)/ $AUC_{(0-\infty)}$;
t_{max}:	Time until C_{max} is reached;
$t_{1/2}$:	Plasma concentration half-life;
λ_z:	Terminal elimination rate constant;
$AUC_{(0-\tau)ss}$:	AUC during a dosage interval at steady state
$t_{max,ss}$:	Time until $C_{max,ss}$ is reached
$C_{max,ss}$:	Maximum plasma concentration at steady state

$C_{min,ss}$:	Minimum plasma concentration at steady state
C_{τ}:	Concentration at the end of the dosing interval
$C_{\tau,ss}$:	Concentration at the end of the dosing interval at steady state
C_{av}	average concentration during a dosing interval ($AUC_{(0-\tau)}$ / τ)
$C_{max(x)}$	Maximum plasma concentration in phase x for multiphasic products
fluctuation	[(C_{max}-C_{min})/C_{av}]
t_{lag}	lag time
PK	Pharmacokinetic

Appendix I: sensitisation and irritation test for transdermal products

This appendix is intended to recommend study designs and scoring systems that can be used to test skin irritation and sensitization during development of transdermal products either as NCE TDDS or generic TDDS. The design can be adapted for the particular situation.

The condition of the skin may influence the absorption of an active substance from a transdermal system and affect the efficacy or safety of the product. Therefore skin irritation and sensitization should be assessed.

To fully evaluate the equivalence of a generic transdermal product to the reference product similarity has also to be shown for skin irritation and sensitization unless otherwise justified by e.g. very similar quantitative and qualitative composition.

The strength chosen for the test is determined by considering the following factors:

- previous human experience in scientific literature
- previous sensitisation/irritation tests in animals
- safety issues derived from the individual API under investigation

Overall Study Design for a generic application

The study suggested has an active- and placebo-controlled, multiple-dose, three-phase, parallel-group design.

In case simultaneous application of test and reference is impossible as doubled amount of API would be given under off-label use and might have life-threatening consequences the use of a lower strength is acceptable for size proportional formulations.

Screening evaluations are performed within a 14-day period prior to application of the patches.

Screening evaluations should consist of a medical history, complete physical examination, 12-lead electrocardiogram (ECG), laboratory evaluations (including serum chemistry, haematology, and urinalysis), and urine drug screen.

Subjects are assigned to one of two analysis groups (Group 1 and Group 2) and are evaluated for both cumulative dermal irritation and contact sensitization. Test, reference and placebo transdermal patches should be applied to randomly assigned test areas on the back or other parts, if permitted by the SmPC, of subjects in the two groups. Skin reactions have to be evaluated by a trained observer blinded to the treatment.

Criteria for discontinuation of the test should be mentioned in order to avoid excessive reaction.

Each subject participates in the following three consecutive study phases.

Induction/Cumulative Irritation Phase

Group 1 subjects apply test, reference, and placebo patches to randomly assigned treatment areas for 21 consecutive days.

Group 2 subjects apply test, reference, and placebo patches to randomly assigned treatment areas three times weekly over a period of 21 days (a total of nine applications). In Group 2, the patches remain in place for 48 hours (on weekdays) and 72 hours (on weekends). The new patch should be

applied to the same site as the previous patch. If the next patch is to be applied within 1 hour after removal of the previous one, the administration period of the new patch can then be reduced for this time period.

Rest Phase

Following the Induction/Cumulative Irritation Phase, each subject enters a 2-week Rest Phase. No patches are applied during the Rest Phase.

Challenge Phase

Following the Rest Phase, patches are applied to new skin sites within the designated areas for 48 hours.

In addition to dermal assessments at 0.5 and 24 hours after patch removal, subjects participating in the Challenge Phase also return for examination on Days 40 and 41 for additional dermal assessments at 48 and 72 hours after removal of the last patch.

To minimize the effect of inter-subject variability, each study participant receives all three treatments simultaneously. In addition, to control for the unlikely possibility of a treatment-by-site-interaction, the three treatments should be randomly assigned to three application areas so that each treatment occupied each application area with approximately equal frequency throughout the panel of study participants.

Group 1	**Cumulative Irritation Phase**				
	Test, Reference Placebo	One patch of each drug applied daily to the back of each subject for 21 days			
	Induction of Contact Sensitization		**Rest Phase**	**Challenge Phase**	
	Test, Reference Placebo	One patch of each drug applied daily to the back of each subject for 21 days	No patches applied tor 2 weeks	Test, Reference Placebo	One patch of each drug applied to the back of each subject; patch removed after 48 hours
Group 2	**Induction of Contact Sensitization**		**Rest Phase**	**Challenge Phase**	
	Test, Reference Placebo	One patch of each drug applied to the back of each subject three times a week over a period of 21 days	No patches applied tor 2 weeks	Test, Reference Placebo	One patch of each drug applied to the back of each subject; patch removed after 48 hours

Dermal response has to be assessed for all subjects in Group 1 and Group 2. Application sites for both groups are evaluated for skin irritation 30 minutes after patch removal (dermal response and other effects scores determined), and new patches are applied 1 hour after removal every time that the patch is removed during the Induction/Cumulative Irritation Phase.

To evaluate contact sensitization during the Challenge Phase, test, reference, and placebo patches are applied simultaneously for 48 hours to previously unused sites on Group 1 and Group 2 subjects. Application sites were evaluated at 0.5, 24, 48, and 72 hours after patch removal.

Skin reactions can be examined and graded using the numerical scores outlined in Table 1 (dermal response) and Table 2 (other effects).

Each application site receives a separate dermal response score and other effects score. Dermal response scores require that at least 25% or more of the patch area demonstrate an observable response. During the Challenge Phase (contact sensitization evaluation), only combined dermal response scores ≥2 are considered a positive response.

Table 1	**Dermal Response Score**
Score	**Definition**
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal oedema or minimal papular response
3	Erythema and papules
4	Definite oedema
5	Erythema, oedema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Table 2	**Other Effect Score**
Score	**Definition**
0	None observed
1	Slight glazed appearance
2	Marked glazing
3	Glazing with peeling and cracking
4	Glazing with fissures Film of dried serous exudates covering all or part of the patch site Small petechial erosions and/or scabs

"Strong" reaction to the test patch are defined as a dermal response score of 3-7 or any dermal score combined with other effects rating of 4 or greater.

Group	**Phase**	**Evaluation by observer**	**Assessment of Test, Reference and Placebo**
Group 1	Cumulative Irritation Phase	Dermal Response Score Other Effects Score	• Mean Irritation Score = average of Dermal Response Scores • Total Cumulative Irritation = Score sum of Dermal Response Scores • Combined Dermal Response = Score sum of Dermal Response Score and Other Effects Score • Mean Combined Dermal Response Score

Group 1 + 2	Challenge Phase (Contact Sensitization)	Dermal Response Score Other Effects Score	-Combined Dermal Response Score 2:2

The primary analysis compares the test and reference treatments for the mean irritation scores (average numeric dermal response over the observations) and the total cumulative irritation scores (sum of the numeric dermal response scores over the observations). A predefined statistical evaluation based on a non-inferiority approach is deemed sufficient to support a positive benefit risk evaluation for such a product. The two one-sided t-test method should be used to compare the irritation scores between treatments. For each parameter, least squares means for each treatment are derived from an ANOVA model where subject and treatment are fixed effects. The ratio of the least squares means of the test treatment to the reference treatment has to be calculated, along with its 90% confidence interval. A 90% confidence interval that falls completely within the interval 0.8 to 1.25 leads to the conclusion that the two treatments are equivalent.

The assessment of contact sensitization consists of tabulations of dermal response scores ≥2 during the Challenge Phase. No statistical analysis has to be performed on these data.

Appendix II: in vivo skin adhesion

1. Applications for a TDDS of a new chemical entity or a known active substance newly developed as TDDS

The investigation of in vivo adhesive performance will be usually part of the efficacy studies. The robustness of the product to normal human behaviours (e.g. moisture resistance to washing, showering, saunas, use of moisturisers and risk of removal during exercise and/or sleeping, possible transfer to partners or family) should be evaluated, as appropriate, based on risk analysis and the instructed conditions of use for the individual products.

Accidental transfer of a patch to the skin of a non- patch wearer has to be prevented as well as other poor-adhesion related risks have to be minimized by ensuring acceptable adhesion characteristics by the patch.

- The adhesion should be measured as the percentage of area that remains adhered at the end of the dosing interval.
- In general, it is expected that the 90% confidence interval of mean adherence for the test product at the end of the dosing interval should lie above 90%.

Any deviation from this requirement has to be justified considering all potential risks associated with the incomplete attachment of the patch.

2. Application for a TDDS referring to a marketed TDDS

The investigation of *in vivo* adhesive performance may be included as an integrated part of human clinical pharmacokinetic (both single dose and multi dose), or may be an independent study with either patients or volunteers. In general these studies should ensure adequate adhesion properties in the intended population, which implies that different studies may be necessary for the adhesion and the pharmacokinetic studies.

For transdermal patches covering a range of different dosage strengths, the largest patch sizes should be tested in vivo, unless otherwise justified.

a. <u>Recommendations on how to conduct an adhesion study:</u>

Generally, patch reinforcement such as over-taping is not allowed. However, in case a product has to be used in accordance to the SmPC with a separate overlay to ensure adequate adhesion, the adhesion studies are to be performed using this separate overlay.

The frequency of assessment should be stated and justified, and should include transdermal patch administration and removal time points. In general the frequency of assessment should depend on the wearing period of the patch. Satisfactory and unsatisfactory performance might also be supported by photographs.

In those cases where adhesion is investigated in the pharmacokinetic multiple dose study, sample size calculation should consider not only the pharmacokinetic endpoints but also the hypothesis of adequate adhesion.

A descriptive summary of the results should be provided. The results should be reported by treatment in explanatory tabular and graphical formats.

In addition to the table including the individual values of percentage of adhesion *vs.* time, with their corresponding descriptive statistics, the table below could be used for descriptive presentation of the study results.

Adherence	Evaluation time point							
	..h		..h		..h		..h	
	Ref. Nr.(%)	Test Nr.(%)	Ref. Nr.(%)	Test Nr.(%)	Ref. Nr.(%)	Test Nr.(%)	Ref. Nr.(%)	Test Nr.(%)
≥ 90%								
≥ 80%								
≥ 70%								
≥ 60%								
≥ 50%								
0% to < 50%								

In addition to the individual and mean plots of percentage of adhesion *vs.* time, a histogram of the adhesiveness in the two treatment groups should be presented.

b. Assessment criteria:

Primary objective:

- The adhesion should be measured as the percentage of area that remains adhered at the end of the dosing interval.
- In general, it is expected that the 90% confidence interval of mean adherence for the test product at the end of the dosing interval should lie above 90%. This should therefore normally be the primary comparison.
- If it is considered unlikely that this requirement can be met it may be possible to establish non-inferiority of the test product to the reference product. This may be possible if the reference product has poor adherence (< 90%). The lower limit of the 90% confidence interval for the difference of adhesiveness (test – reference), using the percentage of adhesion as continuous variable, should not be less than -10%.

In addition, it is necessary to evaluate and compare:

- The percentage of adhesion for all time-points to assess how adhesion changes during study
- The proportion of subjects achieving greater than 90% adherence at each evaluation time-point.
- The proportion of subjects with a meaningful degree of detachment (more than half of the patch lifting off the skin or falling off) for each product at all time points.
- The number of patches that are completely detached at each evaluation time.
- Instances of complete detachment should be discussed, poor adherence events should be investigated and possible causes and risk factors determined.

The qualitative evaluation should also include:

- Residue formation on release liner removal and on transdermal patch removal.
- Cold flow, such as the formation of a dark ring around the transdermal patch during use, patch movement or displacement, wrinkling.

The results of the study should be included in the SmPC.

Appendix III: in vitro in vivo correlation

1. Introduction

An *in vitro in vivo correlation* (IVIVC) is a mathematical model describing the relationship between an *in vitro* property of a dosage form (mainly dissolution or drug release) and a relevant *in vivo* response (mainly drug plasma concentration or amount absorbed). It is self-evident that such a relationship is only likely to exist when the formulation controls the rate of appearance of drug in plasma.

When a modified release formulation is developed, it is highly recommended to establish an IVIVC:

a) to quantify in vivo release and formulation related effect on absorption,

b) to establish the in vivo relevance of in vitro dissolution tests and associated dissolution specifications

c) to support biowaiver claims in later phases of clinical development or post-authorisation if there are changes in formulation.

Historically different levels of IVIVC relationships have been described; including levels A, B and C (see Annex 2, Guideline on quality of oral modified release products EMA/CHMP/QWP/492713/2012. Level A IVIVCs, in contrast to levels B and C, predict the entire concentration-time profile and for this reason are highly encouraged. Where an IVIVC is used to support a biowaiver, a validated level A correlation is generally a prerequisite.

The usefulness of an IVIVC depends on how accurately it can predict resultant plasma concentrations from any given set of in vitro data. This in turn is heavily dependent on the design of the in vitro and in vivo studies used to develop and validate the IVIVC.

2. Study Design Considerations

Generally, two or more formulations exhibiting the same release mechanism with sufficiently different dissolution profiles and an appropriate reference formulation (for the purpose of deconvolution) (RFD) with fast drug release (e.g., oral solution or immediate release formulation) are administered in a crossover study in healthy volunteers. Other designs are also possible (e.g. parallel groups, randomised or partially or fully randomised) and should be decided on a case by case basis depending on the nature of the modified release formulation, variability, tolerability, etc. For modified release products, the IVIVC study is normally conducted in the fasted state, even when the product is recommended to be taken with food. Drug levels (parent or other appropriate analyte according to the guideline on the investigation of bioequivalence; CPMP/EWP/QWP/1401/98) are quantified as a function of time in blood or plasma.

Extrapolation beyond the range of formulations used in IVIVC development and validation is not acceptable for regulatory applications (e.g. specification setting and biowaiver requests). Thus, the choice of formulations requires careful consideration, the various aspects of which (release mechanism, how to assure that formulations are sufficiently different, etc.) are detailed in the Guideline on quality of oral modified release products (EMA/CHMP/QWP/492713/2012). As the sensitivity of the plasma concentration-time profile for a given drug will depend on its particular disposition properties, it is advisable to base formulation selection on expected plasma concentration-time profiles (simulated using an assumed IVIVC relationship or range of possible relationships and the known disposition characteristics of the drug).

While it is acceptable to use different dosage strengths to establish an IVIVC or for external predictability assessment (see Section 3.3), it should be noted that different dosage strengths of the same formulation would generally not be considered to represent "different" release rates. For this reason, judgement of whether the dissolution profiles for different formulations are "different" is normally based on % of labelled (or actual) content.

2.1 Role and Choice of Reference Formulation for Deconvolution

A reference formulation for deconvolution is a fast-releasing formulation included in IVIVC studies to allow estimation of the in vivo release of drug as a function of time for each MR formulation (see Section 3.2). For oral MR products, the in vivo release-time profile is normally obtained by deconvolution and truly reflects drug release in vivo only when the RFD is an oral solution (and there is no precipitation from this solution in the stomach or GI tract). Immediate release formulations can be used as RFDRFDs in IVIVC studies and will also allow adequate approximation of the in vivo drug release from the MR formulations as long as the rate of dissolution from the IR formulation is fast relative to its absorption (which is normally the case for the drugs that are chosen as suitable for MR product development). Sometimes an IV product is used as the RFD for IVIVC. This will also allow adequate approximation of in vivo drug release as long as absorption is fast (i.e. for drugs with high permeability). Where permeability plays a role (in addition to release from the formulation) in the rate of drug absorption from the MR formulations, an oral solution is the best choice of RFD (i.e. better than an IV or IR formulation). For drugs with solubility and/or permeability limitations, particularly where permeability changes throughout the gastrointestinal tract, physiologically based PK modelling approaches to IVIVC may bring value.

For intramuscular/subcutaneous depot formulations, an appropriate RFD would be an aqueous solution administered by the same route (preferable) or an IV formulation. For TDDS, an IV formulation would represent an appropriate RFD.

The RFD should be included in any study where the data will be used to support the development of the IVIVC and internal or external predictability assessment. The advantage of including an RFD in IVIVC studies is that it increases the probability of successful IVIVC development and validation, particularly for external predictability assessment. The RFD is one of the more important design elements of a successful IVIVC because it normalises on an individual basis for differences in drug disposition. It has a role in every method of data analysis for both internal and external validation (described later). It is especially important where between-subject variability is moderate to high and where subject numbers do not compensate. When variability is low and/or subject numbers are high, it may be possible to develop and successfully validate an IVIVC without using an RFD (e.g. using literature data or a previously established population pharmacokinetic model) but it is best to evaluate this by simulation, incorporating known variability and the proposed study design to make an informed decision. It is possible for generic MR products to use the reference MR product to normalise for clearance differences between individuals, although this is likely to be less reliable. This strategy can also be evaluated by simulation taking into account the variability of the RFD and reference MR formulations.

2.2 Sampling Times

Considerations for the choice of in vitro sampling times are discussed in the Guideline on quality of oral modified release products (EMA/CHMP/QWP/467527/2012). The sampling times for in vitro dissolution and in vivo blood/plasma samples should take into consideration that the data will be combined in the IVIVC analysis and thus, an integrated approach to the design of the IVIVC study (including in vitro dissolution testing) is encouraged.

Sampling time decisions for blood/plasma are best made based on simulations using the actual (or modelled) in vitro release data for the clinical batches manufactured for the IVIVC study. If the in vitro dissolution is affected by pH or dependent on rotation speed, dips per minute (dpm) or flow rate (depending on the apparatus), it is useful to do simulations using the range of in vitro dissolution profiles in order to design a sampling regimen to cover the range of potential in vivo behaviours. Also, if there is some *a priori* understanding of the likely IVIVC relationship this is best built into the initial simulation. For example, for injectable controlled release formulations, in vitro release testing is often designed to be complete within 24-48 h, while the in vivo delivery is designed to continue for 1-2 months. Thus, a time-scaling factor (or to account for uncertainty in expected in vivo release, a range of factors) can be anticipated *a priori* and built into the model to provide a more realistic picture of the expected in vivo behaviour and better choice for appropriate sampling times for the test formulations.

2.3 Number of Subjects

The number of subjects to be included in an IVIVC study is dependent on the between and within subject variability in absorption and disposition of the drug from the drug product. Although no firm guidance can be given, a pragmatic approach would be to use no fewer than 12 in a crossover IVIVC study.

3. IVIVC Development and Validation

3.1 General Considerations

The overall goal of IVIVC is to be able to reliably predict the entire time course of plasma concentration from a modified release formulation based on in vitro release data. In principle any methodology that is scientifically sound can be used for this. Although a few are discussed below, methodology will continue to evolve and this list should not be considered to be exhaustive. As the purpose of the IVIVC is to be able to predict without in vivo testing the plasma concentration resulting from a modified formulation with different in vitro release data, it is a prerequisite that a single IVIVC relationship is applicable to all formulations used in its development and validation.

3.2 Acceptable Methods of Data Analysis

Two general categories of mathematical approaches to IVIVC modelling are one- and two-stage methods. The two-stage method is deconvolution-based. One stage approaches include convolution-based and differential equation-based methods and use of physiologically-based pharmacokinetic (PBPK) models.

Deconvolution-based methods involve two stages of data analysis and can be used as the primary IVIVC analysis method or for exploratory analysis to inform the one stage-method(s). The first stage employs deconvolution to estimate the time course of in vivo absorption. Non-compartmental methods of deconvolution are preferred over compartmental methods such as Wagner-Nelson or Loo-Riegelman. Deconvolution methodology is available in commercially available pharmacokinetic analysis software and normally involves fitting of the unit impulse response function (C_δ) to the RFD data for each individual subject followed by deconvolution of individual subject data for each MR formulation according to the following relationship to derive the in vivo input rate, r(t):

$$C(t) = r(t) * C_\delta = \int_0^t C_\delta(t-\tau) r(\tau) d\tau$$

where C is plasma concentration, C_δ is the unit impulse response (i.e. the plasma concentration profile resulting from instantaneous absorption of a unit dose of drug) and * is the convolution operator.

The second stage establishes the relationship between cumulative in vivo absorption and in vitro drug release. As is generally recommended in mathematical modelling, parsimony should be observed and the simplest model to describe the data should be utilised. Normal practice would be to utilise models of increasing complexity, starting with linear relationships and increasing complexity as necessary according to the data and considerations of biological plausibility. A linear relationship between in vivo absorption and in vitro release, although desirable, is not necessary and there are many physiological and physicochemical factors that make this less likely. In principle, any relationship that is applicable to all IVIVC formulations is acceptable including sigmoidal, Hill, incorporation of time-scaling and time-shifting parameters and approaches to account for incomplete absorption (e.g. absorption cut-off time, for oral formulations) with justification based on an understanding of the formulation, physicochemical, pharmacokinetic and physiological factors controlling drug release in vitro and vivo. Different time scales for each formulation points to the absence of a single relationship for the IVIVC formulations. Deconvolution-based methods are particularly helpful for exploratory data analysis during the model building process, as they provide graphical output (cumulative amount absorbed in vivo versus cumulative amount released in vitro and Levy plots: time for a specific % of dose absorbed in vivo versus time for a specific % of dose released in vitro) that can be used to identify appropriate models for the IVIVC relationship and provide appropriate initial parameter estimates necessary for one-stage modelling methods.

Convolution-based differential equation- and PBPK model -based methods are classified as single stage because modelling involves utilising the observed data directly without transformation (i.e. through deconvolution). Single stage approaches offer a number of advantages over deconvolution based methods, as the model predicts directly the plasma concentration-time course; modelling focuses on the ability to predict measured quantities, not indirectly calculated quantities such as the cumulative amount absorbed; and the results are more readily interpreted in terms of the effect of the in vitro release on conventional bioequivalence metrics. Additionally, the compartmental approach allows for nonlinear (e.g. Michaelis-Menten) disposition kinetics, whereas the convolution-based method assumes linear disposition. Although both convolution-based and differential-equation based methods are single stage, they differ in the form of the relationship between in vitro release and plasma drug concentration. The convolution-based approach uses the integral transform, transform shown above for the relationship between concentration for the MR formulation, C(t), given the in vivo input rate, r(t), and unit impulse response, C_δ:

$$C(t) = r(t) * C_\delta = \int_0^t C_\delta(t-\tau) r(\tau) d\tau$$

The differential equation-based approach utilises a traditional compartmental model framework for drug disposition and incorporates an input function.

In both cases, an IVIVC equation quantifies the relationship between drug release in vitro [$r_{dis}(t)$] and drug absorption in vivo [r(t)]. The simplest relationship is where drug dissolution reflects its rate of drug absorption. In this case:

$$r(t) = r_{dis}(t)$$

Various more complex functions that account for time lags for absorption, different time scales for in vitro dissolution and in vivo absorption and changing permeability through the gastrointestinal tract can be incorporated into the IVIVC equation. For example, the following equation includes a lag time (t_0), a time scaling factor (s_1), and a scaling factor (s_r) that allows incomplete absorption or utilisation of different units between in vitro dissolution and in vivo absorption.

$$r(t) = s_r \cdot r_{diss}(t_0 + s_1 \cdot t)$$

The differential equation-based approach utilises a traditional compartmental model framework for drug disposition and incorporates an input function. Alternatively, PBPK model may be used. The PBPK model should be mechanistic and have sufficient experimental data to adequately describe the absorption, metabolism, distribution, and elimination phases of the drug being tested. As with the differential equation-based convolution method, a PBPK approach uses the in vitro release profile as input into the model and a plasma profile will be generated that predicts the in vivo performance of the formulation.

$$r(t) = \varphi_{abs}(t) s_r r_{dis}(t_0 + s_1 t)$$

Where a two-stage approach is utilised, the average absorption profile should be derived from averaging of the individual subject absorption profiles (i.e. from individual deconvolution), rather than by deconvolution of the average concentration-time profiles. Unless the in vitro dissolution data are particularly variable, the use of average dissolution normally has little impact on the outcome of data analysis and is considered an acceptable practice.

3.4 IVIVC Model Qualification and Predictability Assessment

Model selection should be based on an understanding of the physicochemical properties of the drug, its absorption characteristics, the dissolution test characteristics and criteria for assessing goodness of fit (e.g. posterior predictive check). The purpose of the model is to be able to predict with adequate accuracy the expected plasma concentration-time curve from an in vitro dissolution data for a modified formulation. This is demonstrated by a graphical comparison of predicted and observed concentrations and calculation of prediction errors for summary parameters including at least Cmax, $AUC_{0\text{-}t}$ and $_{partial}AUC$ (see Section 6.8.1). General requirements for model evaluation within the nonlinear mixed effects context are outlined in detail in the Guideline on reporting the results of population pharmacokinetic analyses (CHMP/EWP/185990/06).

Where PBPK models are utilised for IVIVC development, it will be necessary to demonstrate that the model predicts the RFD data as well as the MR formulation data. Sufficient data needs to be submitted to support the performance of the model.

Most IVIVC analyses use averaged in vitro dissolution to predict an averaged in vivo concentration-time profile. This approach does not address adequately random variation in vitro, but more importantly, in vivo. From this point of view the one stage approaches offer the advantage that they are amenable to a nonlinear mixed effects analysis framework, which allows individual variability to be incorporated into the model, potentially improving the reliability of the model for inferences regarding the bioequivalence metrics of new formulations.

An IVIVC model is generally accepted as adequately accurate if from visual inspection the entire concentration-time curve is well predicted and the prediction errors are within acceptable limits. Internal predictability is assessed using the IVIVC model to predict the concentration-time profile from the respective dissolution data for each formulation. The summary parameters (Cmax, etc) are calculated from the predicted concentration-time curve and compared to the respective summary parameters for the observed data. The prediction error (PE), defined as %PE =[(observed value - predicted value) /observed value] x 100, is calculated for each of the summary parameters.
The absolute value of the prediction error for all summary parameters should be less than 15% for each formulation and the average prediction error for all formulations included in IVIVC development should be less than 10% for each summary parameter. Where an individual formulation is found to be inadequately predicted by the IVIVC, it is acceptable to redevelop the IVIVC excluding the outlier formulation, resulting in a narrower range of dissolution data included in the IVIVC. However, this will

then determine the range over which the IVIVC is accepted as predictive, impacting on the potential for specification and biowaiver justification. At least two formulations must remain and the exclusion should be supported by discussion of possible reasons for the deviation (e.g. release mechanism, production process).

In addition to evaluation of internal predictability utilising the batches included in a formal IVIVC study, it is encouraged to continue to demonstrate the applicability of the IVIVC with additional development batches (e.g. large scale batches used in pivotal studies, additional dosage strengths, any later formulation changes that were studied in vivo, etc). Ideally, whenever pharmacokinetic studies of formulations of different in vitro release profiles are conducted, these data should be utilised to provide or strengthen the evidence supporting the in vivo relevance of the in vitro dissolution test. This can be done through a cross study IVIVC development (using either one or two stage methods as described above) or through initial IVIVC development using small scale batches and external validation using large scale batches. In either case, any IVIVC development should demonstrate that the relationship holds for batches representative of the to-be-marketed formulation.

The procedure for external predictability analysis is as described above utilising the IVIVC previously developed. The concentration-time profiles are predicted based on the pharmacokinetics of the fast releasing formulation (i.e. the RFD) included in the study for external validation purposes and the in vitro dissolution data for the particular external validation batch. The absolute value of the prediction error for all summary parameters should be less than 10% for each formulation used for external validation.

3.4 Reporting

The IVIVC report should include a listing of all in vivo studies available for the modified release formulation and a rationale for the selection of data included in IVIVC analysis. Data listings should include: individual data and summary statistics for in vitro dissolution data, plasma concentration-time data, derived pharmacokinetic parameters and cumulative amount absorbed (derived from deconvolution, even if a one stage method is used for model development) for all batches used in model development.

Graphical displays should include in vitro dissolution versus time (highlighting batches of clinical significance, such as the to-be-marketed formulation, etc), cumulative amount absorbed versus time, absorption rate versus time, overlay of dissolution and absorption time courses (to judge different time frames, time lags between in vitro and in vivo data) and cumulative amount absorbed in vivo (% relative to RFD) versus amount released (% of dose) at same time in vitro (with overlay of 1:1, regression lines as helpful/appropriate) for all formulations included in IVIVC analysis. A Levy plot (time for a specific fraction released in vivo versus the time for the same fraction in vitro) may also be a useful graphical display where an obvious time difference exists between time courses of in vitro release and in vivo absorption (i.e. deviating from 1:1).

The dissolution test method should be described and a justification of its appropriateness given the physicochemical properties of the drug, etc should be included.

A full description of the modelling methodology and software employed and basis of decisions should be included, supported by a discussion of the formulation, physicochemical, pharmacokinetic and physiological factors controlling drug release in vitro and vivo. Where a compartmental deconvolution method is used (e.g. Wagner-Nelson or Lou-Riegelman), the appropriateness of the approach should be discussed.

Plots evaluating goodness of fit, appropriate to the modelling methodology employed, should be included as well as final parameter estimates for all fitted data (e.g. in vitro dissolution and in vivo absorption in case a model is used for interpolation, as well for the IVIVC model itself).

The final IVIVC model predicted plasma concentration-time data, derived parameters and associated prediction error should be included in a table. Graphical comparison of predicted and observed concentration-time profiles should be provided.

Appendix IV: summary of study recommendations for abridged applications

Prolonged release single unit formulation (SmPC recommends intake under fasting or fasting and fed conditions)

Strength	Single dose fasting study**	Single dose fed Study**	Fasting Multiple dose study*
high	yes	yes	yes
middle	yes	Waiver, if shape is similar	waiver
low	yes	Waiver, if shape is similar	waiver

* see criteria for necessity in section 6.1
** bracketing approach possible if criteria (see section 6.6) are met

Prolonged release single unit formulation (SmPC recommends intake under fed conditions)

Strength	Single dose fasting study**	Single dose fed Study**	Fed Multiple dose study*
high	yes	yes	yes
middle	Waiver, if shape is similar	yes	waiver
low	waiver, if shape is similar	yes	waiver

* see criteria for necessity in section 6.1
** bracketing approach possible if criteria (see section 6.6) are met

= if criteria (see section 6) are met, waivers to some strengths or bracketing approach are possible

Prolonged release multiple unit formulation (SmPC recommends intake under fasting or fasting and fed conditions)

Strength	Single dose fasting study	Single dose fed Study	Fasting Multiple dose study*
high	yes	yes	yes
middle	waiver	waiver	waiver
low	waiver	waiver	waiver

* see criteria for necessity in section 6.1

Prolonged release multiple unit formulation (SmPC recommends intake fed conditions)

Strength	Single dose fasting study	Single dose fed Study	Fed Multiple dose study*
high	yes	yes	yes
middle	waiver	waiver	waiver
low	waiver	waiver	waiver

* see criteria for necessity in section 6.1

= if criteria (see section 6) are met, waivers to some strengths or bracketing approach are possible

Delayed release single unit formulation (SmPC recommends intake under fasting or fasting and fed conditions)

Strength	Single dose fasting study**	Single dose fed Study**
high	yes	yes
middle	yes	waiver, if shape is similar
low	Yes	waiver, if shape is similar

** bracketing approach possible if criteria (see section 6.6) are met

Delayed release single unit formulation (SmPC recommends intake under fed conditions)

Strength	Single dose fasting study**	Single dose fed Study**
high	Yes	yes
middle	waiver, if shape is similar	yes
low	waiver, if shape is similar	yes

** bracketing approach possible if criteria (see section 6.6) are met

= if criteria (see section 6) are met, waivers to some strengths or bracketing approach are possible

Delayed release multiple unit formulation (SmPC recommends intake under fasting or fasting and fed conditions)

Strength	Single dose fasting study	Single dose fed Study
high	yes	yes
middle	waiver	waiver
low	waiver	waiver

Delayed release multiple unit formulation (SmPC recommends intake under fed conditions)

Strength	Single dose fasting study	Single dose fed Study
high	yes	yes
middle	waiver	waiver
low	waiver	waiver

= if criteria (see section 6) are met, waivers to some strengths or bracketing approach are possible

EXHIBIT 10

US008731963B1

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

(10) **Patent No.: US 8,731,963 B1**
(45) **Date of Patent: *May 20, 2014**

(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.: **13/592,202**

(22) Filed: **Aug. 22, 2012**

Related U.S. Application Data

(63) Continuation 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; 707/803

(58) **Field of Classification Search**
USPC 707/803; 705/2, 3
See application file for complete search history.

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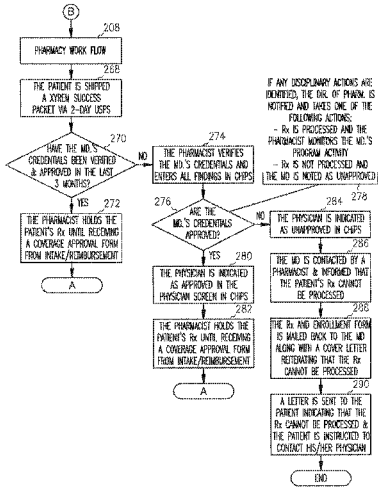
(57) **ABSTRACT**

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

28 Claims, 16 Drawing Sheets



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* cited by examiner

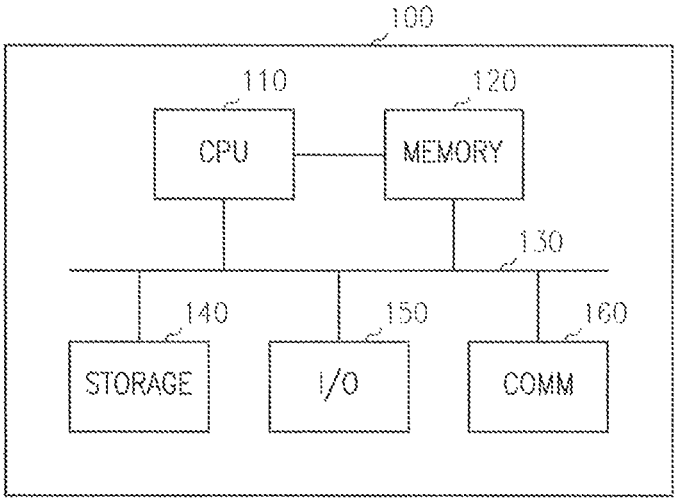

FIG. 1

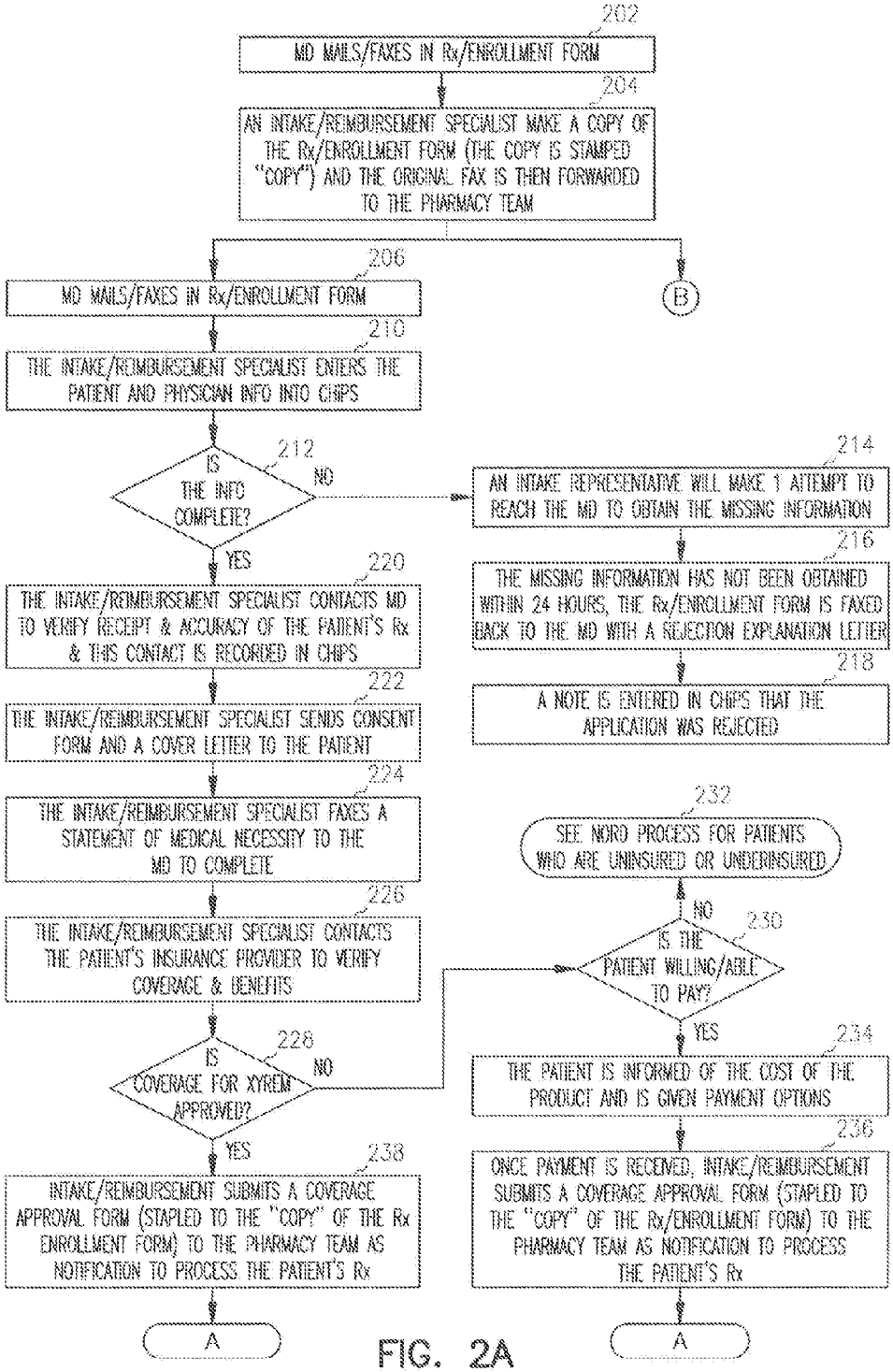
202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE 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
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
236
ONCE PAYMENT IS RECEIVED, INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx/ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
YES
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
A

FIG. 2A

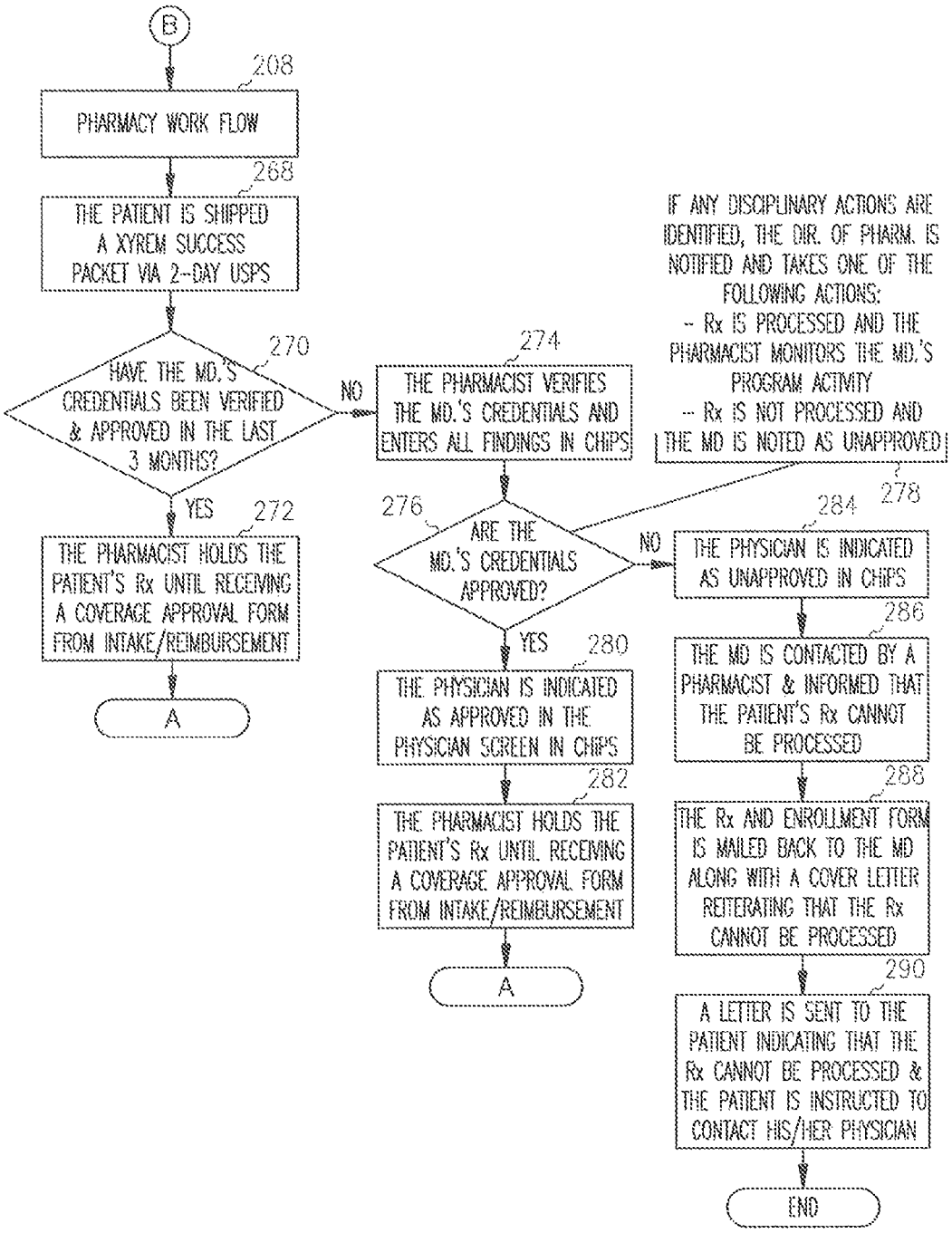
B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHIPS
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
276
ARE THE MD.'S CREDENTIALS APPROVED?
NO
284
THE PHYSICIAN IS INDICATED AS UNAPPROVED IN CHIPS
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
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

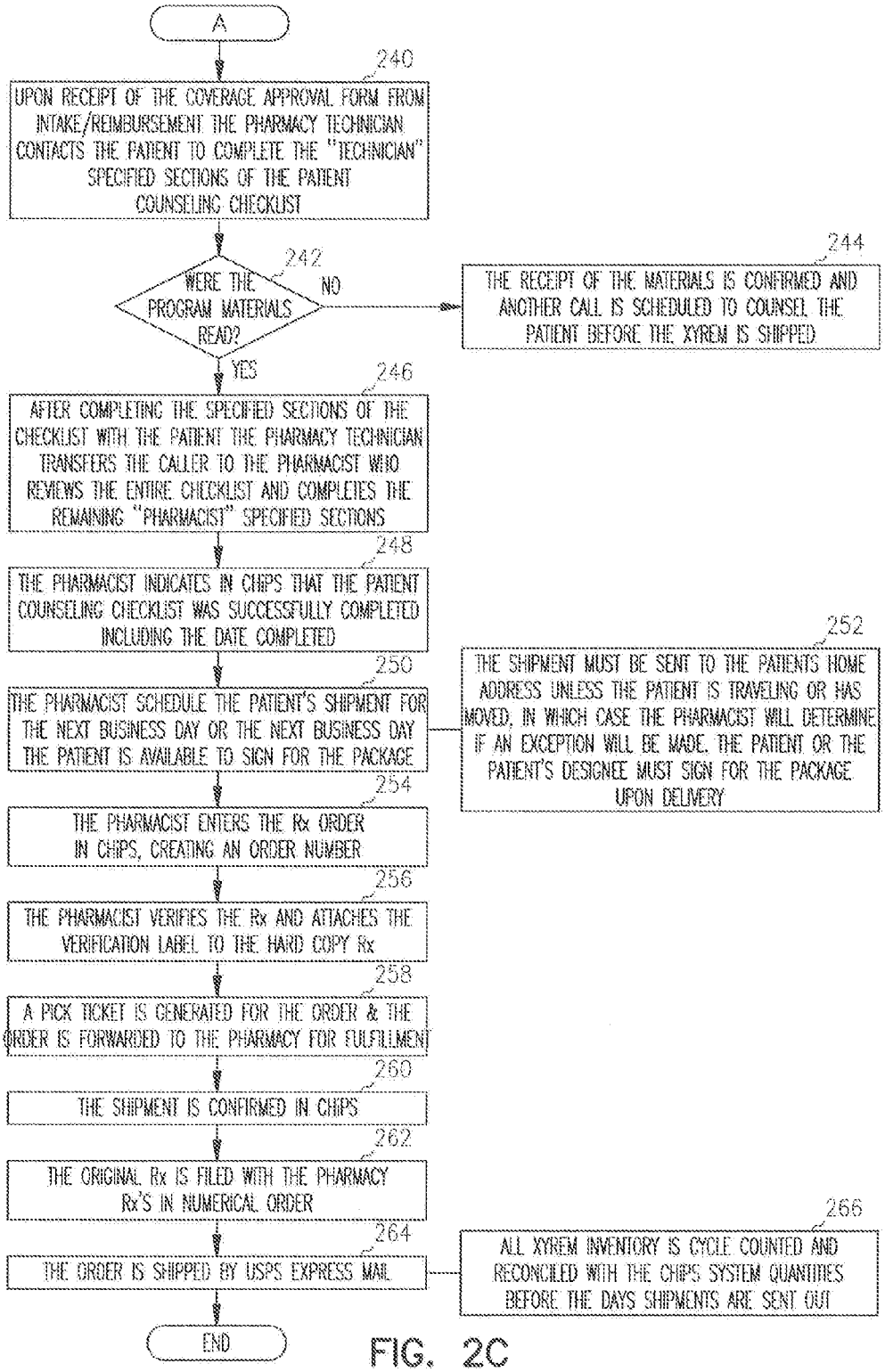
A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER 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

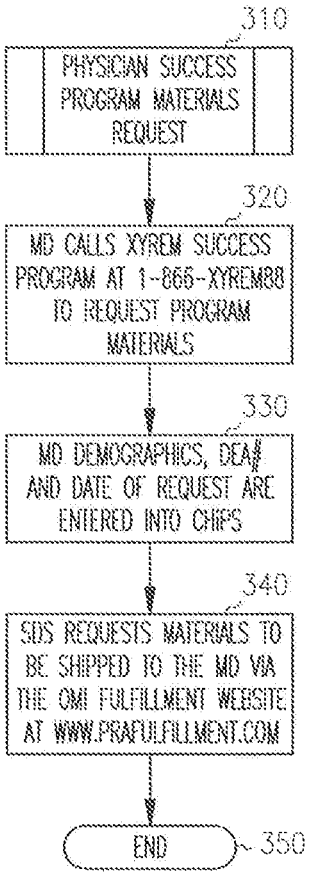
310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM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

FIG. 3

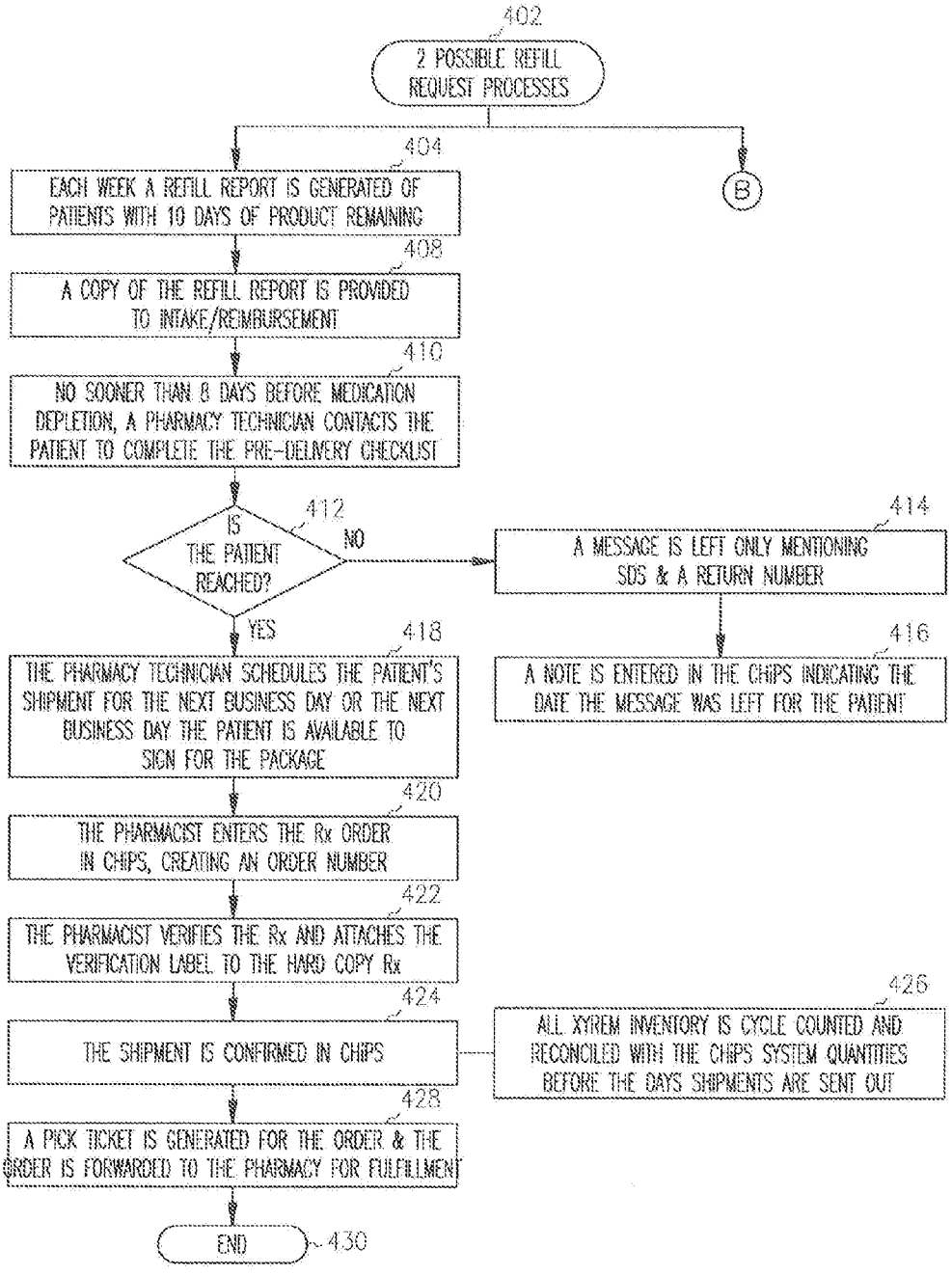
402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE 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

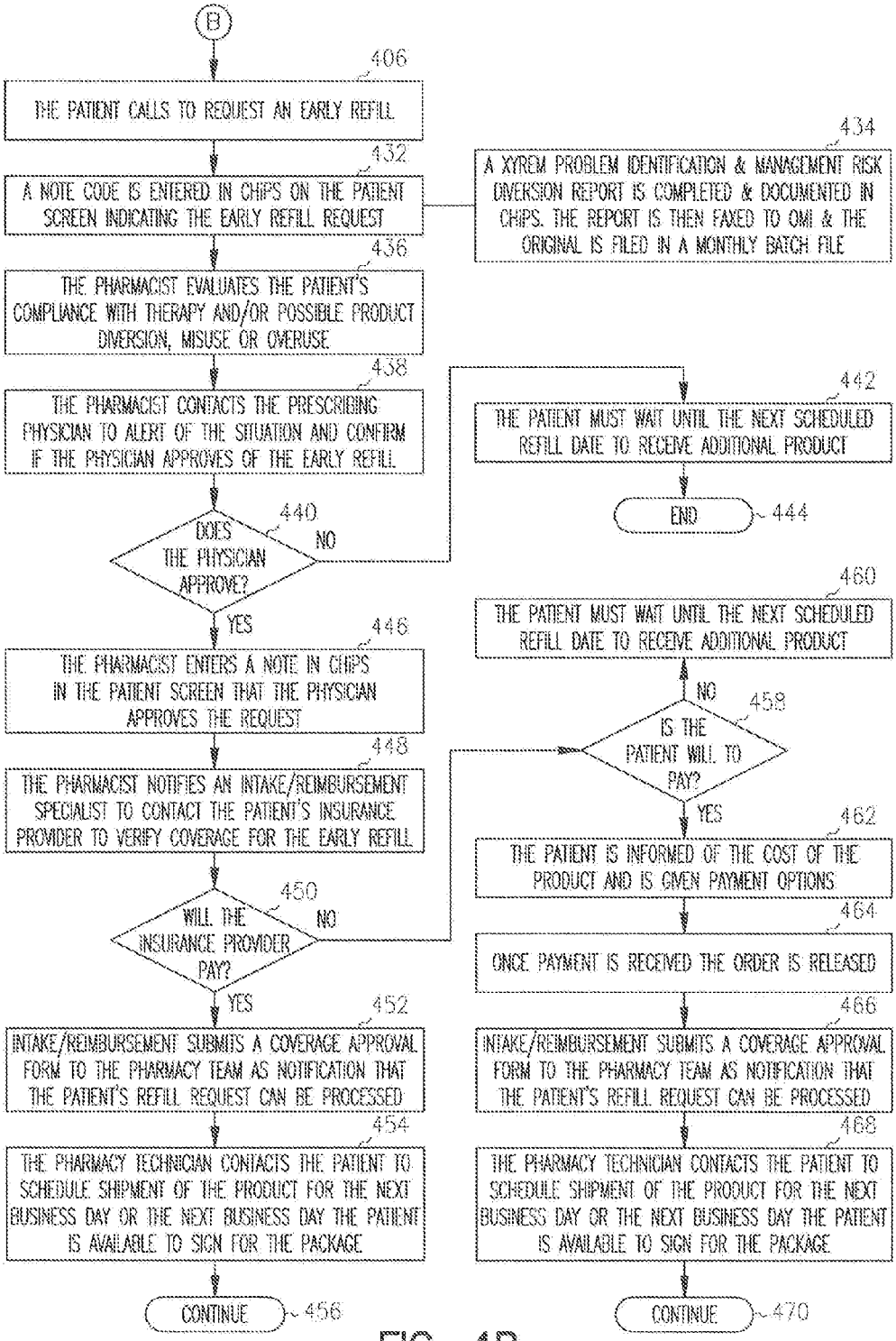
B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYROM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS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

FIG. 4B

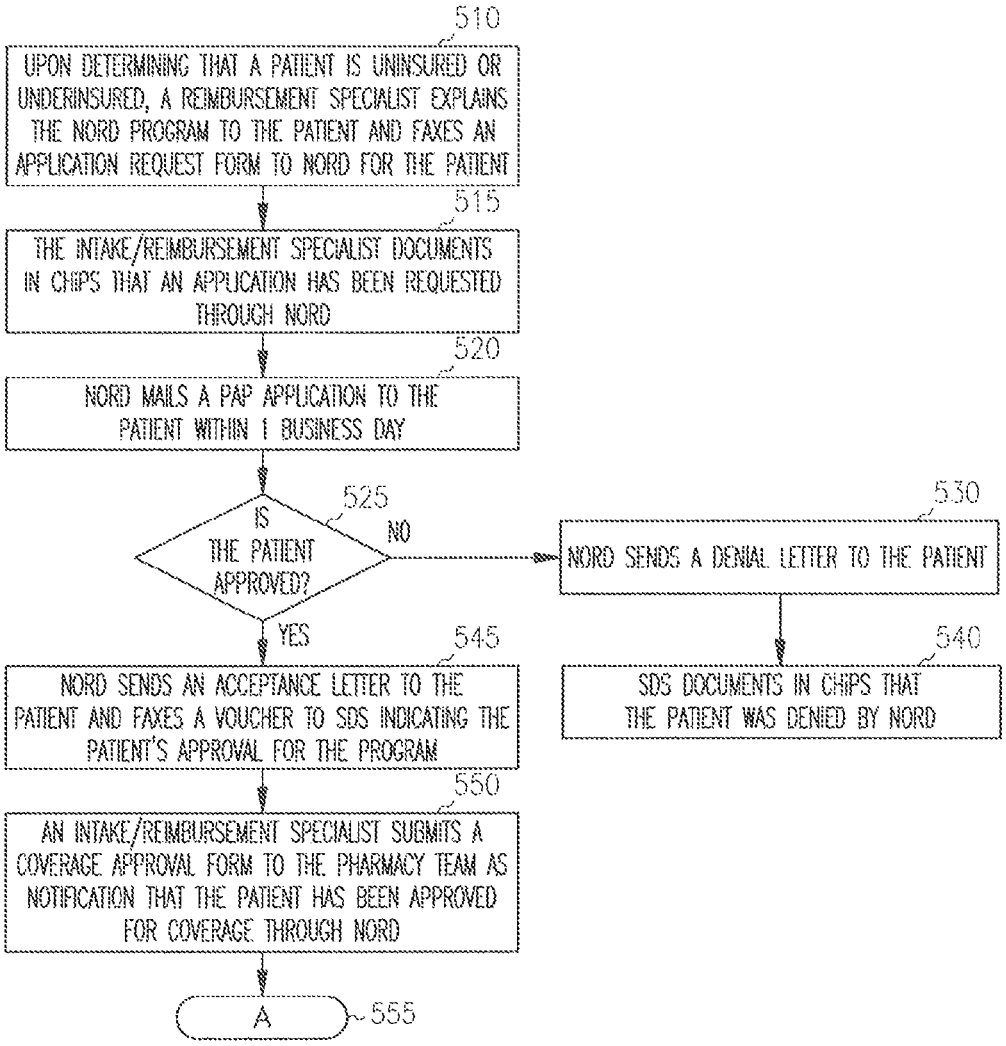
510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHIPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH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

FIG. 5

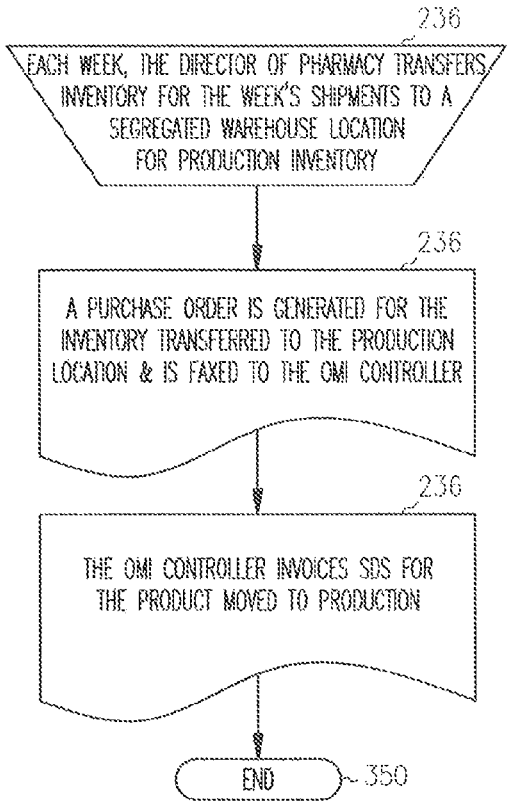

FIG. 6

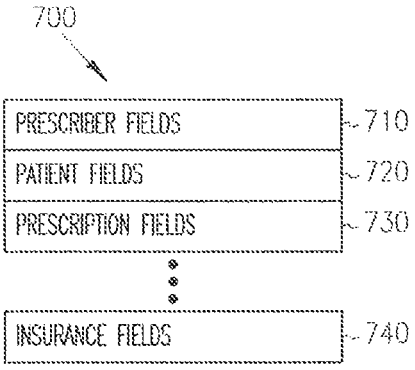

FIG. 7

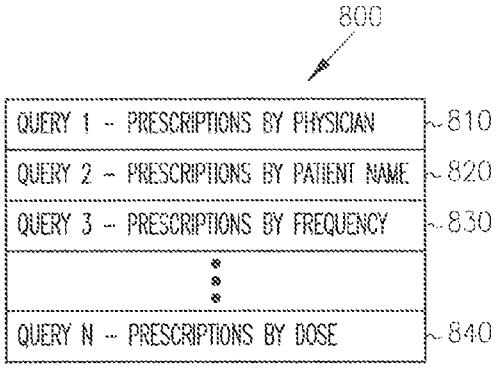

FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

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

PRESCRIPTION FORM

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

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

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

PATIENT INFORMATION

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

PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

FAX COMPLETED FORM TO XYREM SUCCESS PROGRAM (TOLL-FREE) 1-866-470-1744

FOR INFORMATION, CALL THE XYREM TEAM (TOLL FREE) AT 1-866-XYREM88 (1-866-997-3688)

FIG. 9

1000

PATIENT ASSISTANCE APPLICATION REQUEST FORM

DATE:

TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS

FAX #: 203-798-2291

PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:

PATIENT NAME _____

ADDRESS _____

_____

_____

TELEPHONE: ( ) _____

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

_____ BOTTLES (THREE MONTHS SUPPLY)

BACKGROUND INFORMATION:

_____

_____

_____

_____

_____

_____

FIG. 10

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
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

CASE CODE: ********

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

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml btl	1

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

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

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

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

CASE CODE: ********

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

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREM 180ml btl	1

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

APPROVED _____

PHARMACY USE

FIG. 11


1200
SENSITIVE DRUG PHYSICIAN'S CERTIFICATE
OF MEDICAL NEED
PATIENT INFORMATION
DATE: .....
NAME: .....
LAST FIRST M
DATE OF BIRTH: .....
DRUG BEING PRESCRIBED: XYREM
DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: .....
ICD-9: .....
PHYSICIAN INFORMATION
PHYSICIAN'S NAME (PLEASE PRINT): .....
PHYSICIAN'S SIGNATURE: ..... DATE: .....
PLEASE FAX BACK TO SENSITIVE DRUG SUCCESS PROGRAM: (1-800-TOLL FREE NUMBER)

FIG. 12

ACTIVITY REPORTS

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

FIG. 13A

ACTIVITY REPORTS

PHARMACY			
# 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		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 a Continuation 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 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 **30** 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 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. The system of claim **1**, wherein the data processor selectively blocks shipment of the prescription drug to the patient based upon said identifying by the database query.

3. The system of claim **1**, wherein the prescription drug is shipped to the narcoleptic patient if no potential misuse, abuse or diversion is found for the narcoleptic patient.

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

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

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

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

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

9. 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.

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

11. The system of claim **10**, wherein the expected date is based on a prescription for the prescription drug and a date of a previous filling of the prescription.

12. The system of claim **11**, wherein the prescription identifies an amount of the prescription drug to be provided and a schedule for consumption of the prescription drug.

13. 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.

14. 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.

15. The system of claim **14**, wherein one or more controls for distribution of the prescription drug are selected based on the identified pattern.

16. The system of claim **15**, wherein the one or more controls are submitted to an approval body for approval of distribution of the prescription drug.

17. 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.

18. The system of claim **17**, wherein the data processor is used to add further controls until approval is obtained.

19. The system of claim **18**, wherein the approval body is the Food and Drug Administration (FDA) or the Drug Enforcement Agency (DEA).

20. 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.

21. 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.

22. 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.

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

one or more computer memories for storing 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.

24. 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.

25. The system of claim **24**, 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.

26. The system of claim **24**, 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.

27. The system of claim **24**, 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.

28. The system of claim **24**, wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,731,963 B1
APPLICATION NO. : 13/592202
DATED : May 20, 2014
INVENTOR(S) : Reardan et al.

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

ON THE TITLE PAGE:

On page 2, in column 2, under "Other Publications", line 1, delete "mailed" and insert --filed--, therefor

On page 2, in column 2, under "Other Publications", line 24, delete "mailed" and insert --filed--, therefor

On page 2, in column 2, under "Other Publications", line 42, delete "mailed" and insert --filed--, therefor

On page 2, in column 2, under "Other Publications", line 54, delete "mailed" and insert --filed--, therefor

On page 3, in column 2, under "Other Publications", line 54, delete "Sodiium" and insert --Sodium--, therefor

On page 3, in column 2, under "Other Publications", line 57, delete "Sodiium" and insert --Sodium--, therefor

IN THE DRAWINGS:

On sheet 9 of 16, Fig. 6, delete "236" and insert --610--, therefor

On sheet 9 of 16, Fig. 6, delete "236" and insert --612--, therefor

On sheet 9 of 16, Fig. 6, delete "236" and insert --630--, therefor

Signed and Sealed this
Eighteenth Day of November, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

On sheet 9 of 16, Fig. 6, delete "350" and insert --640--, therefor

On sheet 12 of 16, Fig. 11, delete "XYREEM" and insert --XYREM--, therefor

IN THE SPECIFICATION:

In column 4, line 21, delete "RX/enrollment" and insert --Rx/enrollment--, therefor

In column 6, line 16, delete "302" and insert --402--, therefor

In column 6, line 25, after "pre-delivery", delete "30", therefor

IN THE CLAIMS:

In column 11, line 14, in Claim 24, after "drug,", insert --and--, therefor

(12) **INTER PARTES REVIEW CERTIFICATE** (1148th)
United States Patent
Reardan et al.

(10) **Number: US 8,731,963 K1**
(45) **Certificate Issued: Apr. 3, 2019**

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

(75) Inventors: **Dayton T. Reardan**; **Patti A. Engel**; **Bob Gagne**

(73) Assignee: **Jazz Pharmaceuticals, Inc.**

Trial Number:

IPR2015-01903 filed Sep. 14, 2015

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Appl. No.: **13/592,202**
Filed: **Aug. 22, 2012**

The results of IPR2015-01903 are reflected in this inter partes review certificate under 35 U.S.C. 318(b).

INTER PARTES REVIEW CERTIFICATE
U.S. Patent 8,731,963 K1
Trial No. IPR2015-01903
Certificate Issued Apr. 3, 2019

AS A RESULT OF THE INTER PARTES REVIEW PROCEEDING, IT HAS BEEN DETERMINED THAT:

Claims **24**, **26** and **27** are cancelled.

* * * * *

EXHIBIT 11

UPDATED ANNUALLY

Merriam-Webster's Collegiate® Dictionary

TENTH EDITION

THE WORDS YOU NEED TODAY

- Clear and precise
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AN ENCYCLOPÆDIA BRITANNICA® COMPANY

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TENTH EDITION

A GENUINE MERRIAM-WEBSTER

The name *Webster* alone is no guarantee of excellence. It is used by a number of publishers and may serve mainly to mislead an unwary buyer.

Merriam-Webster™ is the name you should look for when you consider the purchase of dictionaries or other fine reference books. It carries the reputation of a company that has been publishing since 1831 and is your assurance of quality and authority.

Library of Congress Cataloging in Publication Data
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Merriam-Webster's collegiate dictionary. — 10th ed.
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1. English language—Dictionaries. I. Merriam-Webster, Inc.
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423—dc21 97-41846
CIP

Made in the United States of America

30313233RT:WC01

car·tog·ra·phy \-fē\ *n* [*cartographie*, fr. *carte* card, map + *-graphie* -graphy — more at CARD] (ca. 1847) : the science or art of making maps — **car·to·graph·ic** \ˌkär-tə-ˈgra-fik\ *also* **car·to·graph·i·cal** \-fi-kəl\ *adj* — **car·to·graph·i·cal·ly** \-fi-k(ə-)lē\ *adv*

¹car·ton \ˈkär-tᵊn\ *n* [F, fr. It *cartone* pasteboard] (1825) : a box or container usu. made of paperboard and often of corrugated paperboard

²carton *vt* (1921) : to pack or enclose in a carton ~ *vi* : to shape cartons from paperboard sheets

car·toon \kär-ˈtün\ *n, often attrib* [It *cartone* pasteboard, cartoon, aug. of *carta* leaf of paper — more at CARD] (1671) **1** : a preparatory design, drawing, or painting (as for a fresco) **2 a** : a drawing intended as satire, caricature, or humor ⟨a political ~⟩ **b** : COMIC STRIP **3** : ANIMATED CARTOON **4** : a ludicrously simplistic, unrealistic, or one-dimensional portrayal or version ⟨the film's villain is an entertaining ~⟩ — **cartoon** *vb* — **car·toon·ing** *n* — **car·toon·ish** \-ˈtü-nish\ *adj* — **car·toon·ish·ly** *adv* — **car·toon·ist** \-ˈtü-nist\ *n* — **car·toon·like** \-ˈtün-ˌlīk\ *adj* — **car·toony** \-ˈtü-nē\ *adj*

car·top \ˈkär-ˌtäp\ *adj* (1946) : suitable in size and weight for carrying on top of an automobile ⟨a ~ fishing boat⟩ — **car·top·per** \-ˌtä-pər\ *n*

car·touche *also* **car·touch** \kär-ˈtüsh\ *n* [F *cartouche*, fr. It *cartoccio*, fr. *carta*] (1611) **1** : a gun cartridge with a paper case **2** : an ornate or ornamental frame **3** : an oval or oblong figure (as on ancient Egyptian monuments) enclosing a sovereign's name

car·tridge \ˈkär-trij, *dial* ˈka-trij\ *n* [alter. of earlier *cartage*, modif. of MF *cartouche*] (1579) : a case or container that holds a substance, device, or material which is difficult, troublesome, or awkward to handle and that usu. can be easily changed: as **a** : a tube (as of metal) containing a complete charge for a firearm and usu. an initiating device (as a primer) **b** : a case containing an explosive charge for blasting **c** : an often cylindrical container for insertion into a larger mechanism or apparatus **d** : CASSETTE 2 **e** : a small case that contains a phonograph needle and transducer and is attached to a tonearm **f** : a case containing a reel of magnetic tape arranged for insertion into a recorder or player **g** : a removable case containing a magnetic tape or one or more disks and used as a computer storage medium **h** : a case for holding printed circuit chips containing a computer program ⟨a video-game ~⟩

cartridge belt *n* (1874) **1** : a belt having a series of loops for holding cartridges **2** : a belt worn around the waist and designed for carrying various attachable equipment (as a cartridge case, canteen, or compass)

car·tu·lary \ˈkär-chə-ˌler-ē\ *n, pl* **-lar·ies** [ML *chartularium*, fr. *chartula* charter — more at CHARTER] (1541) : a collection of charters; *esp* : a book holding copies of the charters and title deeds of an estate

¹cart·wheel \ˈkärt-ˌhwēl, -ˌwēl\ *n* (1855) **1** : a large coin (as a silver dollar) **2** : a lateral handspring with arms and legs extended

²cartwheel *vi* (1917) : to move like a turning wheel; *specif* : to perform cartwheels — **cart·wheel·er** *n*

car·un·cle \ˈkar-ˌəŋ-kəl, kə-ˈrəŋ-\ *n* [obs. F *caruncule*, fr. L *caruncula* little piece of flesh, dim. of *caro* flesh — more at CARNAL] (1615) **1** : a naked fleshy outgrowth (as a bird's wattle) **2** : an outgrowth on a seed adjacent to the micropyle

car·va·crol \ˈkär-və-ˌkrōl, -ˌkrōl\ *n* [ISV, fr. NL *carvi* (specific epithet of *Carum carvi* caraway) + L *acr-*, *acer* sharp — more at CARAWAY, EDGE] (1854) : a liquid phenol $C_{10}H_{14}O$ found in essential oils of various mints (as thyme) and used as a fungicide and disinfectant

carve \ˈkärv\ *vb* **carved; carv·ing** [ME *kerven*, fr. OE *ceorfan*; akin to OHG *kerban* to notch, Gk *graphein* to scratch, write] *vt* (bef. 12c) **1** : to cut with care or precision ⟨*carved* fretwork⟩ **2** : to make or get by or as if by cutting — often used with *out* ⟨~ out a career⟩ **3** : to cut into pieces or slices ⟨*carved* the turkey⟩ ~ *vi* **1** : to cut up and serve meat **2** : to work as a sculptor or engraver — **carv·er** *n*

car·vel–built \ˈkär-vəl-ˌbilt, -ˌvel-\ *adj* [prob. fr. D *karveel-*, fr. *karveel* caravel, fr. MF *carvelle*] (1798) : built with the planks meeting flush at the seams

carv·en \ˈkär-vən\ *adj* (14c) : wrought or ornamented by carving

carv·ing \ˈkär-viŋ\ *n* (13c) **1** : the act or art of one who carves **2** : a carved object, design, or figure

car wash *n* (1956) : an area or structure equipped with facilities for washing automobiles

cary- *or* **caryo-** — see KARY-

cary·at·id \ˌkar-ē-ˈa-təd, ˈkar-ē-ə-ˌtid\ *n, pl* **-ids** *or* **-i·des** \ˌkar-ē-ˈa-tə-ˌdēz\ [L *caryatides*, pl., fr. Gk *karyatides* priestesses of Artemis at Caryae, caryatids, fr. *Karyai* Caryae in Laconia] (1563) : a draped female figure supporting an entablature

caryatid

cary·op·sis \ˌkar-ē-ˈäp-səs\ *n, pl* **-op·ses** \-ˌsēz\ *also* **-si·des** \-sə-ˌdēz\ [NL] (1830) : a small one-seeded dry indehiscent fruit (as of Indian corn or wheat) in which the fruit and seed fuse in a single grain

ca·sa \ˈkä-sə\ *n* [Sp & It, fr. L, cottage] (1844) *chiefly Southwest* : DWELLING

ca·sa·ba \kə-ˈsä-bə\ *n* [*Kasaba* (now Turgutlu), Turkey] (1889) : any of several winter melons with yellow rind and sweet flesh

Ca·sa·no·va \ˌka-zə-ˈnō-və, ˌka-sə-\ *n* [Giacomo Girolamo *Casanova*] (1888) : LOVER; *esp* : a man who is a promiscuous and unscrupulous lover

Cas·bah \ˈkaz-ˌbä, ˈkäz-\ *n* [F, fr. Ar dial. *qaṣbah*] (1944) **1** : a No. African castle or fortress **2** : the native section of a No. African city

cas·ca·bel \ˈkas-kə-ˌbel\ *n* [Sp, lit., small bell] (1639) **1** : a projection behind the breech of a muzzle-loading cannon **2** : a small hollow perforated spherical bell enclosing a loose pellet

¹cas·cade \(ˌ)kas-ˈkād\ *n* [F, fr. It *cascata*, fr. *cascare* to fall, fr. (assumed) VL *casicare*, fr. L *casus* fall] (1641) **1** : a steep usu. small fall of water; *esp* : one of a series **2 a** : something arranged or occurring in a series or in a succession of stages so that each stage derives from or acts upon the product of the preceding ⟨blood clotting involves a biochemical ~⟩ **b** : a fall of material (as lace) that hangs in a zigzag line **3** : something falling or rushing forth in quantity ⟨a ~ of sound⟩ ⟨a ~ of events⟩

²cascade *vb* **cas·cad·ed; cas·cad·ing** *vi* (1702) : to fall, pour, or rush in or as if in a cascade ~ *vt* **1** : to cause to fall like a cascade **2** : to connect in a cascade arrangement

cas·cara \kə-ˈskar-ə\ *n* [Sp *cáscara* husk, bark, prob. fr. *cascar* to crack, break, fr. (assumed) VL *quassicare* to shake, fr. L *quassare* — more at QUASH] (1879) **1** : CASCARA BUCKTHORN **2** : CASCARA SAGRADA

cascara buckthorn *n* (ca. 1900) : a buckthorn (*Rhamnus purshiana*) of the Pacific coast of the U.S. yielding cascara sagrada

cascara sa·gra·da \-sə-ˈgrä-də\ *n* [AmerSp *cáscara sagrada*, lit., sacred bark] (1885) : the dried bark of cascara buckthorn used as a laxative

cas·ca·ril·la \ˌkas-kə-ˈri-lə, -ˈrē-ə\ *n* [Sp, dim. of *cáscara*] (1686) : the aromatic bark of a West Indian shrub (*Croton eluteria*) of the spurge family used for making incense and as a tonic; *also* : this shrub

¹case \ˈkās\ *n* [ME *cas*, fr. OF, fr. L *casus* fall, chance, fr. *cadere* to fall — more at CHANCE] (13c) **1 a** : a set of circumstances or conditions ⟨is the statement true in all three ~*s*⟩ **b** (1) : a situation requiring investigation or action (as by the police) (2) : the object of investigation or consideration **2** : CONDITION; *specif* : condition of body or mind **3** [ME *cas*, fr. MF, fr. L *casus*, trans. of Gk *ptōsis*, lit., fall] **a** : an inflectional form of a noun, pronoun, or adjective indicating its grammatical relation to other words **b** : such a relation whether indicated by inflection or not **4** : what actually exists or happens : FACT **5 a** : a suit or action in law or equity **b** (1) : the evidence supporting a conclusion or judgment (2) : ARGUMENT; *esp* : a convincing argument **6 a** : an instance of disease or injury; *also* : PATIENT **b** : an instance that directs attention to a situation or exhibits it in action : EXAMPLE **c** : a peculiar person : CHARACTER **7** : oneself considered as an object of harassment ⟨get off my ~⟩ *syn* see INSTANCE — **in any case** : without regard to or in spite of other considerations : whatever else is done or is the case ⟨war is inevitable *in any case*⟩ ⟨*in any case* the report will be made public next month⟩ — **in case** : as a precaution ⟨took an umbrella, just *in case*⟩ — **in case of** : in the event of ⟨*in case of* trouble, yell⟩

²case *n* [ME *eas*, fr. ONF *casse*, fr. L *capsa* chest, case, prob. fr. *capere* to take — more at HEAVE] (14c) **1 a** : a box or receptacle for holding something **b** : a box together with its contents **c** : SET; *specif* : PAIR **2 a** : an outer covering or housing ⟨a pastry ~⟩ **b** : a tube into which the components of a round of ammunition are loaded **3** : a divided tray for holding printing type **4** : the frame of a door or window : CASING

³case *vt* **cased; cas·ing** (1575) **1** : to enclose in or cover with or as if with a case : ENCASE **2** : to line (as a well) with supporting material (as metal pipe) **3** : to inspect or study esp. with intent to rob

ca·se·ation \ˌkā-sē-ˈā-shən\ *n* [L *caseus* cheese] (1866) : necrosis with conversion of damaged tissue into a soft cheesy substance — **ca·se·ate** \ˈkā-sē-ˌāt\ *vi*

case·bear·er \ˈkās-ˌbar-ər, -ˌber-\ *n* (ca. 1889) : an insect larva that forms a protective case (as of silk)

case·book \-ˌbůk\ *n* (1762) **1** : a book containing records of illustrative cases that is used for reference and instruction (as in law or medicine) **2** : a compilation of primary and secondary documents relating to a central topic together with scholarly comment, exercises, and study aids that is designed to serve as a sourcebook for short papers (as in a writing course) or as a point of departure for a research paper

cased glass \ˈkāst-\ *n* (1849) : glass consisting of two or more fused layers of different colors often decorated by cutting so that the inner layers show through — called also *case glass*

case goods *n pl* (1922) **1** : furniture (as bureaus or bookcases) that provides interior storage space; *also* : dining-room and bedroom furniture sold as sets **2** : products often sold by the case

case–hard·en \ˈkās-ˌhär-dᵊn\ *vt* (1677) **1** : to harden (a ferrous alloy) so that the surface layer is harder than the interior **2** : to make callous or insensible — **case–hard·ened** *adj*

case history *n* (1894) : a record of history, environment, and relevant details of a case esp. for use in analysis or illustration

ca·sein \ˈkā-ˌsēn, kā-ˈ\ *n* [prob. fr. F *caséine*, fr. L *caseus*] (1841) : a phosphoprotein of milk: as **a** : one that is precipitated from milk by heating with an acid or by the action of lactic acid in souring and is used in making paints and adhesives **b** : one that is produced when milk is curdled by rennet, is the chief constituent of cheese, and is used in making plastics

ca·sein·ate \kā-ˈsē-ˌnāt, ˈkā-si-ˌnāt\ *n* (1904) : a compound of casein with a metal (as calcium or sodium)

case in point (1965) : an illustrative, relevant, or pertinent case

case knife *n* (1704) **1** : SHEATH KNIFE **2** : a table knife

case law *n* (1861) : law established by judicial decision in cases

case·load \ˈkās-ˌlōd\ *n* (1938) : the number of cases handled (as by a court or clinic) usu. in a particular period

case·mate \ˈkās-ˌmāt\ *n* [MF, fr. OIt *casamatta*] (1575) : a fortified position or chamber or an armored enclosure on a warship from which guns are fired through embrasures

case·ment \ˈkās-mənt\ *n* [ME, hollow molding, prob. fr. ONF *encasement* frame, fr. *encasser* to enchase, frame, fr. *en-* + *casse*] (15c) : a window sash that opens on hinges at the side; *also* : a window with such a sash

ca·se·ous \ˈkā-sē-əs\ *adj* [L *caseus* cheese] (1661) : marked by caseation; *also* : CHEESY

ca·sern *or* **ca·serne** \kə-ˈzərn\ *n* [F *caserne*] (1696) : a military barracks in a garrison town

case study *n* (1875) **1** : an intensive analysis of an individual unit (as a person or community) stressing developmental factors in relation to environment **2** : CASE HISTORY

case system *n* (ca. 1889) : a system of teaching law in which instruction is chiefly on the basis of leading or selected cases as primary authorities instead of from textbooks

case·work \ˈkās-ˌwərk\ *n* (1886) : social work involving direct consideration of the problems, needs, and adjustments of the individual case (as a person or family) — **case·work·er** \-ˌwər-kər\ *n*

¹cash \ˈkash\ *n* [modif. of MF or OIt; MF *casse* money box, fr. OIt *cassa*, fr. L *capsa* chest — more at CASE] (1596) **1** : ready money **2** : money or its equivalent (as a check) paid for goods or services at the time of purchase or delivery — **cash·less** \-ləs\ *adj*

EXHIBIT 12

RANDOM HOUSE WEBSTER'S *college dictionary*

with CD-ROM

RANDOM HOUSE
REFERENCE

NEW YORK TORONTO LONDON · SYDNEY AUCKLAND

Random House Webster's College Dictionary

The first Random House college dictionary, the *American College Dictionary,* was published in 1947 to critical acclaim. The first edition of the *Random House Webster's College Dictionary* was published in 1991. Subsequent revisions were published in 1992, 1995, and 1996. A second, completely redesigned, revised, and updated edition was published in 1997, with updates copyright ©2005, 2001, 2000, 1999, 1998, 1996, 1995, 1992, 1991 by Random House, Inc.

New words edited by Barbara Ann Kipfer, Dictionary.com Managing Editor, Lexico Publishing Group.

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Visit the Random House Reference Web site at www.randomwords.com

Typeset and Printed in the United States of America

2001 Second Revised and Updated Random House Edition
9 8 7 6 5 4 3 2 1

style: *to perform with spirit and dash.* **17.** a short race: *the 50-yard dash.* **18.** DASHBOARD (def. 1). **19.** a signal of longer duration than a dot, used in groups of dots, dashes, and spaces to represent letters, as in Morse code. **20.** a hasty stroke, esp. of a pen. **21.** *Archaic.* a violent and rapid blow or stroke. [1250–1300; ME *dasshen*]

dash² (dash), *v.t. Chiefly Brit.* to damn (usu. used interjectionally). [1790–1800; euphemism based on *d—n.* printed form of DAMN]

dash•board (dash′bôrd′, -bōrd′), *n.* **1.** the instrument panel of an automotive vehicle. **2.** a board at the front of an open carriage to deflect mud or dirt. [1840–50]

da•sheen (da shēn′), *n.* TARO. [1895–1900; repr. F *de Chine* of China]

dash•er (dash′ər), *n.* **1.** a person or thing that dashes. **2.** a plunger with paddles at one end, as for churning butter or ice cream. **3.** a person of dashing appearance or manner. [1780–90]

da•shi•ki (də shē′kē, dä-) also **dashiki**, *n., pl.* **-kis.** a loose, often colorfully patterned pullover garment of African origin. [1965–1970; < Yoruba *dànṣíkí* < Hausa *dán cíkí* (with imploded *d*)]

dashiki

dash•ing (dash′ing), *adj.* **1.** energetic and spirited. **2.** elegant and gallant in appearance and manner. [1800–05] **—dash′ing•ly,** *adv.*

das•sie (das′ē, dä′sē), *n.* HYRAX. [1750–90; < Afrik, dim. of *das*, with same sense; cf. D, MD *das* badger]

das•tard (das′tərd), *n.* a mean, sneaking coward. [1400–50; late ME, akin to ME *dasard* term of contempt, perh. der. of *dasen* DAZE]

das•tard•ly (das′tərd lē), *adj.* cowardly; meanly base; sneaking: *a dastardly act.* [1560–70] **—das′tard•li•ness,** *n.*

DAT, digital audiotape.

dat., date.

da•ta (dā′tə, dat′ə, dä′tə), *n.* **1.** a pl. of DATUM. **2.** (*used with a pl. v.*) individual facts, statistics, or items of information. **3.** (*used with a sing. v.*) a body or collection of facts or particulars; information. **—Usage.** DATA is a plural of DATUM, orig. a Latin noun meaning "a thing given." Today, DATA is used in English both as a plural noun meaning "facts or pieces of information" (*These data are described fully on page 8*) and as a singular mass noun meaning "information": *The data has been entered in the computer.* It is almost always treated as a plural in scientific and academic writing, as a singular or plural elsewhere depending on the context. The singular DATUM meaning "a piece of information" occurs most frequently in academic or scientific writing.

da′ta bank′ or **da′ta•bank′,** *n.* DATABASE. [1965–70]

da′ta•base′ or **da′ta base′,** *n.* a collection of organized, related data, esp. one in electronic form that can be accessed and manipulated by specialized computer software. [1965–70]

da′ta high′way, *n.* INFORMATION SUPERHIGHWAY.

da′ta proc′essing, *n.* the automated processing of information, esp. by computers. [1950–55] **—da′ta proc′essor,** *n.*

dat•cha (dä′chə), *n., pl.* **-chas.** DACHA.

date¹ (dāt), *n., v.,* **dat•ed, dat•ing.** *—n.* **1.** a particular month, day, and year at which some event happened or will happen: *July 4, 1776 is an important date in American history.* **2.** the day of the month: *Is today's date the 8th?* **3.** an inscription on a writing, coin, etc., that shows the time, or time and place, of writing, casting, etc. **4.** period in general: *at a late date.* **5.** duration: *Childhood has so short a date.* **6.** an appointment for a particular time, esp. a social engagement arranged beforehand. **7.** a person with whom one has such an appointment. **8.** an engagement to perform. **9. dates,** the birth and death dates, usu. in years, of a person: *Dante's dates are 1265 to 1321.* *—v.i.* **10.** to have or bear a date: *The letter dates from 1873.* **11.** to belong to a particular period: *The architecture dates as far back as 1830.* **12.** to reckon from some point in time: *The custom dates from the Victorian era.* **13.** to go out socially on dates. *—v.t.* **14.** to furnish with a date. **15.** to ascertain the period or point in time of: *to date the archaeological ruins.* **16.** to show to be old-fashioned. **17.** to go out on dates with: *He's dating his best friend's sister.* **—*Idiom.* 18. to date,** until now. **19. up to date,** in accord with the latest styles, information, or technology. [1275–1325; ME < MF < LL *data*, der. of *dare* to give), from the phrase *data (Romae)* written, given (at Rome)] **—dat′a•ble, date′a•ble,** *adj.* **—dat′er,** *n.*

date² (dāt), *n.* the oblong, fleshy fruit of the date palm. [1250–1300; ME < AF; OF *dade, date* < ML *datil(l)us,* L *dactylus*; see DACTYL]

date•book (dāt′bo͝ok′), *n.* a notebook for listing appointments, making entries of events, etc., usu. for the period of a year. [1960–65]

dat•ed (dā′tid), *adj.* **1.** having or showing a date. **2.** out-of-date; old-fashioned; outmoded. [1580–90] **—dat′ed•ness,** *n.*

date•less (dāt′lis), *adj.* **1.** lacking a date; undated. **2.** endless; limitless. **3.** so old as to be undatable. **4.** of permanent interest regardless of age. **5.** having no social engagement. [1585–95]

date′ line′, *n.* INTERNATIONAL DATE LINE. [1875–80]

date•line (dāt′līn′), *n., v.,* **-lined, -lin•ing.** *—n.* **1.** a line at the beginning of a news dispatch, giving the place of origin and usu. the date. *—v.t.* **2.** to furnish (a news story) with a dateline. [1885–90]

date′ palm′, *n.* any tall date-bearing palm of the genus *Phoenix,* esp. *P. dactylifera,* topped by pinnate leaves. [1830–40]

date′ rape′, *n.* forced sexual intercourse that occurs when the victim and perpetrator are dating or on a date. [1970–75]

dat′ing bar′, *n.* SINGLES BAR. [1965–70]

da•tive (dā′tiv), *adj.* **1.** of or designating a grammatical case that typically indicates the indirect object of a verb or the object of certain prepositions. *—n.* **2.** the dative case. **3.** a word or other form in the dative case. [1400–50; *datif* < L *dativus (casus)* dative (case) < *dat(us)* given (see DATE¹)] **—da•ti′val** (-tī′vəl), *adj.* **—da•tive•ly,** *adv.*

da•tum (dā′təm, dat′əm, dä′təm), *n., pl.* **da•ta** (dā′tə, dat′ə, dä′tə), **-tums.** **1.** a single piece of information, as a fact, statistic, or code; an item of data. **2.** any proposition assumed or given, from which conclusions may be drawn. [1640–50; < L: a thing given, neut. ptp. of *dare* to give] **—Usage.** See DATA.

da•tu•ra (də to͝or′ə, -tyo͝or′ə), *n.* **-ras.** any plant of the genus *Datura,* of the nightshade family, usu. having tubular flowers and prickly pods; a source of hallucinogenic alkaloids. Compare JIMSONWEED. [1655–65; < NL < Hindi *dhatūra* jimsonweed < Skt *dhattūra*] **—da•tu′ric,** *adj.*

dau., daughter.

daub (dôb), *v.t.* **1.** to cover or coat with soft, adhesive matter, as plaster, paint, or mud. **2.** to smear, soil, or defile. **3.** to apply unskillfully, as paint or colors. *—v.i.* **4.** to daub something. **5.** to paint unskillfully. *—n.* **6.** material for daubing walls. **7.** something daubed on. **8.** an act of daubing. **9.** a crude painting. [1275–1325; ME < AF, OF *dauber* to whiten, paint] **—daub′er,** *n.* **—daub′ing•ly,** *adv.*

daube (dōb), *n.* a stew of meat, esp. beef, slowly braised in red wine with vegetables and seasonings. [1715–25; < F < It *dobba*]

daugh•ter (dô′tər), *n.* **1.** a girl or woman in relation to her parents. **2.** any female descendant. **3.** a person related as if by the ties binding daughter to parent: *a daughter of the church.* **4.** anything personified as female and considered with respect to its origin. **5.** an isotope formed by radioactive decay of another isotope. *—adj.* **6.** pertaining to a cell or other structure arising from division or replication: *daughter cell; daughter DNA.* [bef. 950; ME *doughter,* OE *dohtor,* c. OS *dohtar,* OHG *tochter,* ON *dōttir,* Go *dauhtar,* Gk *thygátēr,* Skt *duhitṛ́*]

daugh′ter-in-law′, *n., pl.* **daugh•ters-in-law.** the wife of one's son. [1350–1400]

daugh•ter•ly (dô′tər lē), *adj.* pertaining to, befitting, or like a daughter. [1525–35] **—daugh′ter•li•ness,** *n.*

daunt (dônt, dänt), *v.t.* **1.** intimidate. **2.** to dishearten: *Don't be daunted by the work.* [1250–1300; OF *danter* < L *domitāre* to tame] **—daunt′ing•ly,** *adv.* **—daunt′ing•ness,** *n.*

daunt•less (dônt′lis, dänt′-), *adj.* not to be daunted or intimidated; fearless. [1585–95] **—daunt′less•ly,** *adv.* **—daunt′less•ness,** *n.*

dau•phin (dô′fin, dō fan′), *n.* the eldest son of a king of France, used as a title from 1349 to 1830. [1475–85; < F; MF *dalphin*]

dau•phine (dô′fēn, dō-), *n.* the wife of a dauphin. [1860–65; < F; MF *dalfine,* fem. of *dalphin* DAUPHIN]

D.A.V. or **DAV,** Disabled American Veterans.

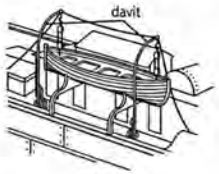
da•ven or **do•ven** (dä′vən), *v.i.* to recite the Jewish prayers. [< Yiddish *davnen, dovnen*]

dav•en•port (dav′ən pôrt′, -pōrt′), *n.* **1.** a large sofa, often one convertible into a bed. **2.** *Chiefly Brit.* a small writing desk. [1850–55; (def. 2) allegedly after a Captain *Davenport,* who first commissioned it]

Da•vid (dā′vid), *n.* died c970 B.C., the second king of Israel, reigned c1010–c970, successor to Saul.

Da•vid•ic (də vid′ik), *adj.* of or pertaining to the Biblical David or his descendants. [1820–30]

dav•it (dav′it, dā′vit), *n.* any of various cranelike devices used on a ship for supporting, raising, and lowering boats, anchors, etc. [1325–75; ME *daviot* < AF, appar. dim. of *Davi* David]



davit

Da′vy Jones′ (jōnz), *n.* the personification of the sea. [1745–55]

Da′vy Jones′s lock′er (jōn′ziz, jōnz), *n.* the bottom of the ocean, esp. when regarded as the grave of all who perish at sea. [1770–80]

daw (dô), *n.* JACKDAW. [1400–50; late ME *dawe*; cf. OHG *taha*]

daw•dle (dôd′l), *v.,* **-dled, -dling.** *—v.i.* **1.** to waste time; idle; trifle; loiter. **2.** to saunter. *—v.t.* **3.** to waste (time) by or as if by trifling (usu. fol. by *away*): *We dawdled away the whole morning.* [1650–60; var. of *daddle* to toddle] **—daw′dler,** *n.* **—Syn.** See LOITER.

dawn (dôn), *n.* **1.** the first appearance of daylight in the morning; daybreak; sunrise. **2.** the beginning or rise of anything; advent: *the dawn of civilization.* *—v.i.* **3.** to begin to grow light in the morning: *The day dawned cloudless.* **4.** to begin to open or develop. **5.** to begin

syn•os•to•sis (sin′o stō′sis), *n., pl.* **-ses** (-sēz). the union of separate bones into a single bone. [1840–50; contr. of *synosteosis*]

syn•o•vi•a (si nō′vē ə), *n.* a clear, viscous lubricating fluid secreted by membranes that surround the body's joints. [1640–50; < NL, perh. = *syn-* SYN- + L *ōv(um)* EGG1 + *-ia* -IA] —**syn•o′vi•al,** *adj.*

syn•o•vi•tis (sin′ə vī′tis), *n.* inflammation of a synovial membrane. [1823–35]

syn•tac•tic (sin tak′tik) also **syn•tac′ti•cal,** *adj.* of or pertaining to syntax. [1570–80; < NL *syntacticus* < Gk *syntaktikós* = *syntakt(ós)* ordered, v. adj. of *syntássein* to arrange together (*syn-* SYN- + *tássein* to arrange) + *-ikos* -IC; cf. TACTIC] —**syn•tac′ti•cal•ly,** *adv.*

syn•tac•tics (sin tak′tiks), *n.* (*used with a sing. v.*) the branch of semiotics dealing with the formal properties of languages and systems of symbols and the relationships of signs to each other. [1935–40]

syn•tag•ma (sin tag′mə) also **syn•tagm** (sin′tam), *n., pl.* **-tag•mas, -tag•ma•ta** (-tag′mə tə) also **-tagms.** a linguistic element that enters into a syntagmatic relationship. [1935–40; < F *syntagme* (1916) < Gk *sýntagma* something put together]

syn•tag•mat•ic (sin′tag mat′ik), *adj.* pertaining to or being a relationship among linguistic elements that occur sequentially, as the relationship between *the sun* and *is shining* or *the* and *sun* in *The sun is shining.* Compare PARADIGMATIC (def. 2). [1935–40; < F *syntagmatique* (1916); see SYNTAGMA, -IC] —**syn′tag•mat′i•cal•ly,** *adv.*

syn•tax (sin′taks), *n.* **1. a.** the study of the patterns of formation of sentences and phrases from words and of the rules for the formation of grammatical sentences in a language. **b.** the patterns or rules so studied: *English syntax.* **2. a.** the study of the well-formed formulas of a logical system. **b.** the set of rules that generate such a system. **3.** *Computers.* the grammatical rules and structural patterns governing the ordered use of appropriate words and symbols for issuing commands, writing code, etc., in a particular software application or programming language. [1565–75; short for earlier *syntaxis* < LL < Gk *sýntaxis* an arranging in order = *syntag-* (base of *syntássein*; see SYNTACTIC) + *-sis* -SIS]

syn•the•sis (sin′thə sis), *n., pl.* **-ses** (-sēz′). **1.** the combining of the constituent elements of separate material or abstract entities into a single or unified entity (opposed to *analysis*). **2.** a complex whole formed by combining. **3.** the forming or building of a more complex chemical substance or compound from elements or simpler compounds. **4.** See under HEGELIAN DIALECTIC. [1580–90; < L < Gk *sýnthesis* = *syn(ti)thé(nai)* to put together, construct (*syn-* SYN- + *tithénai* to put) + *-sis* -SIS] —**syn′the•sist,** *n.*

syn′thesis gas′, *n.* any of several gaseous mixtures consisting essentially of carbon monoxide and hydrogen, used in the synthesis of chemical compounds, as ammonia and alcohols. [1940–45]

syn•the•size (sin′thə sīz′), *v.t.,* **-sized, -siz•ing. 1.** to form (a material or abstract entity) by combining parts or elements (opposed to *analyze*). **2.** to combine (constituent elements) into a single or unified chemical entity. —*v.i.* **3.** to make or form a synthesis. [1820–30] —**syn′the•si•za′tion,** *n.*

syn•the•siz•er (sin′thə sī′zər), *n.* **1.** a person or thing that synthesizes. **2.** an electronic, usu. computerized console or module for creating or modifying the sounds of musical instruments. [1865–70]

syn•the•tase (sin′thə tās′, -tāz′), *n.* **1.** LIGASE. **2.** Also called **tRNA synthetase.** a ligase that assists in translating the genetic code into protein by linking a transfer RNA with a specific amino acid. [1947; SYNTHET(IC) + -ASE]

syn•thet•ic (sin thet′ik), *adj.* **1.** of, pertaining to, proceeding by, or involving synthesis (opposed to *analytic*). **2.** pertaining to or denoting compounds, materials, etc., formed through a chemical process by human agency, as opposed to those of natural origin: *synthetic fiber; synthetic drugs.* **3.** not real or genuine; artificial; feigned: *a synthetic chuckle.* **4.** (of a language) characterized by the use of affixes, rather than separate words, to express syntactic relationships, as Latin. Compare ANALYTIC (def. 3), POLYSYNTHETIC. **5.** Also, **syn•thet′i•cal.** *Logic.* of or pertaining to a noncontradictory proposition in which the predicate is not included in, or entailed by, the subject. **6.** noting a gem mineral manufactured so as to be physically, chemically, and optically identical with the mineral as found in nature. —*n.* **7.** something made by a synthetic, or chemical, process. [1690–1700; < NL *syntheticus* < Gk *synthetikós* = *synthet(ós)* placed together, v. adj. of *syntithénai* to put together (see SYNTHESIS) + *-ikos* -IC] —**syn•thet′i•cal•ly,** *adv.*

synth•pop (sinth′pop′), *n.* popular music played with synthesizers. [1980–85; SYNTH(ESIZER) + POP2]

syph•i•lis (sif′ə lis), *n.* a chronic infectious disease caused by a spirochete, *Treponema pallidum,* usu. venereal in origin but often congenital, affecting almost any body organ, esp. the genitals, skin, brain, and nervous tissue. [< NL, coined by Giovanni Fracastoro (1478–1553), Italian physician, in his poem *Syphilis, sive morbus Gallicus* ("Syphilis, or the French Disease")] —**syph′i•lit′ic,** *adj.*

sy•phon (sī′fən), *n., v.t., v.i.* SIPHON.

Syr•i•ac (sēr′ē ak′), *n.* a form of Aramaic based on the speech of Edessa in the 1st to 3rd centuries A.D., used historically in the liturgy and literature of a number of Christian confessions of the Near East. [1611; < L *Syriacus* < Gk *Syriakós.* See SYRIA, -AC]

sy•rin•ga (sə ring′gə), *n., pl.* **-gas.** MOCK ORANGE (def. 1). [1655–65; < NL, ML (see SYRINGE); so called from the use of mock orange stems in pipe-making]

sy•ringe (sə rinj′, sir′inj), *n., v.,* **-ringed, -ring•ing.** —*n.* **1.** a small tube with a narrow outlet and fitted with a piston or rubber bulb for drawing in or ejecting fluid. **2.** any similar device for pumping and spraying liquids through a small aperture. —*v.t.* **3.** to cleanse, wash, inject, etc., by means of a syringe. [1375–1425; late ME *syring* < ML *syringa,* new sing. from LL *sýringēs,* pl. of *sýrinx* SYRINX]

sy•rin•go•my•e•li•a (sə ring′gō mī ē′lē ə), *n.* a disease of the spinal cord in which the nerve tissue is replaced by a fluid-filled cavity. [1875–80; *syringo-* (comb. form of Gk *sýrinx* SYRINX) + *myelia* (see MYELO-, -IA)] —**sy•rin′go•my•el′ic** (-el′ik), *adj.*

syr•inx (sir′ingks), *n., pl.* **sy•rin•ges** (sə rin′jēz), **syr•inx•es. 1.** the vocal organ of birds, situated in the lower part of the trachea where it divides into the bronchi. **2.** PANPIPE. [1600–10; < Gk *sýrinx* pipe]

syr•phid (sûr′fid) also **syr•phi•an** (-fē ən), *n.* **1.** SYRPHID FLY. —*adj.* **2.** belonging or pertaining to the family Syrphidae. [1890–95; < NL *Syrphidae* family name < Gk *sýrphos* gnat]

syr′phid fly′ also **syr′phus fly′** (sûr′fəs), *n.* any of numerous beelike or wasplike flies of the family Syrphidae that feed on nectar and pollen and have larvae that prey on aphids.

syr•up (sir′əp, sûr′-), *n.* **1.** any of various thick, sweet liquids prepared for table use from molasses, glucose, etc. **2.** any of various preparations consisting of fruit juices, water, etc., boiled with sugar. —*v.t.* **3.** to bring to the form or consistency of syrup. **4.** to cover, fill, or sweeten with syrup. [1350–1400; ME *sirop* < MF < ML *syrupus* < Ar *sharāb* a drink] —**syr′up•like′,** *adj.*

syr•up•y (sir′ə pē, sûr′-), *adj.* **1.** having the appearance or quality of syrup; thick or sweet. **2.** sentimental or saccharine. [1700–10]

sys•op (sis′op′), *n. Informal.* a person who operates a computer bulletin board. [1980–85; *sys(tems) op(erator)*]

syst., system.

sys•tal•tic (si stôl′tik, -stal′-), *adj.* rhythmically contracting, as the heart. [1670–80; < LL *systalticus* < Gk *systaltikós,* der. of *systéllein* to contract; see SYSTOLE]

sys•tem (sis′təm), *n.* **1.** an assemblage or combination of things or parts forming a complex or unitary whole. **2.** any assemblage or set of correlated members. **3.** an ordered and comprehensive assemblage of facts, principles, doctrines, or the like in a particular field. **4.** a coordinated body of methods or a scheme or plan of procedure; organizational scheme: *a system of government.* **5.** any formulated, regular, or special method or plan of procedure. **6. a.** an assemblage of organs or related tissues concerned with the same function: *the digestive system.* **b.** the entire human or animal body considered as a functioning unit: *an ingredient toxic to the system.* **7. a.** a number of heavenly bodies associated and acting together according to certain natural laws, as the solar system. **b.** a hypothesis or theory of the characteristics of heavenly bodies by which their phenomena, motions, changes, etc., are explained: *the Copernican system.* **8.** one's psychological makeup, esp. with reference to desires or preoccupations: *to get something out of one's system.* **9.** a method or scheme of classification: *the Linnaean system.* **10.** (*sometimes cap.*) the prevailing structure or organization of society, business, or politics or of society in general; establishment (usu. prec. by *the*): *to work within the system.* **11.** a major division of rocks comprising sedimentary deposits and igneous masses formed during a single geologic period. **12.** *Physical Chem.* a combination of two or more phases, each of which consists of one or more substances, that is attaining or is in equilibrium. **13.** a working combination of computer hardware, software, and data communications devices. [1610–20; < LL *systēma* < Gk *sýstēma* = *systē-,* var. s. of *synistánai* to combine, organize (*syn-* SYN- + *histánai* to STAND) + *-ma,* n. suffix of result]

sys•tem•at•ic (sis′tə mat′ik) also **sys′tem•at′i•cal,** *adj.* **1.** having, showing, or involving a system, method, or plan: *systematic efforts.* **2.** given to or using a system or method; methodical: *a systematic person.* **3.** arranged in or comprising an ordered system: *systematic theology.* **4.** concerned with classification: *systematic botany.* **5.** pertaining to, based on, or in accordance with a system of classification: *the systematic names of plants.* [1670–80; < LL *systēmaticus* < Gk *systēmatikós* = *systēmat-,* s. of *sýstēma* SYSTEM + *-ikos* -IC] —**sys′tem•at′i•cal•ly,** *adv.* —**sys′tem•at′i•cal•ness,** *n.*

sys•tem•at•ics (sis′tə mat′iks), *n.* (*used with a sing. v.*) **1.** the study of systems or of classification. **2.** any system of classification. **3.** the classification of organisms; taxonomy. [1885–90]

sys•tem•a•tism (sis′tə mə tiz′əm, si stem′ə-), *n.* **1.** the practice of systematizing. **2.** adherence to system or method. [1840–50]

sys•tem•a•tist (sis′tə mə tist, si stem′ə-), *n.* **1.** a specialist in systematics, esp. a taxonomist. **2.** a person who constructs or adheres to a system. [1690–1700]

sys•tem•a•tize (sis′tə mə tīz′), *v.t.,* **-tized, -tiz•ing.** to arrange in or according to a system; reduce to a system; make systematic. [1755–65] —**sys′tem•a•ti•za′tion,** *n.* —**sys′tem•a•tiz′er,** *n.*

sys•tem•a•tol•o•gy (sis′tə mə tol′ə jē), *n.* the science of systems or their formation. [1885–90]

sys•tem•ic (si stem′ik), *adj.* **1.** of or pertaining to a system. **2.** pertaining to, affecting, or circulating through the entire body: *systemic disease; systemic pesticide.* [1795–1805] —**sys•tem′i•cal•ly,** *adv.*

system′ic lu′pus er•y•the•ma•to′sus (er′ə thē′mə tō′səs, -them′ə-), *n.* an autoimmune inflammatory disease of the connective tissues, chiefly characterized by skin eruptions, joint pain, recurrent pleurisy, and kidney disease. [1950–55]

sys•tem•ize (sis′tə mīz′), *v.t.,* **-ized, -iz•ing.** SYSTEMATIZE. [1770–80] —**sys′tem•i•za′tion,** *n.* —**sys′tem•iz′er,** *n.*

EXHIBIT 13

The American Heritage® Dictionary of the English Language

FOURTH EDITION

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Manufactured in the United States of America

Marked by showy elegance; splendid: *a dashing coat.* See synonyms at **fashionable.** —**dash′ing•ly** *adv.*

dash•pot (dăsh′pŏt′) *n.* A device consisting of a piston that moves within a cylinder containing oil, used to dampen and control motion.

Dasht-e-Ka•vir (dăsht′ĕ-kə-vēr′, dăsh′tĕ-kä-vēr′) *n.* A salt desert of north-central Iran southeast of the Elburz Mountains.

Dasht-e-Lut (dăsht′ĕ-lōōt′) *n.* A sand and stone desert of eastern Iran extending southward from the Dasht-e-Kavir.

das•sie (dăs′ē) *n.* See **hyrax.** [Afrikaans, diminutive of *das,* badger, from Middle Dutch. See **teks-** in Appendix I.]

das•tard (dăs′tərd) *n.* A sneaking, malicious coward. [Middle English, probably alteration of Old Norse *dæstr,* exhausted, from past participle of *dasa,* to languish, decay.]

das•tard•ly (dăs′tərd-lē) *adj.* Cowardly and malicious; base. —**das′tard•li•ness** *n.*

das•y•ure (dăs′ē-yŏor′) *n.* Any of various often carnivorous marsupials of the family Dasyuridae of Australia, Tasmania, and adjacent islands, including marsupial mice and rats, native cats, the Tasmanian devil, and the Tasmanian wolf. [New Latin *Dasyūrus,* genus name : Greek *dasus,* hairy + *oura,* tail; see **ors-** in Appendix I.]

DAT *abbr.* digital audiotape

dat. *abbr.* dative

da•ta (dā′tə, dăt′ə, dä′tə) *pl.n. (used with a sing. or pl. verb)* **1.** Factual information, especially information organized for analysis or used to reason or make decisions. **2.** *Computer Science* Numerical or other information represented in a form suitable for processing by computer. **3.** Values derived from scientific experiments. **4.** Plural of **datum** (sense 1). [Latin, pl. of *datum.* See DATUM.]

Usage Note The word *data* is the plural of Latin *datum,* "something given," but it is not always treated as a plural noun in English. The plural usage is still common, as this headline from the *New York Times* attests: *"Data Are Elusive on the Homeless."* Sometimes scientists think of *data* as plural, as in *These data do not support the conclusions.* But more often scientists and researchers think of data as a singular mass entity like information, and most people now follow this in general usage. Sixty percent of the Usage Panel accepts the use of *data* with a singular verb and pronoun in the sentence *Once the data is in, we can begin to analyze it.* A still larger number, 77 percent, accepts the sentence *We have very little data on the efficacy of such programs,* where the quantifier *very little,* which is not used with similar plural nouns such as *facts* and *results,* implies that *data* here is indeed singular.

data bank or **da•ta•bank** (dā′tə-băngk′, dăt′ə-) *n.* **1.** See **database.** **2.** An organization chiefly concerned with building, maintaining, and using a database.

da•ta•base (dā′tə-bās′, dăt′ə-) *Computer Science n.* also **data base** A collection of data arranged for ease and speed of search and retrieval. Also called *data bank.* ❖ *tr.v.* **-based, -bas•ing, -bas•es** To put (data) into a database.

data carrier *n.* A medium, such as magnetic tape, that is selected to record and often transport or communicate data.

data highway *n.* **1.** A network of computer networks, other devices, and switching systems used for the transfer of digitized information. **2.** The integrated circuitry of a computer chip.

data processing *n.* **1.** Conversion of data into a form that can be processed by computer. **2.** The storing or processing of data by a computer. —**da′ta-pro′cess′ing** (dā′tə-prŏs′ĕs′ĭng, -prō′sĕs′-, dăt′ə-) *adj.*

data processor *n.* **1.** A device, such as a calculator or computer, that performs operations on data. **2.** A person who processes data.

data set *n.* **1.** An electronic device that provides an interface in the transmission of data to a remote station. **2.** A collection of related data records on a computer-readable medium, such as a disk.

data type *n.* **1.** In programming, a classification identifying one of various types of data, as floating-point, integer, or Boolean, stating the possible values for that type, the operations that can be done on that type, and the way the values of that type are stored. **2.** In databases or spreadsheets, a classification identifying one of various kinds of data, as a name, date, or dollar amount, found in a specific data field.

date[1] (dāt) *n.* **1a.** Time stated in terms of the day, month, and year. **b.** A statement of calendar time, as on a document. **2.** A specified day of a month. **3a.** A particular point or period of time at which something happened or existed, or is expected to happen. **b. dates** The years of someone's birth and death: *Beethoven's dates were 1770 to 1827.* **4.** The time during which something lasts; duration. **5.** The time or historical period to which something belongs: *artifacts of a later date.* **6.** An appointment: *a luncheon date with a client.* See synonyms at **engagement. 7a.** An engagement to go out socially with another person, often out of romantic interest. **b.** One's companion on such an outing. **8.** An engagement for a performance: *has four singing dates.* ❖ *v.* **dat•ed, dat•ing, dates** —*tr.* **1.** To mark or supply with a date: *date a letter.* **2.** To determine the date of: *date a fossil.* **3.** To betray the age of: *Pictures of old cars date the book.* **4.** To go on a date or dates with. —*intr.* **1.** To have origin in a particular time in the past: *This statue dates from 500 B.C.* **2.** To become old-fashioned. **3.** To go on dates. —***idioms:*** **out of date** No longer in style; old-fashioned: *clothes that went out of date last year.* **to date** Until now: *To date, only half of those invited have responded.* **up to date** In or into accordance with current information, styles, or technology: *brought me up to date.* [Middle English, from Old French, from Medieval Latin *data,* from Latin *data (Romae),* issued (at Rome) (on a certain day), feminine past participle of *dare,* to give. See **dō-** in Appendix I.] —**dat′a•ble, date′a•ble** *adj.* —**dat′er** *n.*

date[2] (dāt) *n.* **1.** The sweet, edible, oblong or oval fruit of the date palm, containing a narrow, hard seed. **2.** A date palm. [Middle English, from Old French, from Old Provençal *datil,* from Latin *dactylus,* from Greek *daktulos,* finger, date (from its shape).]

date•book (dāt′bo͝ok′) *n.* A notebook or calendar for listing appointments, events, and other work-related or social information.

dat•ed (dā′tĭd) *adj.* **1.** Marked with or displaying a date. **2.** Old-fashioned; out-of-date. —**dat′ed•ly** *adv.* —**dat′ed•ness** *n.*

date•less (dāt′lĭs) *adj.* **1.** Having no date whatsoever. **2.** So ancient that no date can be determined. **3.** Having no limits in time; timeless.

date•line (dāt′līn′) *n.* **1.** A phrase at the beginning of a newspaper or magazine article that gives the date and place of the origin of the article. —**date′line′** *v.*

date line *n.* The International Date Line.

date palm *n.* A palm tree (*Phoenix dactylifera*) of western Asia and northern Africa and cultivated also in California, having featherlike leaves and bearing clusters of dates.

date rape *n.* Rape perpetrated by the victim's social escort.

da•tive (dā′tĭv) *adj.* Of, relating to, or being the grammatical case that marks the recipient of action, that often indicates the indirect object of the verb, and that can be used with prepositions or other function words corresponding in meaning to English *to* and *for.* ❖ *n.* **1.** The dative case. **2.** A word or form in the dative case. [Middle English *datif,* from Latin (*casus*) *dativus,* (case) of giving (translation of Greek *dotikē ptōsis*), from *datus,* past participle of *dare,* to give. See **dō-** in Appendix I.] —**da′tive•ly** *adv.*

Da•tong (dä′tôông′) also **Ta•tung** (tä′tôông′) A city of northeast China west of Beijing. It is an important industrial and railroad center. Population: 1,277,310.

dATP (dē′ā′tē′pē′) *n.* One of the two purine nucleotides that are used to synthesize DNA. [D(EOXY)– + ATP.]

da•tum (dā′təm, dăt′əm, dä′təm) *n.* **1.** *pl.* **-ta** (-tə) A fact or proposition used to draw a conclusion or make a decision. See Usage Note at **data. 2.** *pl.* **-tums** A point, line, or surface used as a reference, as in surveying, mapping, or geology. [Latin, something given, from neuter past participle of *dare,* to give. See **dō-** in Appendix I.]

da•tu•ra (də-to͝or′ə, -tyo͝or′ə) *n.* Any of several plants of the genus *Datura,* having trumpet-shaped flowers up to 25 centimeters (10 inches) long and usually prickly fruits. The leaves and seeds yield alkaloids with narcotic properties. Also called *thorn apple.* [New Latin *Datura,* genus name, from Hindi *dhatūrā,* from Sanskrit *dhattūrāḥ,* thorn apple.]

daub (dôb) *v.* **daubed, daub•ing, daubs** —*tr.* **1.** To cover or smear with a soft adhesive substance such as plaster, grease, or mud. **2.** To apply paint to (a surface) with hasty or crude strokes. **3.** To apply with quick or crude strokes: *daubed glue on the paper.* —*intr.* **1.** To apply paint or coloring with crude, unskillful strokes. **2.** To make crude or amateurish paintings. **3.** To daub a sticky material. ❖ *n.* **1.** The act or a stroke of daubing. **2.** A soft adhesive coating material such as plaster, grease, or mud. **3.** Matter daubed on. **4.** A crude, amateurish painting or picture. [Middle English *dauben,* from Old French *dauber,* from Latin *dealbāre,* to whitewash : *dē-,* intensive pref.; see DE– + *albus,* white; see **albho-** in Appendix I.] —**daub′er** *n.* —**daub′er•y** (dô′bə-rē) *n.*

Dau•bi•gny (dō-bē-nyē′), **Charles François** 1817–1878. French landscape painter best known for his sensitive portrayal of light, which influenced the later impressionists.

Dau•det (dō-dā′), **Alphonse** 1840–1897. French writer of the naturalist school whose stories of life in his native Provence include *Lettres de mon Moulin* (1869).

Daudet, Léon 1867–1942. French writer known for his highly charged political essays and numerous volumes of memoirs.

Dau•gav•pils (dou′gəf-pīlz′, -gäf-pēlz′) A city of southeast Latvia southeast of Riga. Founded in the 13th century, it was held by Lithuania and Poland before being ceded to Russia in 1771. The city later passed to independent Latvia (1918–1940) and the USSR (1940–1991). Population: 124,000.

daugh•ter (dô′tər) *n.* **1.** One's female child. **2.** A female descendant. **3.** A woman considered as if in a relationship of child to parent: *a daughter of the nation.* **4.** One personified or regarded as a female descendant: *"Culturally Japan is a daughter of Chinese civilization"* (Edwin O. Reischauer). **5.** *Physics* The immediate product of the radioactive decay of an element. ❖ *adj.* **1.** Possessing the characteristics of a daughter; having the relationship of a daughter. **2.** *Biology* Of or relating to a cell, organelle, or other structure produced by division or replication: *daughter cell; daughter DNA.* **3.** *Physics* Produced by or resulting from the decay of a radioactive element: *daughter atom; daughter nuclide.* [Middle English *doughter,* from Old English *dohtor.* See **dhughater-** in Appendix I.] —**daugh′ter•ly** *adj.*

daugh•ter-in-law (dô′tər-ĭn-lô′) *n., pl.* **daugh•ters-in-law** (dô′tərz-) The wife of one's son.

Dau•mier (dō-myā′), **Honoré** 1808–1879. French artist best known for his bitterly satirical lithographs of scenes from bourgeois society.

daunt (dônt, dänt) *tr.v.* **daunt•ed, daunt•ing, daunts** To abate the courage of; discourage. See synonyms at **dismay.** [Middle English *daunten,* from Old French *danter,* from Latin *domitāre,* frequentative of *domāre,* to tame. See **demə-** in Appendix I.] —**daunt′er** *n.* —**daunt′ing•ly** *adv.*

daunt•less (dônt′lĭs, dänt′-) *adj.* Incapable of being intimidated or discouraged; fearless. See synonyms at **brave.** —**daunt′less•ly** *adv.* —**daunt′less•ness** *n.*

dau•phin (dô′fĭn) *n.* **1.** The eldest son of the king of France from 1349 to 1830. **2.** Used as a title for such a nobleman. [Middle English, from Old French, title of the lords of Dauphiné, from *Dalphin, Dalfin,* a

date palm
Phoenix dactylifera

ă pat	oi boy
ā pay	ou out
âr care	o͝o took
ä father	o͞o boot
ĕ pet	ŭ cut
ē be	ûr urge
ĭ pit	th thin
ī pie	th this
îr pier	hw which
ŏ pot	zh vision
ō toe	ə about, item
ô paw	♦ regionalism

Stress marks: ′ (primary); ″ (secondary), as in **dictionary** (dĭk′shə-nĕr′ē)

sys•tal•tic (sĭ-stôl′tĭk, -stäl′-) *adj.* Alternately contracting and dilating, as the heart; pulsating. [Late Latin *systalticus*, from Greek *sustaltikos*, from *sustellein*, to contract : *sun-*, syn- + *stellein*, to send; see **stel-** in Appendix I.]

sys•tem (sĭs′təm) *n.* **1.** A group of interacting, interrelated, or interdependent elements forming a complex whole. **2.** A functionally related group of elements, especially: **a.** The human body regarded as a functional physiological unit. **b.** An organism as a whole, especially with regard to its vital processes or functions. **c.** A group of physiologically or anatomically complementary organs or parts: *the nervous system; the skeletal system.* **d.** A group of interacting mechanical or electrical components. **e.** A network of structures and channels, as for communication, travel, or distribution. **f.** A network of related computer software, hardware, and data transmission devices. **3.** An organized set of interrelated ideas or principles. **4.** A social, economic, or political organizational form. **5.** A naturally occurring group of objects or phenomena: *the solar system.* **6.** A set of objects or phenomena grouped together for classification or analysis. **7.** A condition of harmonious, orderly interaction. **8.** An organized and coordinated method; a procedure. See synonyms at **method. 9.** The prevailing social order; the establishment. Used with *the*: *You can't beat the system.* [Late Latin *systēma*, *systēmat-*, from Greek *sustēma*, from *sunistanai*, to combine : *sun-*, syn- + *histanai*, set up, establish; see **stă-** in Appendix I.]

system administrator *n.* One who manages and maintains computer systems and software, as for a business or institution.

sys•tem•at•ic (sĭs′tə-măt′ĭk) also **sys•tem•at•i•cal** (-ĭ-kəl) *adj.* **1.** Of, characterized by, based on, or constituting a system. **2.** Carried on using step-by-step procedures. **3.** Purposefully regular; methodical. See synonyms at **orderly. 4.** Of or relating to classification or taxonomy. —**sys′tem•at′i•cal•ly** *adv.*

sys•tem•at•ics (sĭs′tə-măt′ĭks) *n.* (*used with a sing. verb*) **1.** The science of systematic classification. **2.** A system of classification, as biosystematics. **3.** *Biology* The systematic classification of organisms and the evolutionary relationships among them; taxonomy.

sys•tem•a•tism (sĭs′tə-mə-tĭz′əm, sĭ-stēm′ə-) *n.* **1.** The practice of classifying or systematizing. **2.** Adherence to a system or systems.

sys•tem•a•tist (sĭs′tə-mə-tĭst, sĭ-stēm′ə-) *n.* **1.** One who adheres to or formulates a system or systems. **2.** A taxonomist.

sys•tem•a•tize (sĭs′tə-mə-tīz′) *tr.v.* **-tized, -tiz•ing, -tiz•es** To formulate into or reduce to a system: *"The aim of science is surely to amass and systematize knowledge"* (V. Gordon Childe). See synonyms at **arrange.** —**sys′tem•a•ti•za′tion** (-tĭ-zā′shən) *n.* —**sys′tem•a•tiz′er** *n.*

sys•tem•ic (sĭ-stēm′ĭk, -stĕm′ĭk) *adj.* **1.** Of or relating to systems or a system. **2a.** Relating to or affecting the entire body or an entire organism: *systemic symptoms; a systemic poison.* **b.** Relating to or affecting a particular body system, especially the nervous system: *a systemic lesion.* **c.** *Physiology* Of or relating to systemic circulation. —**sys•tem′i•cal•ly** *adv.*

systemic circulation *n.* The general circulation of the blood through the body, as opposed to the circulation of the blood from the heart to the lungs and back to the heart.

systemic lupus er•y•the•ma•to•sus (ĕr′ə-thē′mə-tō′sĭs) *n.* *Abbr.* **SLE** An inflammatory, multisystemic, autoimmune disease of the connective tissue, characterized by fever, skin lesions, joint pain or arthritis, and anemia, and often affecting the kidneys, spleen, and various other organs.

sys•tem•ize (sĭs′tə-mīz′) *tr.v.* **-ized, -iz•ing, -iz•es** To systematize. —**sys′tem•i•za′tion** (-tə-mĭ-zā′shən) *n.* —**sys′tem•iz′er** *n.*

system operator *n.* One who operates a bulletin board system.

sys•tems analysis (sĭs′təmz) *n.* **1.** The study of an activity or procedure to determine the desired end and the most efficient method of obtaining this end. **2.** The act, process, or profession of systems analysis.

systems analyst *n.* One who performs systems analysis.

systems programming *n.* The development and management of programs that are a part of an operating system.

sys•to•le (sĭs′tə-lē) *n.* The rhythmic contraction of the heart, especially of the ventricles, by which blood is driven through the aorta and pulmonary artery after each dilation or diastole. [Greek *sustolē*, contraction, from *sustellein*, to contract. See SYSTALTIC.] —**sys•tol′ic** (sĭ-stŏl′ĭk) *adj.*

systolic pressure *n.* Blood pressure within the arteries when the heart muscle is contracting.

Syz•ran (sĭz′rən) A city of western Russia on the Volga River west of Samara. It is a major river port and rail center. Population: 174,947.

syz•y•gy (sĭz′ə-jē) *n., pl.* **-gies 1.** *Astronomy* **a.** Either of two points in the orbit of a celestial body where the body is in opposition to or in conjunction with the sun. **b.** Either of two points in the orbit of the moon when the moon lies in a straight line with the sun and Earth. **c.** The configuration of the sun, the moon, and Earth lying in a straight line. **2.** The combining of two feet into a single metrical unit in classical prosody. [Late Latin *sȳzygia*, from Greek *suzugiā*, union, from *suzugos*, paired : *sun-*, *su-*, syn- + *zugon*, yoke; see **yeug-** in Appendix I.] —**sy•zyg′i•al** (sĭ-zĭj′ē-əl) *adj.*

.sz *abbr.* Swaziland (in Internet addresses)

Szcze•cin (shchĕ′chēn′) also **Stet•tin** (stə-tēn′, shtĕ-) A city of northwest Poland near the mouth of the Oder River. It was ruled by Sweden from 1648 to 1720, when it was ceded to Prussia. After World War II the city became part of Poland. Population: 413,561.

Sze•chuan (sĕch′wän′) See **Sichuan.**

Szechuan pepper or **Szechwan pepper** *n.* A Chinese tree or shrub (*Zanthoxylum simulans*) having aromatic bark, pinnately compound leaves, and spicy, two-valved, reddish, dry fruits.

Sze•chwan (sĕch′wän′) See **Sichuan.**

Sze•ged (sĕg′ĕd′) A city of southern Hungary on the Tisza River near the Yugoslavian border. It is a major river port and an agricultural center. Population: 178,690.

Szé•kes•fe•hér•vár (sā′kĕsh-fĕ′hār-vär′) A city of central Hungary on the Danube River south-southwest of Budapest. It was the coronation and burial place of Hungary's kings from 1027 to 1527. Population: 109,714.

Szell (zĕl, zĕl), **George** 1897–1970. Hungarian-born American conductor who was best known as the musical director of the Cleveland Orchestra (1946–1970).

Szent-Györ•gyi (sānt-jôr′jē, sĕnt-dyœr′dyē), **Albert** 1893–1986. Hungarian-born American biochemist. He was the first to isolate vitamin C and won the 1937 Nobel Prize for discoveries relating to biological combustion.

Szi•ge•ti (sĭg′ĭ-tē, sĭ-gĕt′ē), **Joseph** 1892–1973. Hungarian-born American violinist known especially for his interpretations of complex modern works, including compositions by Bartók and Prokofiev.

Szi•lard (zĭl′ərd, zə-lärd′), **Leo** 1898–1964. Hungarian-born American physicist and biologist. A member of the Manhattan Engineering Project, he helped develop the first atomic bomb. Szilard was later opposed to the construction and use of all nuclear weapons and devoted himself to studying molecular biology.

Szold (zōld), **Henrietta** 1860–1945. American Zionist leader who was a founder of Hadassah (1912), the Women's Zionist Organization of America.

Szol•nok (sôl′nōk′) A city of central Hungary east-southeast of Budapest. It is an industrial and commercial center. Population: 79,619.

Szom•bat•hely (sōm′bôt-hā′) A city of western Hungary near the Austrian border. Founded in Roman times, it is an industrial center and an important railroad junction. Population: 85,830.

Szym•bor•ska (shĭm-bôr′skə), **Wislawa** Born 1923. Polish poet noted for her metaphysical and witty poems concerning daily life and her many translations of French poetry into Polish. She won the 1996 Nobel Prize for literature.

ă pat	oi boy
ā pay	ou out
âr care	o͝o took
ä father	o͞o boot
ĕ pet	ŭ cut
ē be	ûr urge
ĭ pit	th thin
ī pie	*th* this
îr pier	hw which
ŏ pot	zh vision
ō toe	ə about, item
ô paw	♦ regionalism

Stress marks: ′ (primary); ˈ (secondary), as in **dictionary** (dĭk′shə-nĕr′ē)

EXHIBIT 14

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–ORIGIN Middle English: of unknown origin; apparently related to French (Walloon dialect) *darnelle*.

darn•er |ˈdärnər| ▸n. **1** a darning needle.
2 a large slender-bodied dragonfly. Also called **DARNING NEEDLE, DEVIL'S DARNING NEEDLE.** [ORIGIN: said to be so named because of the popular belief that the dragonfly sews up the lips and eyelids of people sleeping.]
•Family Aeshnidae: several genera.

darn•ing |ˈdärniNG| ▸n. the skill or activity of one who darns: *long hours of tedious darning.*
■ articles being darned or needing to be darned: *Aunt Edie bent her head to her darning.*

darn•ing egg ▸n. an egg-shaped piece of wood or other smooth hard material used to stretch and support material being darned.

darn•ing nee•dle ▸n. a long sewing needle with a large eye, used in darning.
■ another term for **DARNER** (sense 2).

Darn•ley |ˈdärnlē|, Henry Stewart (or Stuart), Lord (1545–67), Scottish nobleman; second husband of Mary, Queen of Scots; father of James I of England.

Dar•row |ˈdarō|, Clarence Seward (1857–1938), US lawyer. He served as defense counsel in several well-publicized trials, including that of John T. Scopes, a teacher in Dayton, Tennessee, who was charged with violating state law for teaching evolution in a public school in 1925.

dar•shan |ˈdərˌshən; -shän| ▸n. Hinduism an opportunity or occasion of seeing a holy person or the image of a deity.
–ORIGIN via Hindi from Sanskrit *darśana* 'sight or seeing.'

Dart |därt|, Raymond Arthur (1893–1988), South African anthropologist and anatomist; born in Australia. In 1925, he found the first specimen of the hominid species *A. africanus*, for which he coined the genus name *Australopithecus*.

dart |därt| ▸n. **1** a small pointed missile that can be thrown or fired.
■ a small pointed missile with a feather or plastic tail, used in the game of darts. ■ an act of running somewhere suddenly and rapidly: *the cat made a dart for the door.* ■ figurative a sudden, intense pang of a particular emotion: *a dart of panic.* ■ Zoology a dartlike calcareous organ of a snail forming part of the reproductive system, exchanged during copulation.
2 a tapered tuck stitched into a garment in order to shape it.
▸v. [no obj., with adverbial of direction] move or run somewhere suddenly or rapidly: *she darted across the street.*
■ [with obj. and adverbial of direction] cast (a look or one's eyes) suddenly and rapidly in a particular direction: *the darted a glance across the table.* ■ [trans.] archaic throw (a missile). ■ [trans.] shoot (an animal) with a dart, typically in order to administer a drug.
–ORIGIN Middle English: from Old French, accusative of *darz, dars*, from a West Germanic word meaning 'spear, lance.'

dart•board |ˈdärtˌbôrd| ▸n. a circular board marked with numbered segments, used as a target in the game of darts.

dart•er |ˈdärtər| ▸n. **1** another term for **ANHINGA.**
2 a small North American freshwater fish, the male of which may develop bright coloration during the breeding season.
•Genera *Etheostoma* and *Percina*, family Percidae: numerous species.

darts |därts| ▸plural n. [usu. treated as sing.] an indoor game in which small pointed missiles with feather or plastic flights are thrown at a circular target marked with numbers in order to score points.

Dar•win |ˈdärwən|, Charles (Robert) (1809–82), English natural historian and geologist; a proponent of the theory of evolution by natural selection. While the naturalist on HMS *Beagle* for her voyage around the southern hemisphere 1831–36, he collected the material that became the basis for his ideas on natural selection. Notable works: *On the Origin of Species* (1859) and *The Descent of Man* (1871).

Dar•win•i•an |därˈwinēən| ▸adj. of or relating to Darwinism.
▸n. an adherent of Darwinism.

Dar•win•ism |ˈdärwiˌnizəm| ▸n. the theory of the evolution of species by natural selection advanced by Charles Darwin.
Darwin argued that since offspring tend to vary slightly from their parents, mutations that make an organism better adapted to its environment will be encouraged and developed by the pressures of natural selection, leading to the evolution of new species differing widely from one another and from their common ancestors. Darwinism was later developed by the findings of Mendelian genetics (see **NEO-DARWINIAN**).
–DERIVATIVES **Dar•win•ist** n. & adj.

Dar•win's finch•es ▸plural n. a group of songbirds related to the buntings and found on the Galapagos Islands, discovered by Charles Darwin and used by him to illustrate his theory of natural selection. They are believed to have evolved from a common ancestor and have developed a variety of bills to suit various modes of life.
•Family Emberizidae (subfamily Emberizinae): four to six genera, esp. *Geospiza* (the **ground finches**) and *Camarhynchus* (the **tree finches**).

Da•sein |ˈdäˌzīn| ▸n. Philosophy (in Hegelianism) existence or determinate being; (in existentialism) human existence.
–ORIGIN mid 19th cent.: German, from *dasein* 'exist,' from *da* 'there' + *sein* 'be.'

dash |dash| ▸v. **1** [no obj., with adverbial of direction] run or travel somewhere in a great hurry: *I dashed into the garden | I must dash, I'm late.*
■ (often **dash about/around**) move about in a great hurry, esp. in the attempt to do several things in a short period of time: *I dash about for four days in a manic fit to straighten things up.*
2 [with obj. and adverbial of direction] strike or fling (something) somewhere with great force, esp. so as to have a destructive effect; hurl: *the ship was dashed upon the rocks.*
■ [no obj., with adverbial of direction] strike forcefully against something: *a gust of rain dashed against the bricks.* ■ [trans.] destroy or frustrate (a person's hopes or expectations): *the budget dashed hopes of an increase in funding.* ■ [trans.] cause (someone) to lose confidence; dispirit: *I won't tell Stuart—I think he'll be dashed.*
▸exclam. Brit., informal or dated used to express mild annoyance: *"Dash it all, I am in charge."*
▸n. **1** [in sing.] an act of running somewhere suddenly and hastily: *she made a dash for the door.*
■ a journey or period of time characterized by urgency or eager haste: *a 20-mile dash to the airport.* ■ a short fast race run in one heat; a sprint: *the 100-yard dash.*
2 a small quantity of a substance, esp. a liquid, added to something else: *whiskey with a dash of soda.*
■ figurative a small amount of a particular quality adding piquancy or distinctiveness to something else: *a casual atmosphere with a dash of sophistication.*
3 a horizontal stroke in writing or printing to mark a pause or break in sense, or to represent omitted letters or words.
■ the longer signal of the two used in Morse code. Compare with **DOT**[1]. ■ Music a short vertical mark placed above or beneath a note to indicate that it is to be performed in a very staccato manner.
4 impetuous or flamboyant vigor and confidence; panache: *he has youthful energy, dash, and charisma.*
5 short for **DASHBOARD.**
▸**dash something off** write something hurriedly and without much premeditation.
–ORIGIN Middle English (in the sense 'strike forcibly against'): probably symbolic of forceful movement and related to Swedish and Danish *daska*.

dash•board |ˈdashˌbôrd| ▸n. the panel facing the driver of a vehicle or the pilot of an aircraft, containing instruments and controls.
■ historical a board of wood or leather in front of a carriage, to keep out mud.

dashed |dashtˈ| ▸adj. [attrib.] **1** Brit., informal or dated used for emphasis: *it's a dashed shame* | [as submodifier] *she was dashed rude.*
2 (of a line on a piece of paper) composed of dashes.

da•sheen |daˈSHēn| ▸n. another term for **TARO.**
–ORIGIN late 19th cent. (originally West Indian): of unknown origin.

dash•er |ˈdashər| ▸n. **1** informal a person who dresses or acts flamboyantly or stylishly.
2 a plunger for agitating cream in a churn.
3 Hockey the ledge along the top of the boards of a rink.

da•shi•ki |dəˈshēkē| ▸n. (pl. **dashikis**) a loose, brightly colored shirt or tunic, originally from West Africa.
–ORIGIN from Yoruba or Hausa.

dash•ing |ˈdashiNG| ▸adj. (of a man) attractive in a romantic, adventurous way: *a dashing pirate on the high seas.*
■ stylish or fashionable: *a dashing S-type Jaguar.*
–DERIVATIVES **dash•ing•ly** adv.

dash•pot |ˈdashˌpät| ▸n. a device for damping shock or vibration.

das•sie |ˈdäsē| ▸n. (pl. **-ies**) a hyrax, esp. the rock hyrax of southern Africa.
•Family Procaviidae, in particular *Procavia capensis*.
–ORIGIN late 18th cent.: from Afrikaans, from South African Dutch *dasje*, diminutive of Dutch *das* 'badger.'

das•tard |ˈdastərd| ▸n. dated, humorous a dishonorable or despicable person.
–ORIGIN late Middle English (in the sense 'stupid person'): probably from *dazed*, influenced by *dotard* and *bastard*.

das•tard•ly |ˈdæstərdlē| ▸adj. dated, humorous wicked and cruel: *pirates and their dastardly deeds.*
–DERIVATIVES **das•tard•li•ness** n.
–ORIGIN mid 16th cent. (in the sense 'dull or stupid'): from **DASTARD** in the obsolete sense 'base coward.'

das•y•ure |ˈdæsəˌyo͝or| ▸n. another term for **QUOLL.**
–ORIGIN mid 19th cent.: from French, from modern Latin *dasyurus*, from Greek *dasus* 'rough, hairy' + *oura* 'tail.'

DAT |dæt| ▸abbr. digital audiotape.

da•ta |ˈdeɪtə; ˈdatə| ▸n. facts and statistics collected together for reference or analysis. See also **DATUM.**
■ Computing the quantities, characters, or symbols on which operations are performed by a computer, being stored and transmitted in the form of electrical signals and recorded on magnetic, optical, or mechanical recording media. ■ Philosophy things known or assumed as facts, making the basis of reasoning or calculation.
–ORIGIN mid 17th cent. (as a term in philosophy): from Latin, plural of **DATUM.**

USAGE: Data was originally the plural of the Latin word *datum*, 'something (e.g., a piece of information) given.' **Data** is now used as a singular where it means 'information': *this data was prepared for the conference.* It is used as a plural in technical contexts and when the collecion of bits of information is stressed: *all recent data on hurricanes are being compared.* Avoid *datas* and *datae*, which are false plurals, neither English nor Latin.

da•ta bank (also **databank**) ▸n. Computing a large repository of data on a particular topic, sometimes formed from more than one database, and accessible by many users.

da•ta•base |ˈdeɪtəˌbās; ˈdä-| ▸n. a structured set of data held in a computer, esp. one that is accessible in various ways.

da•ta•base man•age•ment sys•tem (abbr.: **DBMS**) ▸n. Computing software that handles the storage, retrieval, and updating of data in a computer system.

dat•a•ble |ˈdāt̬əbəl| (also **dateable**) ▸adj. able to be dated to a particular time.

da•ta com•mu•ni•ca•tions ▸n. the electronic transmission of encoded information to, from, or between computers.

da•ta dic•tion•ar•y ▸n. Computing a set of information describing the contents, format, and structure of a database and the relationship between its elements, used to control access to and manipulation of the database.

da•ta•glove |ˈdeɪtəˌgləv; ˈdä-| ▸n. Computing a device, worn like a glove, that allows the manual manipulation of images in virtual reality.

da•ta min•ing ▸n. Computing the practice of examining large databases in order to generate new information.

da•ta proc•ess•ing ▸n. a series of operations on data, esp. by a computer, to retrieve, transform, or classify information.
–DERIVATIVES **da•ta proc•es•sor** n.

da•ta set ▸n. Computing a collection of related sets of information that is composed of separate elements but can be manipulated as a unit by a computer.

da•ta ter•mi•nal ▸n. Computing a terminal at which a person can enter data into a computer-based system or receive data from one.

da•ta type ▸n. Computing a particular kind of data item, as defined by the values it can take, the programming language used, or the operations that can be performed on it.

da•ta ware•house ▸n. Computing a large store of data accumulated from a wide range of sources within a company and used to guide management decisions.
–DERIVATIVES **da•ta ware•hous•ing** n.

date[1] |dāt| ▸n. **1** the day of the month or year as specified by a number: *what's the date today?* | *please give your name, address, and date of birth.*
■ a particular day or year when a given event occurred or will occur: *significant dates like 1776 and 1789 | they've set a date for the wedding.* ■ (**dates**) the years of a person's birth and death or of the beginning and end of a period or event: *giving the dates of kings and queens.* ■ the period of time to which an artifact or structure belongs: *the church is the largest of its date.* ■ a written, printed, or stamped statement on an item giving the day, month, and year of writing, publication, or manufacture: *these Roman coins bear an explicit date.*
2 informal a social or romantic appointment or engagement: *a college student on a date with someone he met in class.*
■ a person with whom one has such an engagement:

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syn•sac•rum |sinˈsākrəm; -ˈsā-| ▸n. (pl. **synsacra** |-krə| or **synsacrums**) Zoology an elongated composite sacrum containing a number of fused vertebrae, present in birds and some extinct reptiles.

syn•tac•tic |sinˈtaktik| ▸adj. of or according to syntax: *syntactic analysis.*
- DERIVATIVES **syn•tac•ti•cal•ly** adj.; **syn•tac•ti•cal•ly** |-ik(ə)lē| adv.
- ORIGIN early 19th cent.: from Greek *suntaktikos*, from *suntassein* 'arrange together' (see **SYNTAX**).

syn•tagm |ˈsinˌtam| (also **syntagma** |sinˈtagmə|) ▸n. (pl. **syntagms** or **syntagmas** or **syntagmata** |sinˈtagmətə|) a linguistic unit consisting of a set of linguistic forms (phonemes, words, or phrases) that are in a sequential relationship to one another. Often contrasted with **PARADIGM**.
- the relationship between any two such forms.
- ORIGIN mid 17th cent.: via late Latin from Greek *suntagma*, from *suntassein* 'arrange together.'

syn•tag•mat•ic |ˌsintəgˈmatik| ▸adj. of or denoting the relationship between two or more linguistic units used sequentially to make well-formed structures. Contrasted with **PARADIGMATIC**.
- DERIVATIVES **syn•tag•mat•i•cal•ly** |-ik(ə)lē| adv.; **syn•tag•mat•ics** n.

syn•tax |ˈsinˌtaks| ▸n. the arrangement of words and phrases to create well-formed sentences in a language; *the syntax of English.*
- a set of rules for or an analysis of this: *generative syntax.* ■ the branch of linguistics that deals with this.
- ORIGIN late 16th cent.: from French *syntaxe*, or via late Latin from Greek *suntaxis*, from *sun-* 'together' + *taxis* 'arrange.'

syn•ten•ic |sinˈtenik| ▸adj. Genetics (of genes) occurring on the same chromosome: *syntenic sequences.*
- DERIVATIVES **syn•te•ny** |ˈsintənē| n.
- ORIGIN 1970s: from **SYN-** 'together' + Greek *tainia* 'band, ribbon' + **-IC**.

synth |sinTH| ▸n. informal short for **SYNTHESIZER**.

synth•ase |ˈsinˌTHās; -ˌzH āz| ▸n. [often with adj.] Biochemistry an enzyme that catalyzes the linking together of two molecules, esp. without the direct involvement of ATP: *nitric oxide synthases.* Compare with **LIGASE**.

syn•the•sis |ˈsinTHəsis| ▸n. (pl. **syntheses** |-ˌsēz|) combination or composition, in particular:
- the combination of ideas to form a theory or system: *the synthesis of intellect and emotion in his work* | *the ideology represented a synthesis of certain ideas.* Often contrasted with **ANALYSIS**. ■ the production of chemical compounds by reaction from simpler materials: *the synthesis of methanol from carbon monoxide and hydrogen.* ■ (in Hegelian philosophy) the final stage in the process of dialectical reasoning, in which a new idea resolves the conflict between thesis and antithesis. ■ Grammar the process of making compound and derivative words. ■ Linguistics the use of inflected forms rather than word order to express grammatical structure.
- DERIVATIVES **syn•the•sist** n.
- ORIGIN early 17th cent.: via Latin from Greek *suntheis*, from *suntithenai* 'place together.'

syn•the•sis gas ▸n. a mixture of carbon monoxide and hydrogen produced industrially, esp. from coal, and used as a feedstock in making synthetic chemicals.

syn•the•size |ˈsinTHəˌsīz| (also **synthetize** |-ˌtīz|) ▸v. [trans.] make (something) by synthesis, esp. chemically: *man synthesizes new chemical poisons and sprays the countryside wholesale.*
- combine (a number of things) into a coherent whole: *pupils should synthesize the data they have gathered* | *Darwinian theory has been synthesized with modern genetics.* ■ produce (sound) electronically: *trigger chips that synthesize speech* | [as adj.] (**synthesized**) *synthesized chords.*

syn•the•siz•er |ˈsinTHəˌsīzər| ▸n. an electronic musical instrument, typically operated by a keyboard, producing a wide variety of sounds by generating and combining signals of different frequencies.

syn•thet•ic |sinˈTHetik| ▸adj. relating to or using synthesis.
- (of a substance) made by chemical synthesis, esp. to imitate a natural product: *synthetic rubber.* ■ (of an emotion or action) not genuine; insincere: *their tears are a bit synthetic.* ■ Logic (of a proposition) having truth or falsity determinable by recourse to experience. Compare with **ANALYTIC**. ■ Linguistics (of a language) characterized by the use of inflections rather than word order to express grammatical structure. Contrasted with **AGGLUTINATIVE** and **ANALYTIC**.
- ▸n. (usu. **synthetics**) a synthetic material or chemical, esp. a textile fiber.
- DERIVATIVES **syn•thet•i•cal** adj.; **syn•thet•i•cal•ly** |-ik(ə)lē| adv.
- ORIGIN late 17th cent.: from French *synthétique* or modern Latin *syntheticus*, from Greek *suntheticos*, based on *suntithenai* 'place together.'

syn•thet•ic res•in ▸n. see **RESIN**.

syn•thon |ˈsinˌTHän| ▸n. Chemistry a constituent part of a molecule to be synthesized that is regarded as the basis of a synthetic procedure.
- ORIGIN 1960s: from **SYNTHESIS** + **-ON**.

syn•ton•ic |sinˈtänik| ▸adj. Psychology (of a person) responsive to and in harmony with their environment so that affect is appropriate to the given situation: *culturally syntonic.*
- [in combination] (of a psychiatric condition or psychological process) consistent with other aspects of an individual's personality and belief system: *this phobia was ego-syntonic.* ■ historical relating to or denoting the lively and responsive type of temperament that was considered liable to manic-depressive psychosis. See also **CYCLOTHYMIA**.
- DERIVATIVES **syn•tone** |ˈsinˌtōn| n.
- ORIGIN late 19th cent.: from German *Syntonie* 'state of being syntonic' + **-IC**.

syn•type |ˈsinˌtīp| ▸n. Botany & Zoology each of a set of type specimens of equal status, upon which the description and name of a new species is based. Compare with **HOLOTYPE**.

syph•i•lis |ˈsifələs| ▸n. a chronic bacterial disease that is contracted chiefly by infection during sexual intercourse, but also congenitally by infection of a developing fetus.
- This is caused by the spirochete *Treponema pallidum*. The infection progresses in four successive stages: **primary syphilis**, characterized by a chancre in the part infected; **secondary syphilis**, affecting chiefly the skin, lymph nodes, and mucous membranes; **tertiary syphilis**, involving the spread of tumorlike lesions (gummas) throughout the body, frequently damaging the cardiovascular and central nervous systems; **quaternary syphilis** neurosyphilis.
- DERIVATIVES **syph•i•lit•ic** |ˌsifəˈlitik| adj. & n.
- ORIGIN early 18th cent.: modern Latin, from *Syphilis, sive Morbus Gallicus*, the title of a Latin poem (1530), from the name of the character *Syphilus*, the supposed first sufferer of the disease.

sy•phon ▸n. & v. variant spelling of **SIPHON**.

SYR ▸abbr. Syria (international vehicle registration).

Syr•a•cuse |ˈsirəˌkyōōs; -kyōōz| 1 a port on the eastern coast of Sicily; pop. 125,000. Italian name **SIRACUSA**. 2 a city in New York, southeast of Lake Ontario; pop. 147,306. The site of salt springs, it was an important center of salt production during the 19th century.

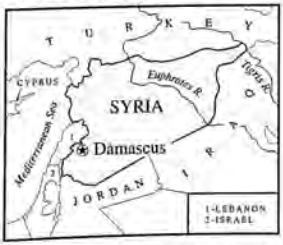
Syr•ah |səˈrä; ˈsirə| ▸n. another term for **SHIRAZ**[2].

syr•ette |siˈret| ▸n. Medicine, trademark a disposable injection unit comprising a collapsible tube with an attached hypodermic needle and a single dose of a drug, commonly morphine.
- ORIGIN 1940s: from **SYRINGE** + **-ETTE**.

Syr•i•a |ˈsirēə| a country in the Middle East, on the eastern Mediterranean Sea; pop. 12,824,000; capital, Damascus; language, Arabic (official).

Syria was the site of various early civilizations, most notably that of the Phoenicians. Falling successively within the empires of Persia, Macedon, and Rome, it became a center of Islamic power and civilization from the 7th century and a province of the Ottoman Empire in 1516. After the Turkish defeat in World War I, Syria was mandated to France and became independent with the ejection of Vichy troops by the Allies in 1941. From 1958 to 1961, Syria was united with Egypt as the United Arab Republic.

- DERIVATIVES **Syr•i•an** adj. & n.



Syr•i•ac |ˈsirēˌak| ▸n. the language of ancient Syria, a western dialect of Aramaic in which many important early Christian texts are preserved, and that is still used by Syrian Christians as a liturgical language.
▸adj. of or relating to this language.

sy•rin•ga |səˈriNGə| ▸n. 1 a plant of the genus *Syringa* (family Oleaceae), esp. (in gardening) the lilac. 2 informal another term for **MOCK ORANGE**.
- ORIGIN modern Latin, from Greek *surinx*, *surinx* 'tube' (with reference to the use of its stems as pipe stems).

sy•ringe |səˈrinj; ˈsirinj| ▸n. Medicine a tube with a nozzle and piston or bulb for sucking in and ejecting liquid in a thin stream, used for cleaning wounds or body cavities, or fitted with a hollow needle for injecting or withdrawing fluids. ■ any similar device used in gardening or cooking.


medical syringe

▸v. (**syringing** |səˈrinjiNG; ˈsirinjiNG|) [trans.] spray liquid into (the ear or a wound) with a syringe: *I had my ears syringed.* ■ spray liquid over (plants) with a syringe: *syringe the leaves frequently during warm weather.*
- ORIGIN late Middle English: from medieval Latin *syringa*, from *syrinx* (see **SYRINX**).

sy•rin•go•my•e•li•a |səˌriNGōmīˈēlēə; -ˈēlyə| ▸n. Medicine a chronic progressive disease in which longitudinal cavities form in the cervical region of the spinal cord. This characteristically results in wasting of the muscles in the hands and a loss of sensation.
- ORIGIN late 19th cent.: modern Latin, from Greek *surinx*, *surinx-* 'tube, channel' + *muelos* 'marrow.'

syr•inx |ˈsiriNGks| ▸n. (pl. **syrinxes** |ˈsiriNGksiz|) 1 a set of panpipes. 2 Ornithology the lower larynx or voice organ in birds, situated at or near the junction of the trachea and bronchi and well developed in songbirds.
- ORIGIN early 17th cent.: via Latin from Greek *surinx* 'pipe, channel.'

Syro- ▸comb. form Syrian; Syrian and . . . : *Syro-Palestinian.*
- relating to Syria.

syr•phid |ˈsərfid| ▸n. Entomology a fly of the hoverfly family (Syrphidae).
- ORIGIN late 19th cent.: from modern Latin *Syrphidae* (plural), from the genus name *Syrphus*, from Greek *surphos* 'gnat.'

syr•ta•ki |sərˈtäkē; -ˈtākē| (also **sirtaki**) ▸n. (pl. **syrtakis**) a Greek folk dance in which dancers form a line or chain.
- ORIGIN modern Greek, from Greek *surtos* 'drawn, led' + the diminutive suffix *-aki*.

syr•up |ˈsirəp; ˈsər-| (also **sirup**) ▸n. a thick sweet liquid made by dissolving sugar in boiling water, often used for preserving fruit.
- a thick sweet liquid containing medicine or used as a drink: *cough syrup.* ■ a thick sticky liquid derived from a sugar-rich plant, esp. sugar cane, corn, and maple. ■ figurative excessive sweetness or sentimentality of style or manner: *Mr. Gurney's poems are almost all of them syrup.*
- ORIGIN late Middle English: from Old French *sirop* or medieval Latin *siropus*, from Arabic *šarāb* 'beverage'; compare with **SHERBET** and **SHRUB**[2].

syr•up of figs ▸n. a laxative syrup made from dried figs, typically with senna and carminatives.

syr•up•y |ˈsirəpē; ˈsər-| (also **sirupy**) ▸adj. having the consistency or sweetness of syrup: *syrupy desserts.* ■ figurative excessively sentimental: *a particularly syrupy moment from a corny film.*

sys•op |ˈsiˌsäp| ▸n. Computing a system operator.
- ORIGIN 1980s: abbreviation.

syst. ▸abbr. system.

sys•tem |ˈsistəm| ▸n. 1 a set of connected things or parts forming a complex whole, in particular:
- a set of things working together as parts of a mechanism or an interconnecting network: *the state railway system* | *fluid is pushed through a system of pipes or channels.* ■ Physiology a set of organs in the body with a common structure or function: *the digestive system.* ■ the human or animal body as a whole: *you need to get the cholesterol out of your system.* ■ Computing a group of related hardware units or programs or both, esp. when dedicated to a single application. ■ Geology (in chronostratigraphy) a major range of strata that corresponds to a period in time, subdivided into series. ■ Astronomy a group of celestial objects connected by their mutual attractive forces, esp. moving in orbits about a center: *the system of bright stars known as the Gould Belt.* ■ short for **CRYSTAL SYSTEM**.

2 a set of principles or procedures according to which

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something is done; an organized scheme or method: *a multiparty system of government* | *the public school system.* ■ orderliness; method: *there was no system at all in the company.* ■ a method of choosing one's procedure in gambling. ■ a set of rules used in measurement or classification: *the metric system.* ■ **(the system)** the prevailing political or social order, esp. when regarded as oppressive and intransigent: *don't try bucking the system.*

3 Music a set of staves in a musical score joined by a brace.

–PHRASES **get something out of one's system** informal get rid of a preoccupation or anxiety: *she let her get the crying out of her system.*

–DERIVATIVES **sys•tem•less** adj.

–ORIGIN early 17th cent.: from French *système* or late Latin *systema*, from Greek *sustēma*, from *sun-* 'with' + *histanai* 'set up.'

sys•tem•at•ic |ˌsistəˈmatik| ▸adj. done or acting according to a fixed plan or system; methodical: *a systematic search of the whole city.*

–DERIVATIVES **sys•tem•at•i•cal•ly** |-ik(ə)lē| adv.; **sys•tem•a•tist** |ˈsistəməˌtist| n.

–ORIGIN early 18th cent.: from French *systématique*, via late Latin from late Greek *sustēmatikos*, from *sustēma* (see SYSTEM).

sys•tem•at•ic de•sen•si•ti•za•tion ▸n. Psychiatry a treatment for phobias in which the patient is exposed to progressively more anxiety-provoking stimuli and taught relaxation techniques.

sys•tem•at•ic er•ror ▸n. Statistics an error having a nonzero mean, so that its effect is not reduced when observations are averaged.

sys•tem•at•ics |ˌsistəˈmatiks| ▸plural n. [treated as sing.] the branch of biology that deals with classification and nomenclature; taxonomy.

sys•tem•at•ic the•ol•o•gy ▸n. a form of theology in which the aim is to arrange religious truths in a self-consistent whole.

–DERIVATIVES **sys•tem•at•ic the•o•lo•gian** n.

sys•tem•a•tize |ˈsistəməˌtīz| ▸v. [trans.] arrange according to an organized system; make systematic: *Gardens set about systematizing medical thought* | [as adj.] **(systematized)** *systematized reading schemes.*

–DERIVATIVES **sys•tem•a•ti•za•tion** |ˌsistəməˌtəˈzāshən| n.; **sys•tem•a•tiz•er** n.

sys•tem•ic |sɔˈstemik| ▸adj. **1** of or relating to a system, esp. as opposed to a particular part: *the disease is localized rather than systemic.* ■ (of an insecticide, fungicide, or similar substance) entering the plant via the roots or shoots and passing through the tissues.

2 Physiology denoting the part of the circulatory system concerned with the transportation of oxygen to and carbon dioxide from the body in general, esp. as distinct from the pulmonary part concerned with the transportation of oxygen from and carbon dioxide to the lungs.

–DERIVATIVES **sys•tem•i•cal•ly** |-ik(ə)lē| adv.

–ORIGIN early 19th cent.: formed irregularly from SYSTEM + **-IC.**

sys•tem in•te•gra•tor (also **systems integrator**) ▸n. see INTEGRATOR.

sys•tem•ize |ˈsistəˌmīz| ▸v. another term for SYSTEMATIZE.

–DERIVATIVES **sys•tem•i•za•tion** |ˌsistəmiˈzāshən| n.; **sys•tem•iz•er** n.

sys•tem op•er•a•tor (also **systems operator**) ▸n. Computing a person who manages the operation of a computer system, such as an electronic bulletin board.

sys•tems an•a•lyst ▸n. a person who analyzes a complex process or operation in order to improve its efficiency, esp. by applying a computer system.

–DERIVATIVES **sys•tems a•na•ly•sis** n.

sys•to•le |ˈsistəlē| ▸n. Physiology the phase of the heartbeat when the heart muscle contracts and pumps blood from the chambers into the arteries. Often contrasted with DIASTOLE.

–DERIVATIVES **sys•tol•ic** |siˈstälik| adj.

–ORIGIN late 16th cent.: via late Latin from Greek *sustolē*, from *sustellein* 'to contract.'

syz•y•gy |ˈsizijē| ▸n. (pl. **-ies**) Astronomy a conjunction or opposition, esp. of the moon with the sun: *the planets were aligned in syzygy.* ■ a pair of connected or corresponding things: *animus and anima represent a supreme pair of opposites, the syzygy.*

–ORIGIN early 17th cent.: via late Latin from Greek *suzugia*, from *suzugos* 'yoked, paired,' from *sun-* 'with, together' + the stem of *zeugnumai* 'to yoke.'

Szcze•cin |ˈSHCHECHēn| a city in northwestern Poland, a port on the Oder River, near the border with Germany; pop. 413,000. German name **STETTIN.**

Sze•chuan |ˈsecHˈwän| (also **Szechwan**) variant of SICHUAN.

Sze•ged |ˈseg,ed| a city in southern Hungary, a port on the Tisza River, near the border with Serbia; pop. 178,000.

Szent-Györ•gyi |sānt ˈjörj(ē)|, Albert von (1893–1986), US biochemist, born in Hungary. He discovered ascorbic acid, which was later identified with vitamin C.

Szi•lard |ˈzil,ärd; ˈsil-; -ərd|, Leo (1898–1964), US physicist and molecular biologist, born in Hungary. He fled from Nazi Germany to the US, where he became a central figure in the Manhattan Project, which developed the atom bomb.

EXHIBIT 15

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10 9 8 7 6 5 4 3 2 1

3 [C] a narrow pointed fold made in a piece of clothing by sewing so that it has a better shape or fits better
4 [singular] **[+of]** *literary* a sudden, quick, and usually short feeling of fear, anger etc

dartboard /'dɑːtˌbɔːd/ noun [C] a round board that you throw darts at in the game of DARTS

darts /dɑːts/ noun [U] a game in which you throw small pointed objects called **darts** at a round board called a **dartboard** in order to score points

Darwinian /dɑː'wɪnɪən/ adj relating to Darwinism

Darwinism /'dɑːwɪˌnɪz(ə)m/ noun [U] a theory of EVOLUTION

From *Charles Darwin*, a 19th-century British scientist who was the first person to develop this theory.

dash[1] /dæʃ/ verb ★
1 [I] **[+into/out of/across etc]** to run or go somewhere very quickly because you are in a hurry: *I dashed out into the street, still in my pyjamas.* ♦ *Maria came dashing down the stairs.*
2 [T] **[dash sth against/onto/to etc]** to throw or hit something very violently onto a surface, usually so that it breaks: *Picking up the glass, he dashed it against the wall.* ♦ *In a fit of rage James had dashed the priceless vase to the ground.* **2a.** [I] **[+against]** if water dashes against something, it hits it violently: *Huge waves dashed against the side of the boat.*

dash sb's hopes to make it impossible for someone to do what they hoped to do: *Saturday's defeat has dashed their hopes of success in the FA Cup this year.* ♦ *Hopes for an early economic recovery have now been dashed.*
dash it (all) *informal old-fashioned* used when you are annoyed about something
I must dash/I have to dash *spoken* used for saying that you must leave quickly because you are in a hurry

dash 'off phrasal vb **1** [I] to leave quickly or suddenly because you are in a hurry: *I've got to dash off straight after lunch to meet a client.* **2** [T] to write or draw something quickly because you are in a hurry: *I sat down and dashed off a couple of notes.*

dash[2] /dæʃ/ noun ★

1 act of running/hurrying	**5** where car controls are
2 small amount of sth	**6** style/confidence/energy
3 symbol in writing	**7** short very fast race
4 signal in Morse code	+ PHRASES

1 [singular] an act of running or going somewhere very quickly because you are in a hurry: **make a dash for sb/sth** *She made a sudden dash for the door.* ♦ **make a dash for it** (=run very quickly to escape or reach a place) *He looked at his guards and wondered whether he should make a dash for it.* ♦ **a mad dash** (=in an extremely fast uncontrolled way) *We had a mad dash around town in search of a present for Dad.*
2 [C usually singular] **[+of]** a small amount of a substance added to food or drink to give it a special flavour: *Add a dash of soy sauce for that authentic Chinese taste.*
2a. **[+of]** a small amount of an interesting or unusual quality that something contains or has added to it: *A dash of glamour was supplied by the presence of a couple of minor TV celebrities.*
3 [C] the symbol –, used in writing to separate different parts of a sentence
4 [C] a long signal used for sending messages in MORSE CODE. Short signals are called **dots**.
5 [C] *informal* the DASHBOARD of a car
6 [U] *old-fashioned* a combination of style, confidence, and energy
7 [C] *mainly Am E* a short race in which people run as fast as they can: SPRINT

cut a dash *Br E old-fashioned* to look very attractive because you are wearing nice clothes that people will notice: *The captain cut quite a dash in his uniform.*

dashboard /'dæʃˌbɔːd/ noun [C] the part inside a car where the SPEEDOMETER and other instruments are —*picture* → C8

dashed /dæʃt/ adj, adv *informal old-fashioned* used for emphasizing what you are saying, especially when you are annoyed about something

dashing /'dæʃɪŋ/ adj *old-fashioned* a dashing man is attractive and fashionable in an exciting way **a.** used about a man's appearance, clothes, or behaviour

dastardly /'dæstədli/ adj *old-fashioned* very cruel or evil: *a dastardly villain*

DAT /dæt/ noun [C] digital audio tape: a type of AUDIOTAPE used for recording sound or information

data /'deɪtə/ noun [U] ★★★
1 facts or information used for making calculations or decisions: can be followed by a plural verb in scientific English, in which case the singular is **datum**: *The analysis was based on data collected in the field.*
2 information in a form that a computer can use: *The new format carries 30 times more data than a CD-ROM.*

'data ˌbank noun [C] *computing* **1** *old-fashioned* a DATABASE **2** a large amount of information, especially when it is used by computers: *data bank searches on product information*

database /'deɪtəˌbeɪs/ noun [C] *computing* ★★ a large amount of information stored in a computer in an organized way that allows individual pieces of information to be found quickly

'data ˌcapture noun [U] *computing* the process of collecting DATA and putting it into a computer by electronic methods

'data ˌmining noun [U] *computing* the process of searching a DATABASE using special software in order to find out information, for example what type of people buy a product. It is often used by companies as a way of trying to increase sales.

Datapost /'deɪtəˌpəʊst/ *trademark* a service provided by the Royal Mail in the UK for sending letters and parcels very quickly

data processing /ˌdeɪtə 'prəʊsesɪŋ/ noun [U] *computing* the operations performed by a computer in order to store, organize, or find information

ˌdata pro'tection noun [U] legal control over who can see or use information kept by computers

'data ˌset noun [C] *computing* an amount of information stored as a file on a computer

ˌdata 'warehouse noun [C] *computing* a large amount of information from a company stored on a computer and used for making business decisions

date[1] /deɪt/ noun ★★★
1 [C] the name and number of a particular day or year: *The date on the report is 24 October, 1998.* ♦ **today's date** *'What's today's date?' 'The 25th.'* **1a.** [C] a particular day, month, or year when something happens: **+of** *The precise date of the book's publication is not yet known.* ♦ *I made a note of the date and time of his arrival.* ♦ **set/fix a date** (=choose it) *Should we set a date for the next meeting?*
1b. [singular] a time in the past or future: **at a later/future date** *The exact details of the scheme will be worked out at a later date.* ♦ **at an earlier date** *Johnson had agreed at an earlier date to take on the role of chairman.* → DATE OF BIRTH, USE-BY DATE
2 [C] an arrangement to meet someone you are having or starting a sexual or romantic relationship with: **have a date (with sb)** *I've got a date with one of the boys on my course tonight.* ♦ **go (out) on a date (with sb)** *Phil phoned me last night, and we're going on a date this evening.*
2a. *mainly Am E* someone you have arranged to meet as part of a sexual or romantic relationship: *So come on, tell us, who's your date this evening?* **2b.** **make a date (with sb)** to arrange to meet someone on a particular day
3 [C] a sweet brown sticky fruit with a hard narrow seed inside that grows on PALM trees

to date *formal* until now: *There have been no reports of the animal being seen to date.*
→ OUT-OF-DATE, UP-TO-DATE

date[2] /deɪt/ verb ★★★

1 write date on sth	**4** show you are getting old
2 discover how old sth is	**5** have relationship with sb
3 seem no longer modern	+ PHRASES

1 [T] to write the date on something: *The letter was dated 23 February.* ♦ *a memo dated 16th June*
2 [T] to discover exactly how old something is or when it was made by examining it carefully or making scientific tests: *The paintings have not yet been accurately dated by the museum's experts.*

system /'sɪstəm/ noun ★★★
1 [C] a set of connected things that work together for a particular purpose: *a central heating system* ♦ *I decided to install a security system after the shop was burgled.* ♦ *the capital's inadequate public transport system* **1a.** a set of organs, tubes etc in your body that work together: **cardiovascular/circulatory system** *First, check that the circulatory system is working properly.* **1b.** your body considered as a set of connected organs, tubes etc: *Lack of sleep can be hard on the system.* **1c.** a set of pieces of equipment or computer programs that work together: *a new computer system* ♦ *The magazine is produced using a desktop publishing system.* ♦ **system requirements** (=the type of software, hardware, and the amount of memory needed to operate a program) *The system requirements for this program are listed below.*
2 [C/U] a method of organizing or doing things: *a legal/educational/political system* ♦ *a two-party/multiparty system* ♦ *the criminal justice system* ♦ **+for** *They are introducing a very sophisticated system for delivering information.* ♦ **+of** *a democratic system of government* ♦ **+to** *There is simply no system to the way Joshua works.* **2a. the system** rules that decide how a society, country, or organization should operate and that cannot be changed even though they seem unfair to you: *You can't beat the system.* → BUCK²
all systems go used for saying that everything is ready for an event or activity to begin: *Once she got the money for the new business it was all systems go.*
get sb/sth out of your system *informal* to get rid of a strong wish to do something or strong feelings about someone: *Rob just let her talk and get it all out of her system.*
→ IMMUNE SYSTEM

systematic /ˌsɪstə'mætɪk/ adj ★★ done according to a careful plan and in a thorough way: *a systematic approach to the cleanup of hazardous waste* ♦ *the systematic study of social policy* —**systematically** /ˌsɪstə'mætɪkli/ adv: *We know that human rights are being systematically violated.* ♦ *The collection has not been systematically updated.*

systematise /'sɪstəmə,taɪz/ a Br E spelling of **systematize**

systematize /'sɪstəmə,taɪz/ verb [T] *formal* to organize something according to a system

systemic /sɪ'stiːmɪk/ adj *very formal* affecting all of something: *The committee will try to make the case for systemic reform.* **a.** *medical* affecting your whole body: *systemic illness* —**systemically** /sɪ'stiːmɪkli/ adv

ˌsystem 'operator noun [C] someone whose job is to manage a BULLETIN BOARD or a computer system

ˌsystems 'analyst noun [C] someone whose job is to plan or improve the way a business or organization uses computers —**ˌsystems a'nalysis** noun [U]

EXHIBIT 16

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.

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

(65) **Prior Publication Data**

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Related U.S. Application Data

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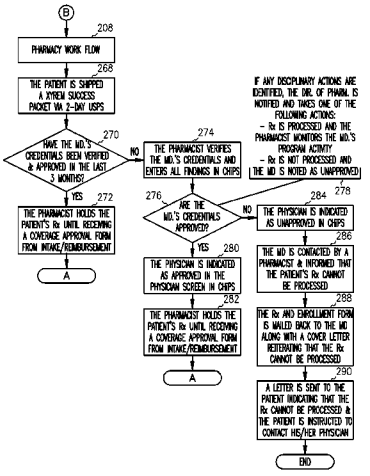
Primary Examiner—Jerry O'Connor
Assistant Examiner—Lena Najarian
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg & Woessner, P.A.

(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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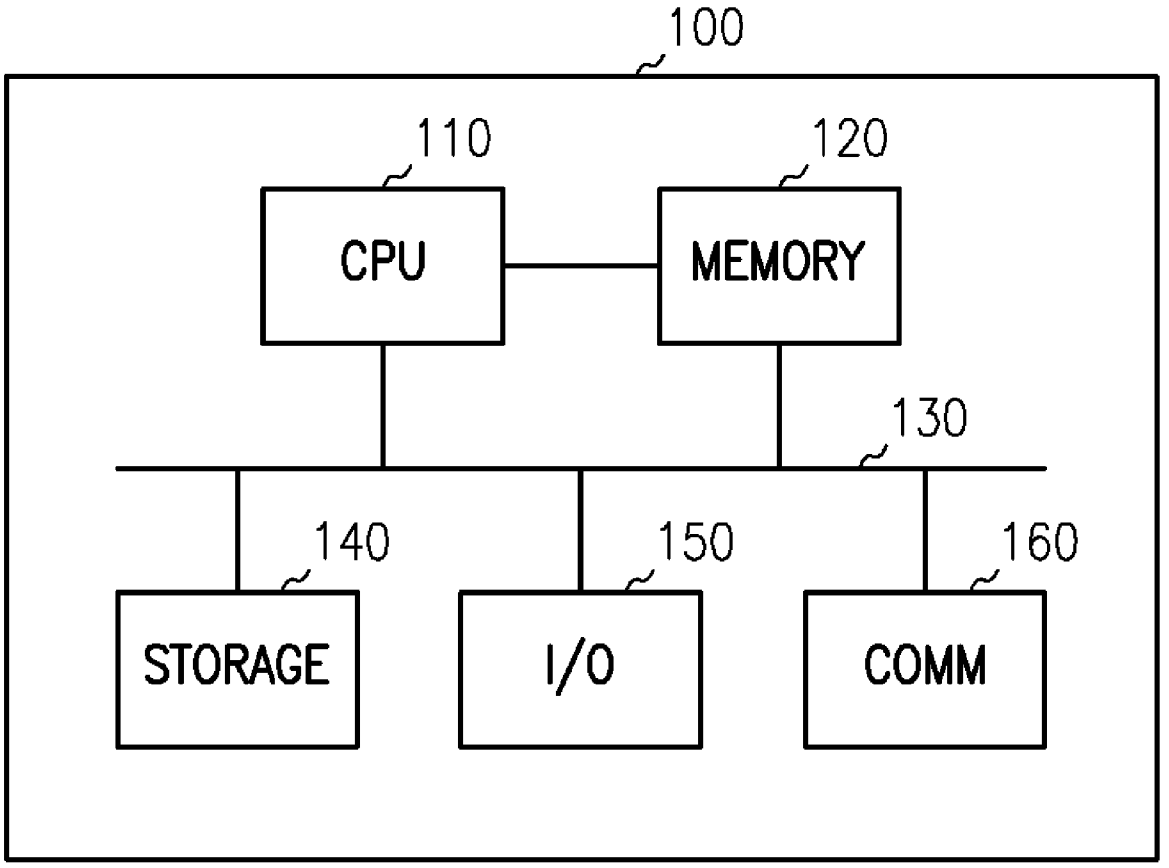

FIG. 1

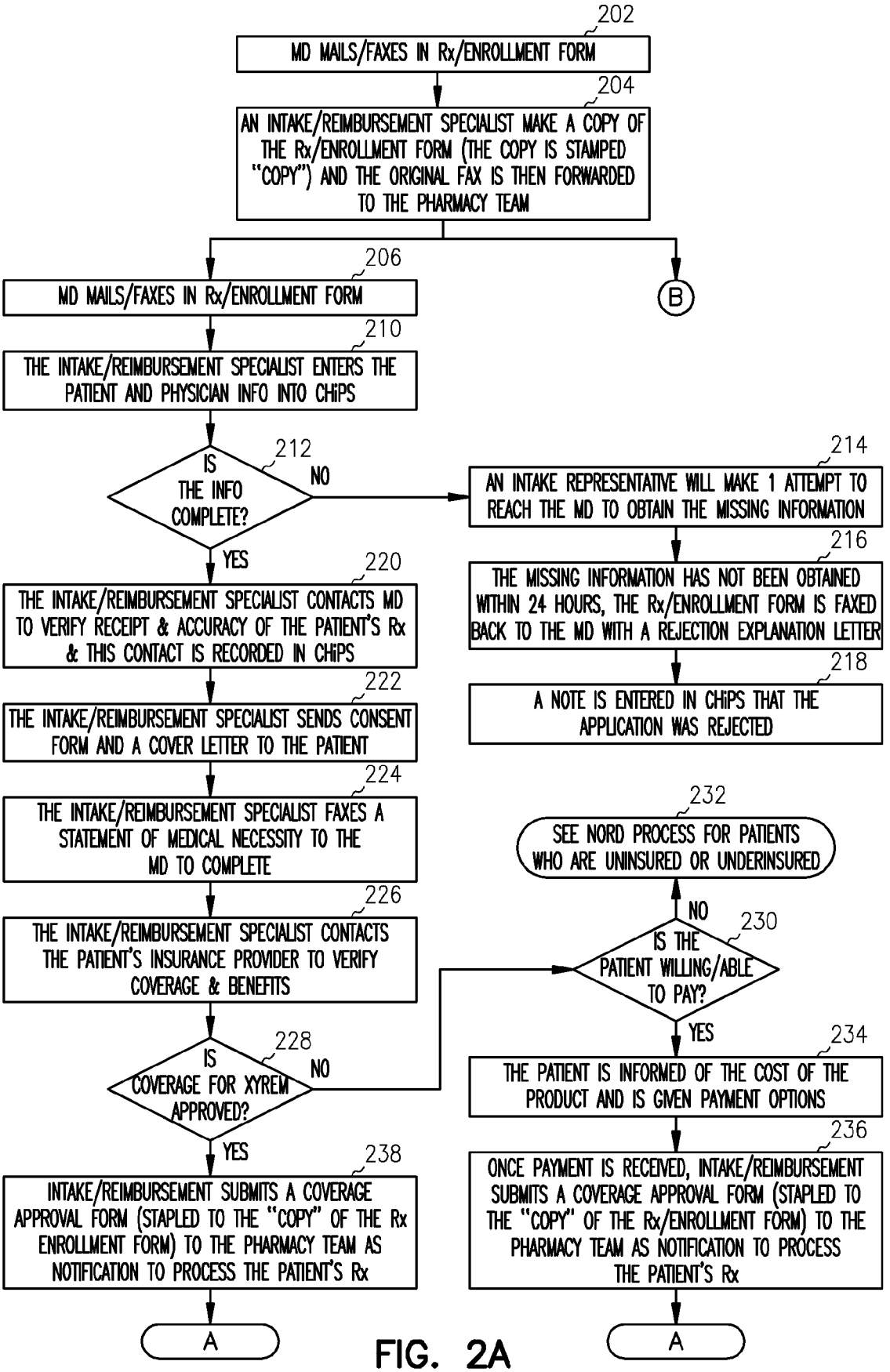
202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE 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
232
SEE NORD PROCESS FOR PATIENTS WHO ARE UNINSURED OR UNDERINSURED
226
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE & BENEFITS
NO
230
IS THE PATIENT WILLING/ABLE TO PAY?
228
IS COVERAGE FOR XYREM APPROVED?
NO
YES
234
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
YES
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
236
ONCE PAYMENT IS RECEIVED, INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx/ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
A

FIG. 2A

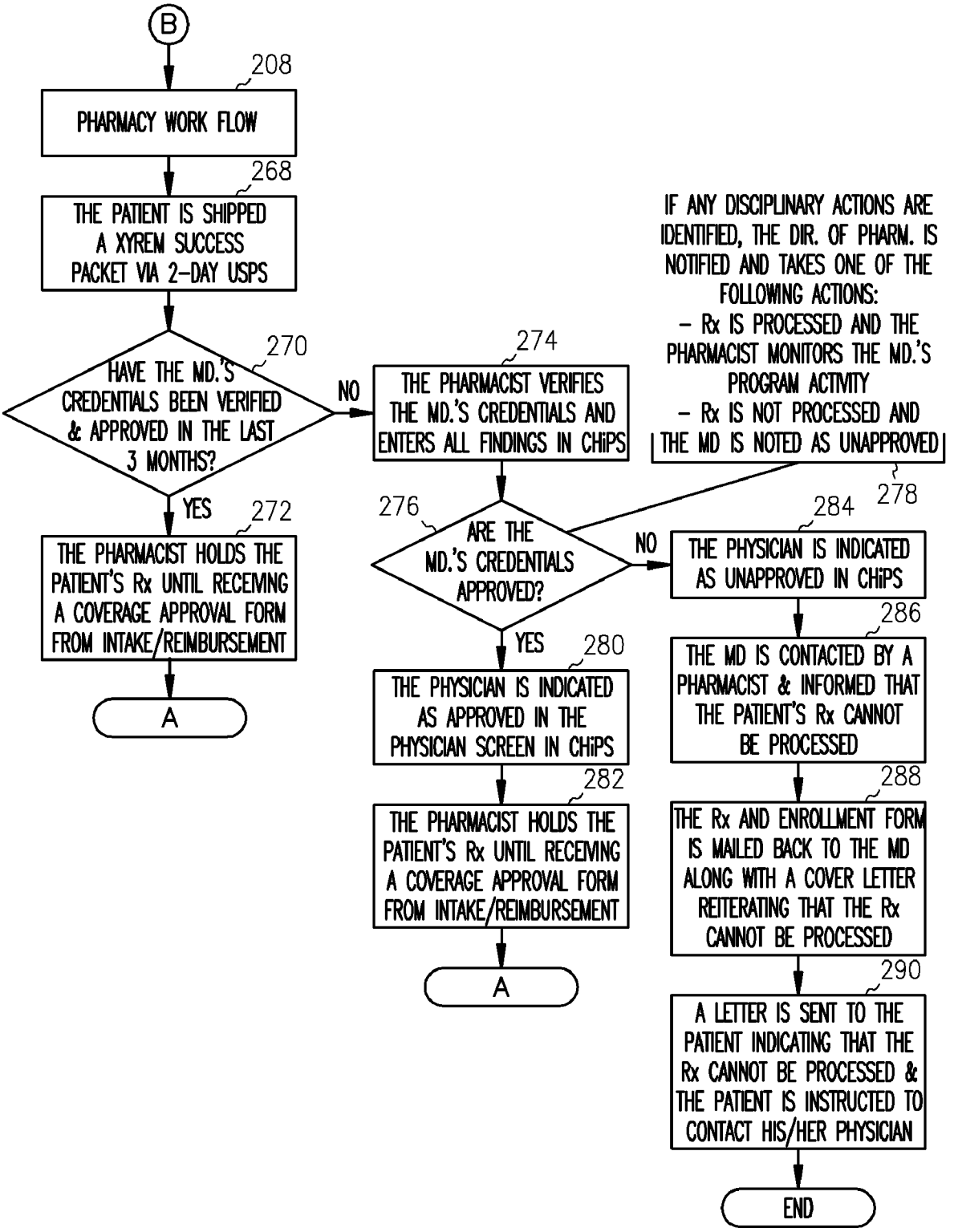
B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST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

FIG. 2B

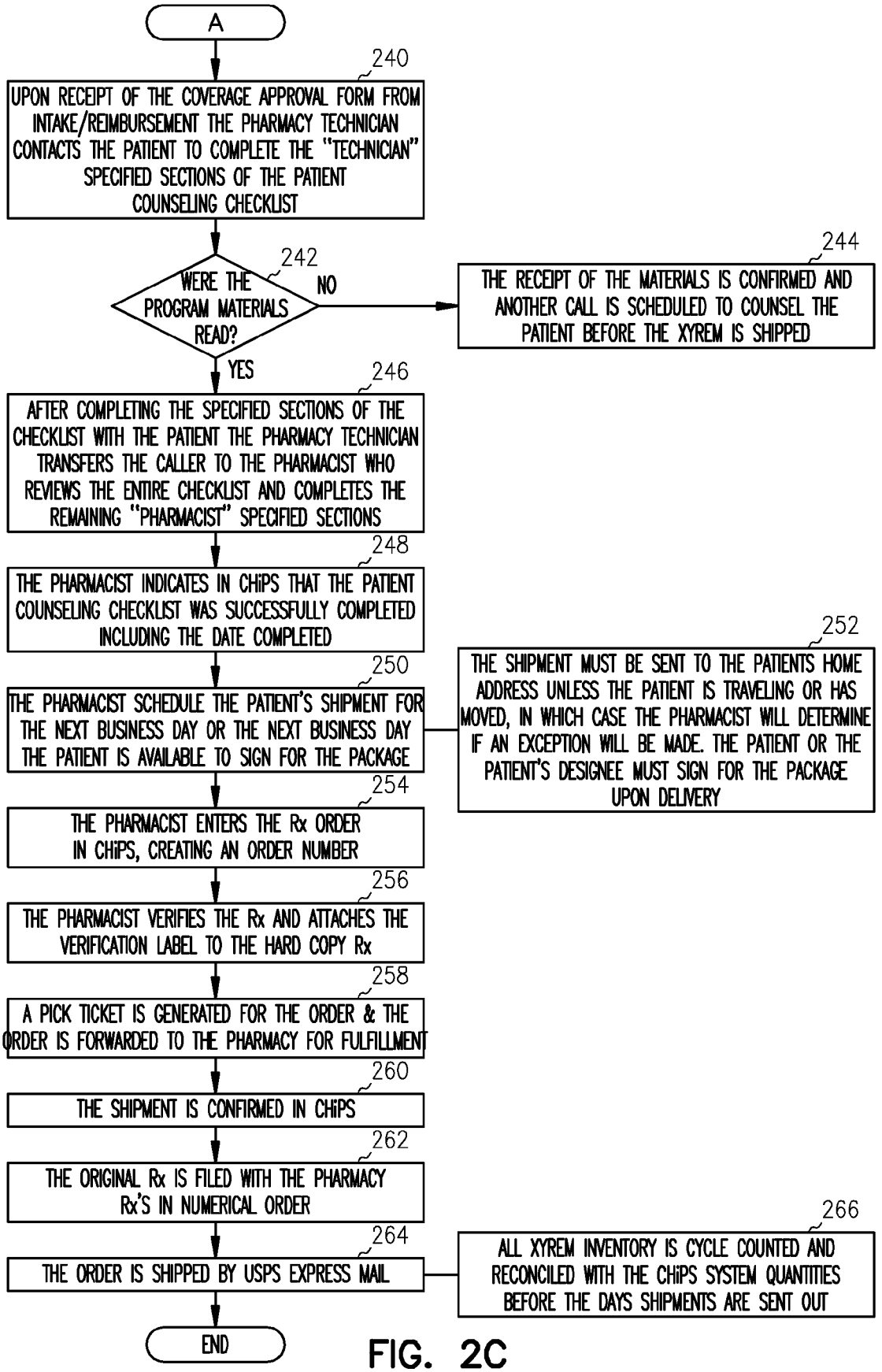
A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER CALL IS SCHEDULED TO COUNSEL THE PATIENT BEFORE THE XYREM IS SHIPPED
YES
246
AFTER COMPLETING THE SPECIFIED SECTIONS OF THE CHECKLIST WITH THE PATIENT THE PHARMACY TECHNICIAN TRANSFERS THE CALLER TO THE PHARMACIST WHO REVIEWS THE ENTIRE CHECKLIST AND COMPLETES THE REMAINING "PHARMACIST" SPECIFIED SECTIONS
248
THE PHARMACIST INDICATES IN CHIPS THAT THE PATIENT COUNSELING CHECKLIST WAS SUCCESSFULLY COMPLETED INCLUDING THE DATE COMPLETED
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

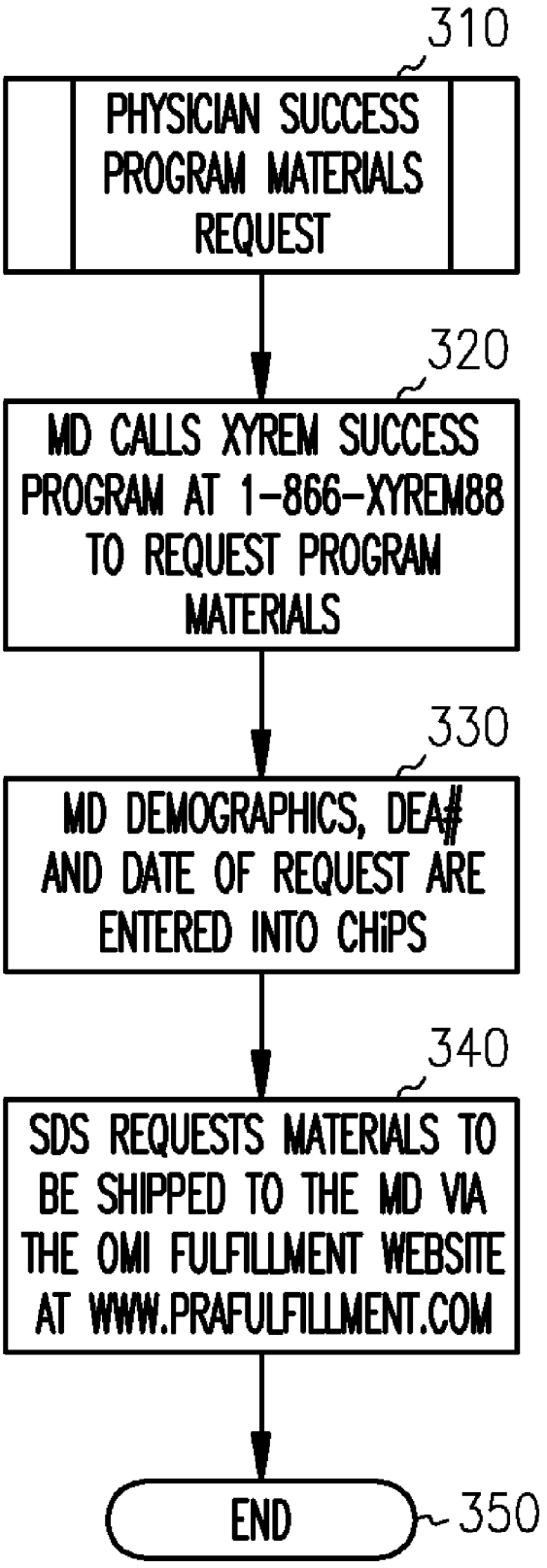
310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHiPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM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

FIG. 3

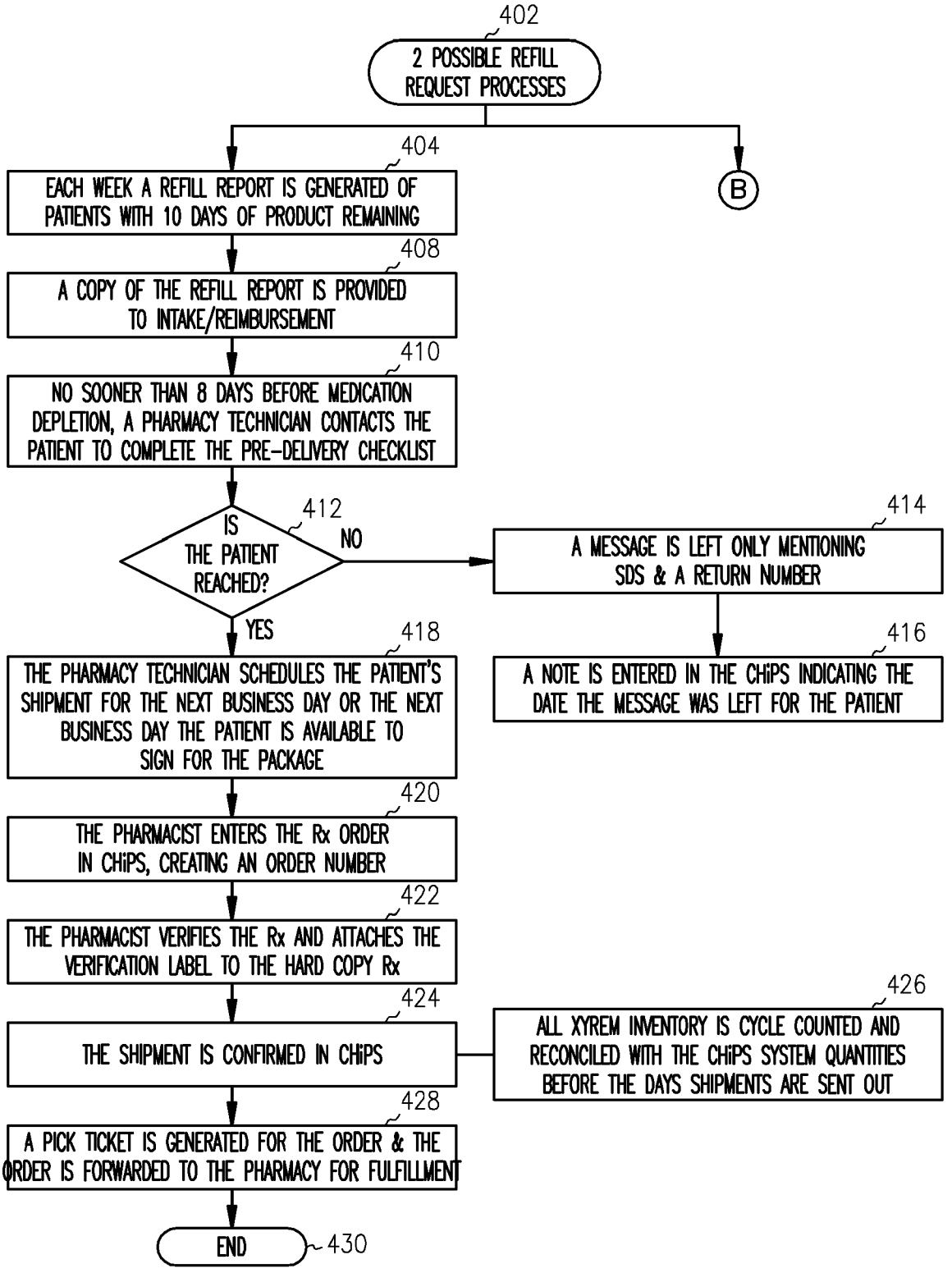
402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE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

FIG. 4A

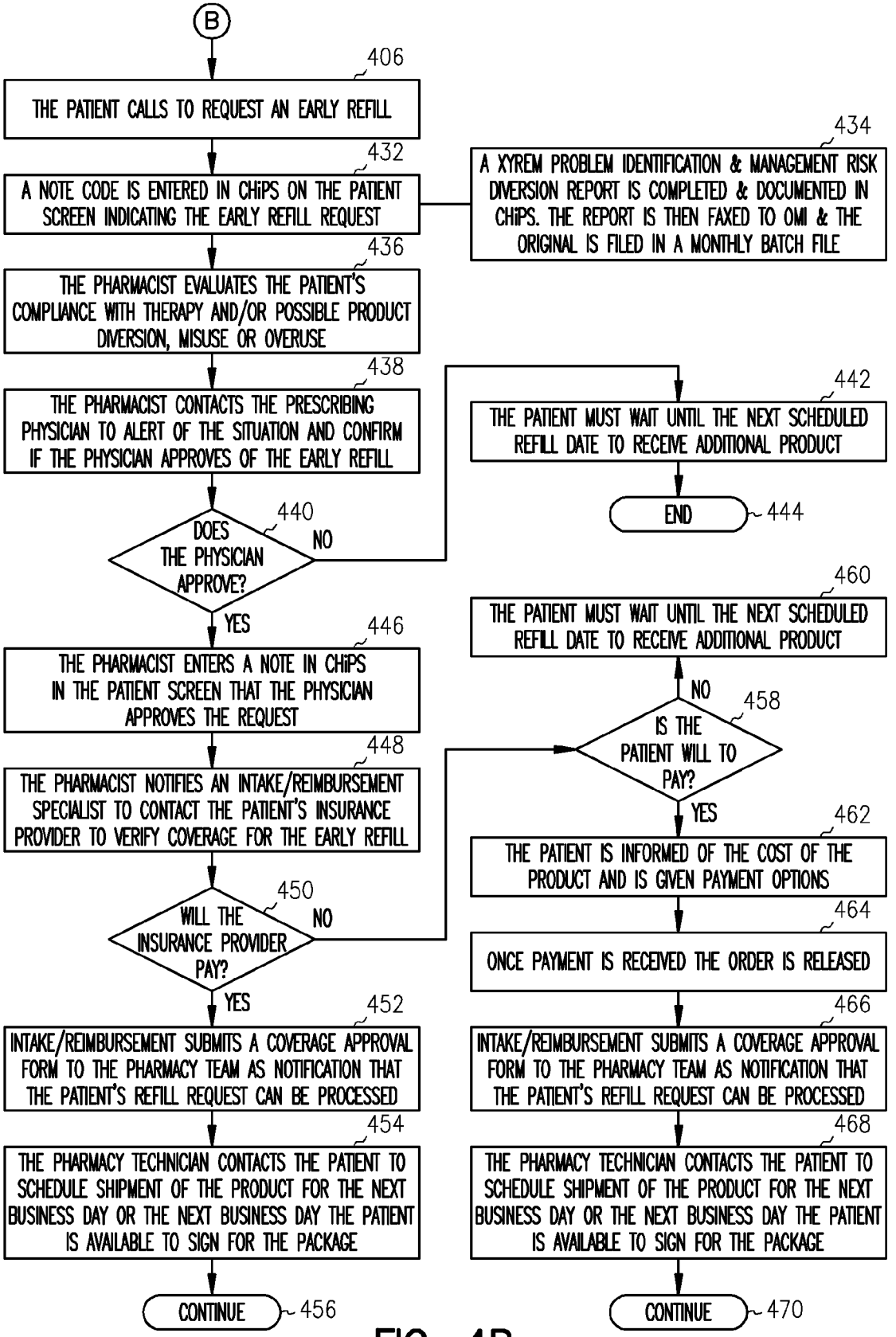
B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHiPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYREM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHiPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS FILED IN A MONTHLY BATCH FILE
436
THE PHARMACIST EVALUATES THE PATIENT'S COMPLIANCE WITH THERAPY AND/OR POSSIBLE PRODUCT DIVERSION, MISUSE OR OVERUSE
438
THE PHARMACIST CONTACTS THE PRESCRIBING PHYSICIAN TO ALERT OF THE SITUATION AND CONFIRM IF THE PHYSICIAN APPROVES OF THE EARLY REFILL
440
DOES THE PHYSICIAN APPROVE?
NO
442
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
END
444
YES
446
THE PHARMACIST ENTERS A NOTE IN CHiPS IN THE PATIENT SCREEN THAT THE PHYSICIAN APPROVES THE REQUEST
448
THE PHARMACIST NOTIFIES AN INTAKE/REIMBURSEMENT SPECIALIST TO CONTACT THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE FOR THE EARLY REFILL
450
WILL THE INSURANCE PROVIDER PAY?
NO
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

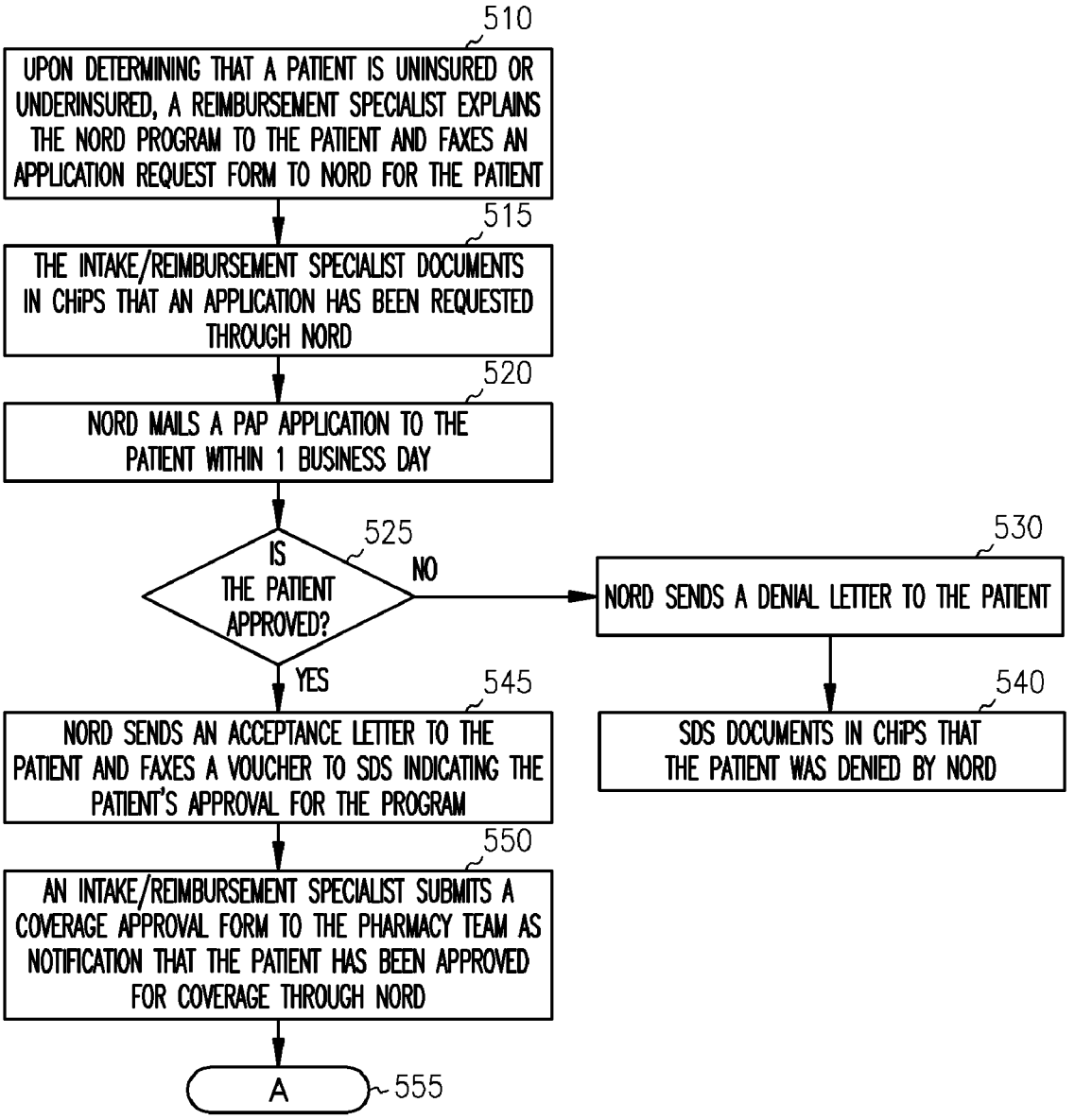
510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHiPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH 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

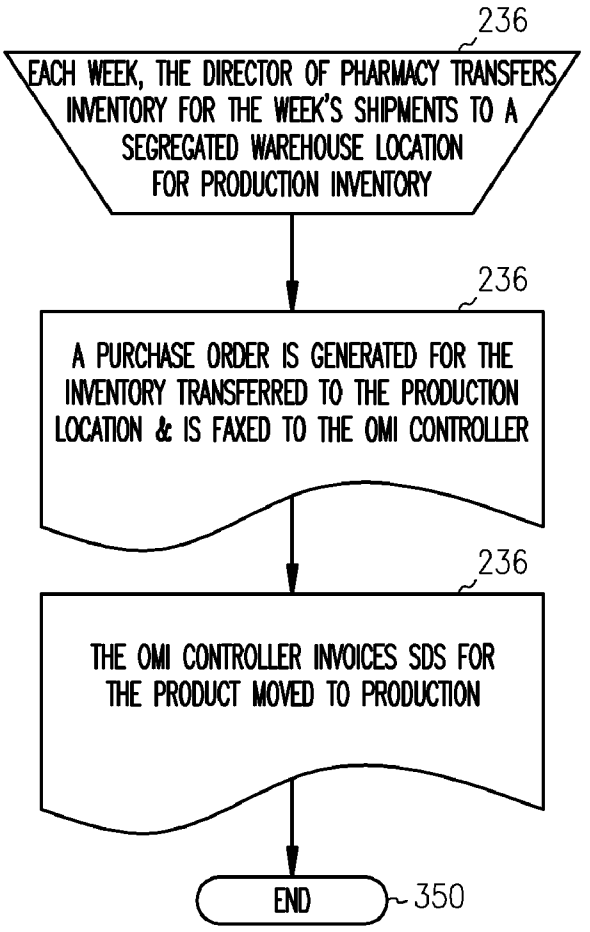

FIG. 6

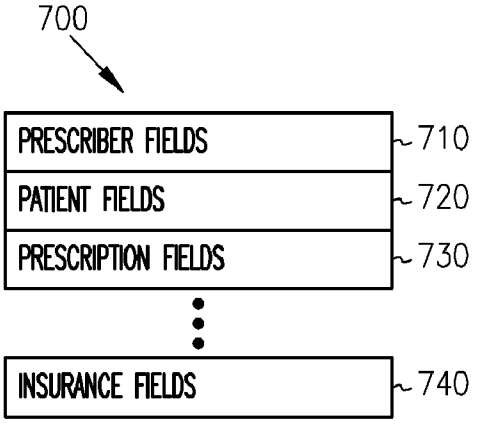

FIG. 7

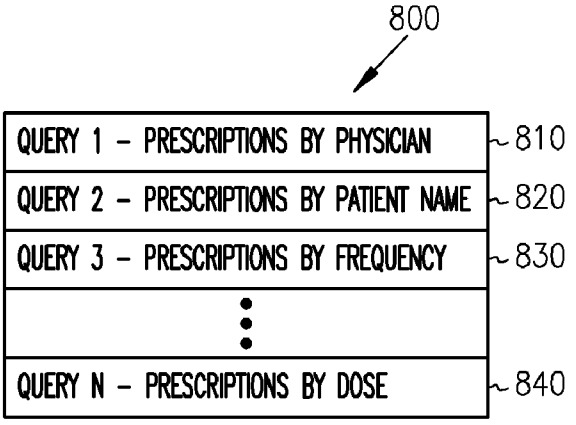

FIG. 8

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
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

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

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml btl	1

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

APPROVED_____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

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

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

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

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREM 180ml btl	1

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

APPROVED_____

PHARMACY USE

FIG. 11

1200

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE OF MEDICAL NEED

PATIENT INFORMATION

DATE: _____

NAME: _____
LAST FIRST M

DATE OF BIRTH: _____

DRUG BEING PRESCRIBED: XYREM

DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: _____

ICD-9: _____

PHYSICIAN INFORMATION

PHYSICIAN'S NAME (PLEASE PRINT): _____

PHYSICIAN'S SIGNATURE: _____ DATE: _____

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

FIG. 12

ACTIVITY REPORTS

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

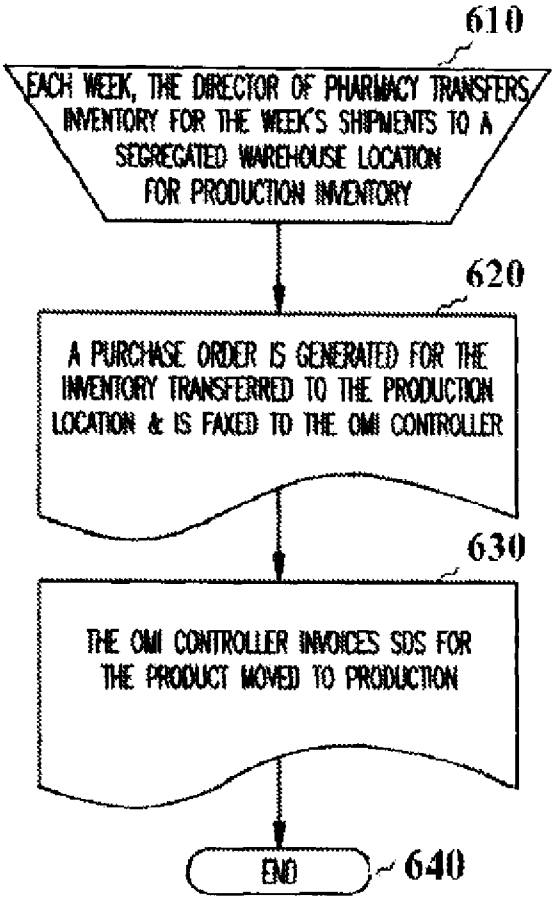

FIG. 6

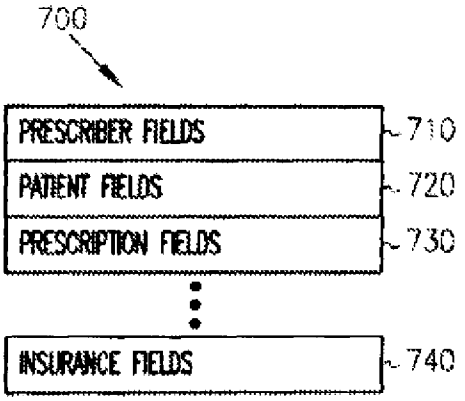

FIG. 7

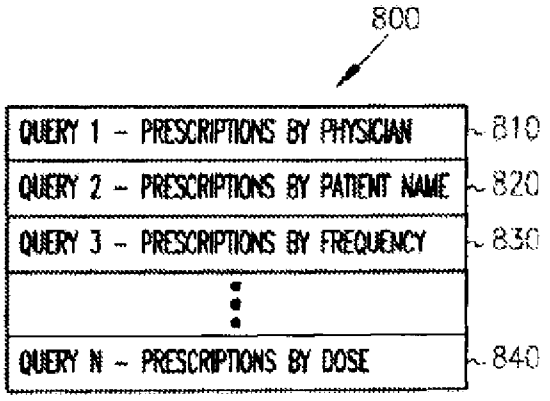

FIG. 8

EXHIBIT 17

US007765106B2

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

(10) **Patent No.: US 7,765,106 B2**
(45) **Date of Patent: *Jul. 27, 2010**

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

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

(73) Assignee: **JPI Commercial, LLC**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1645 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/979,665**

(22) Filed: **Nov. 2, 2004**

(65) **Prior Publication Data**

US 2005/0090425 A1 Apr. 28, 2005

Related U.S. Application Data

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

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

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

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

See application file for complete search history.

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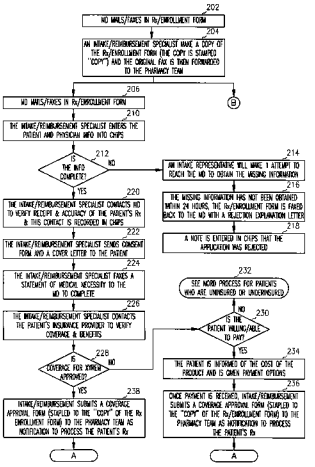
Assistant Examiner—Lena Najarian
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg & Woessner, P.A.

(57) **ABSTRACT**

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

8 Claims, 16 Drawing Sheets



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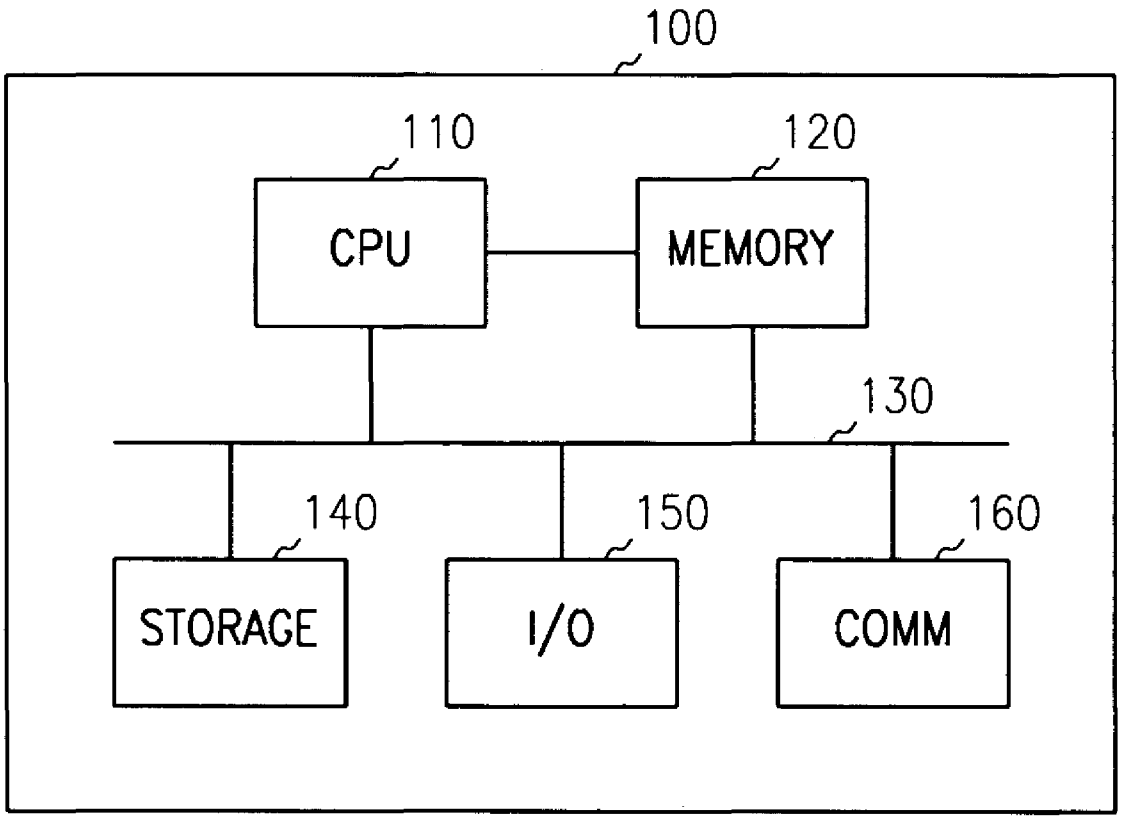


FIG. 1

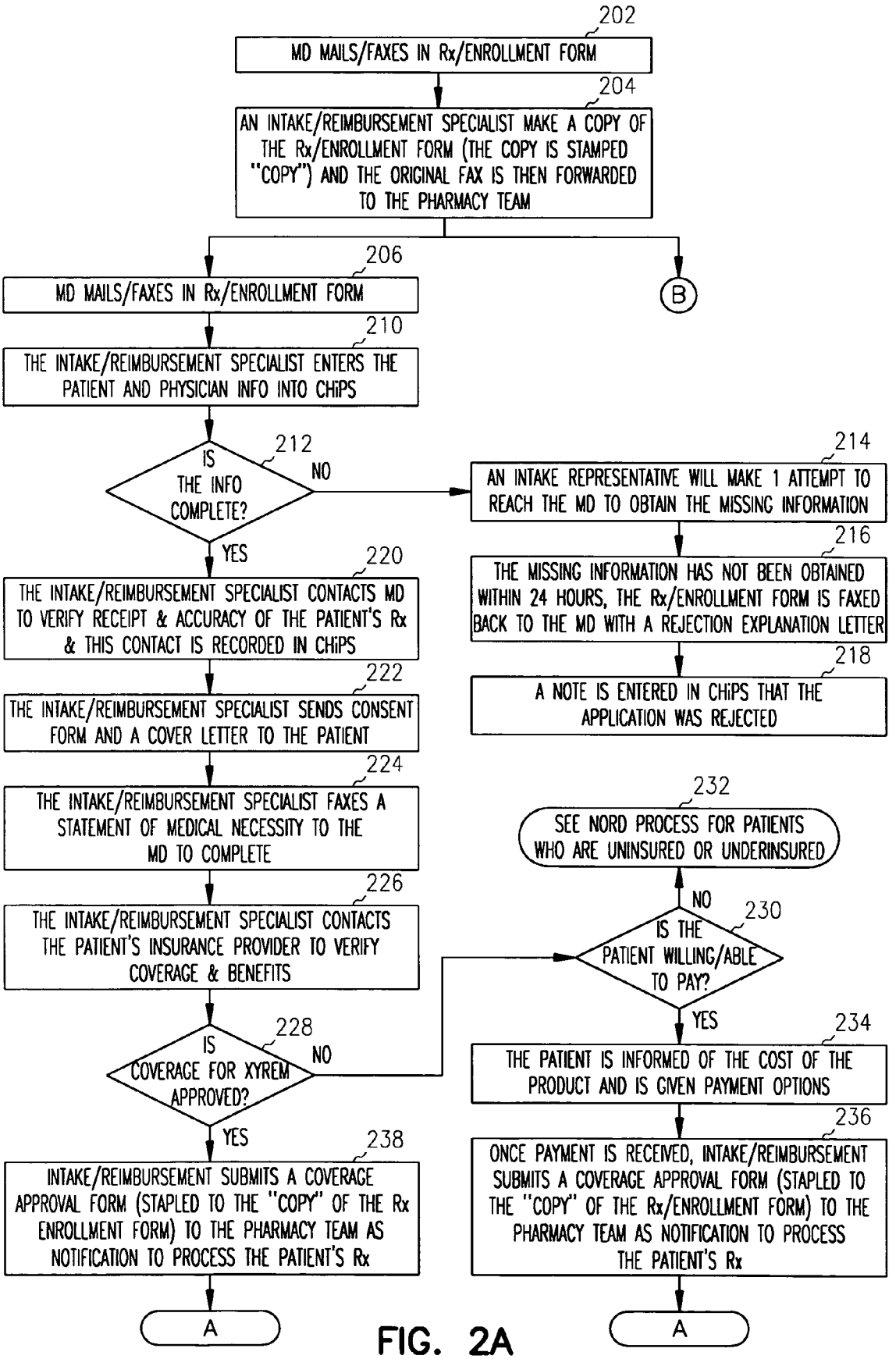

202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHiPS
212
IS THE INFO COMPLETE?
NO
YES
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
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
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
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

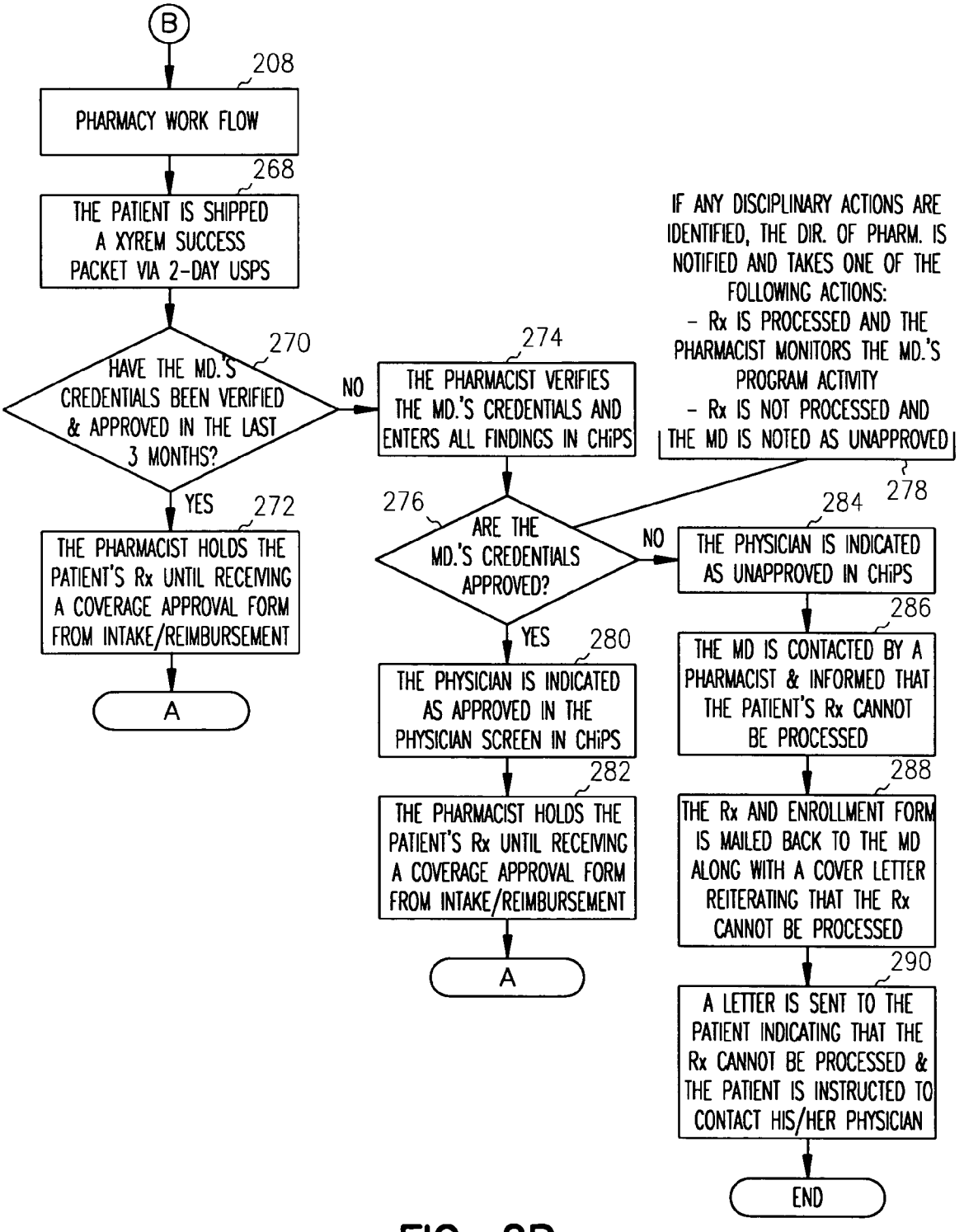

B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST 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

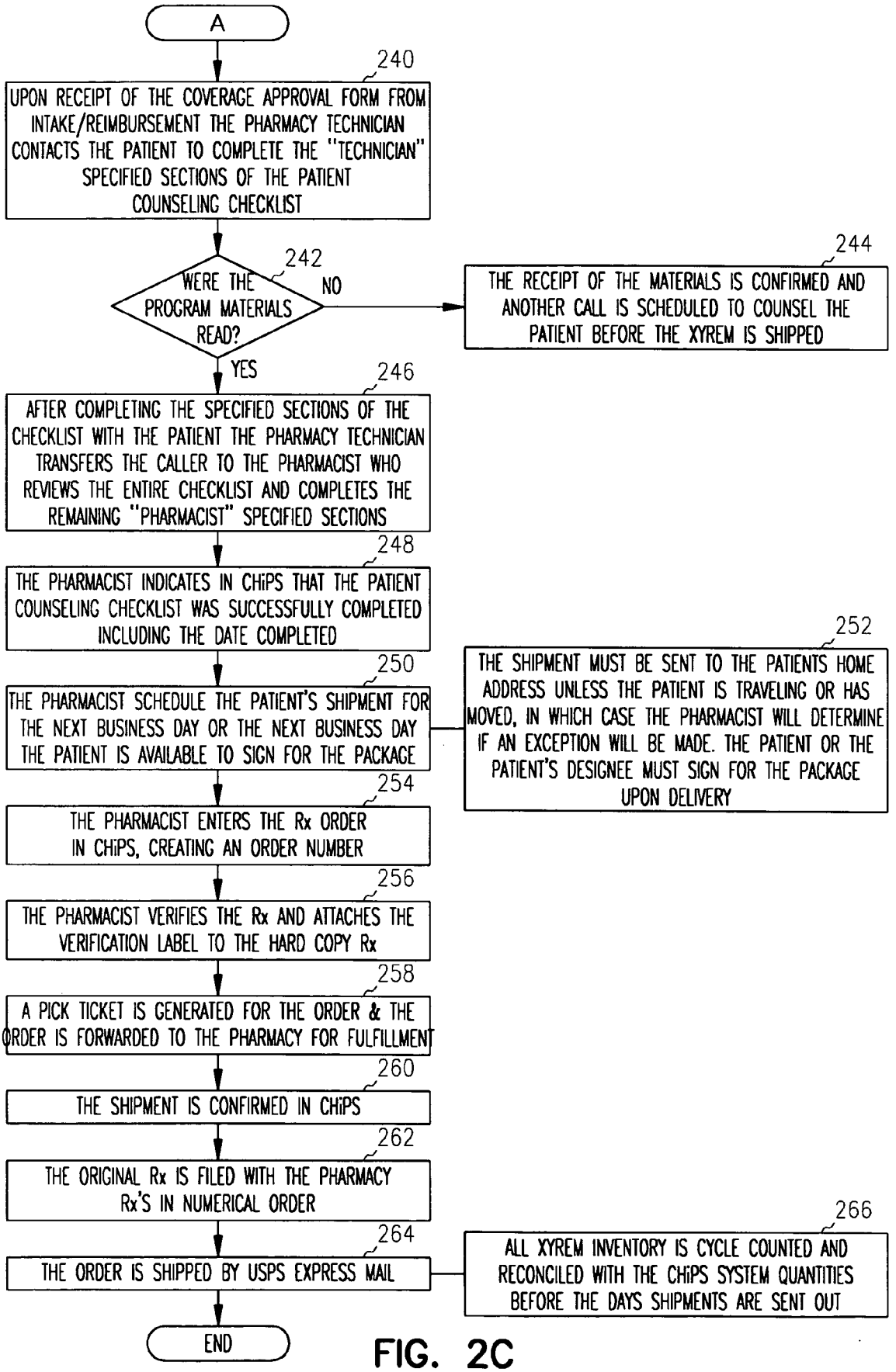

A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER 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
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

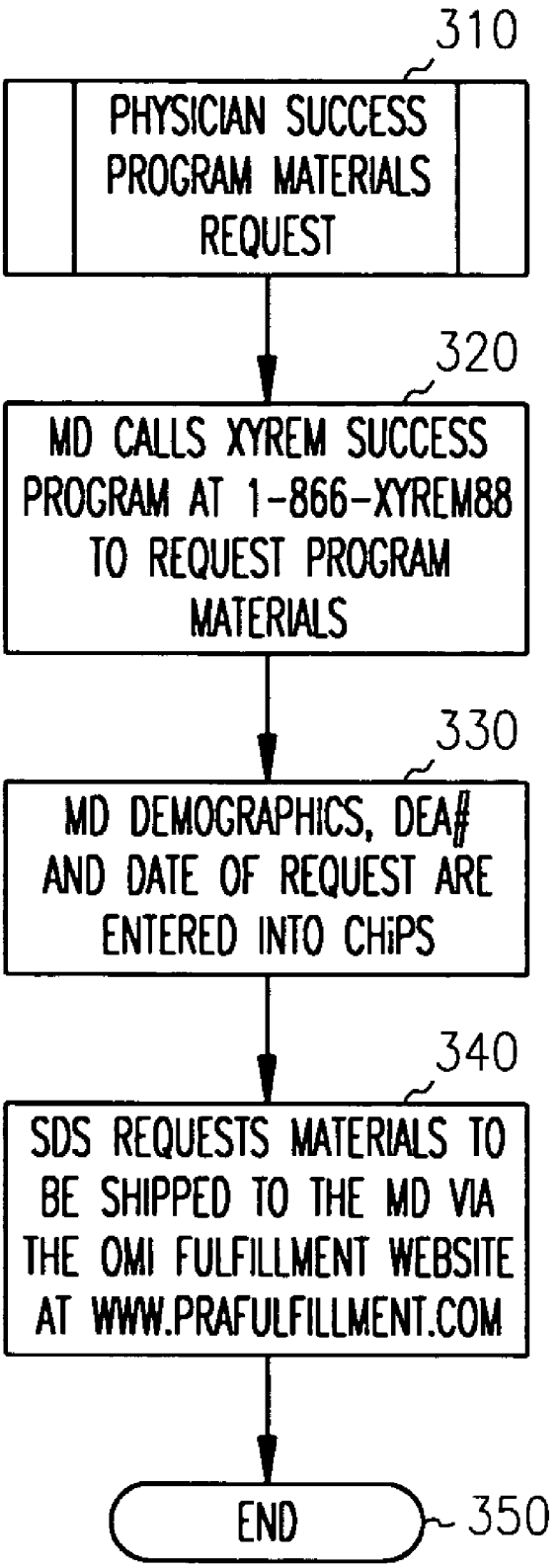

310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHIPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM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

FIG. 3

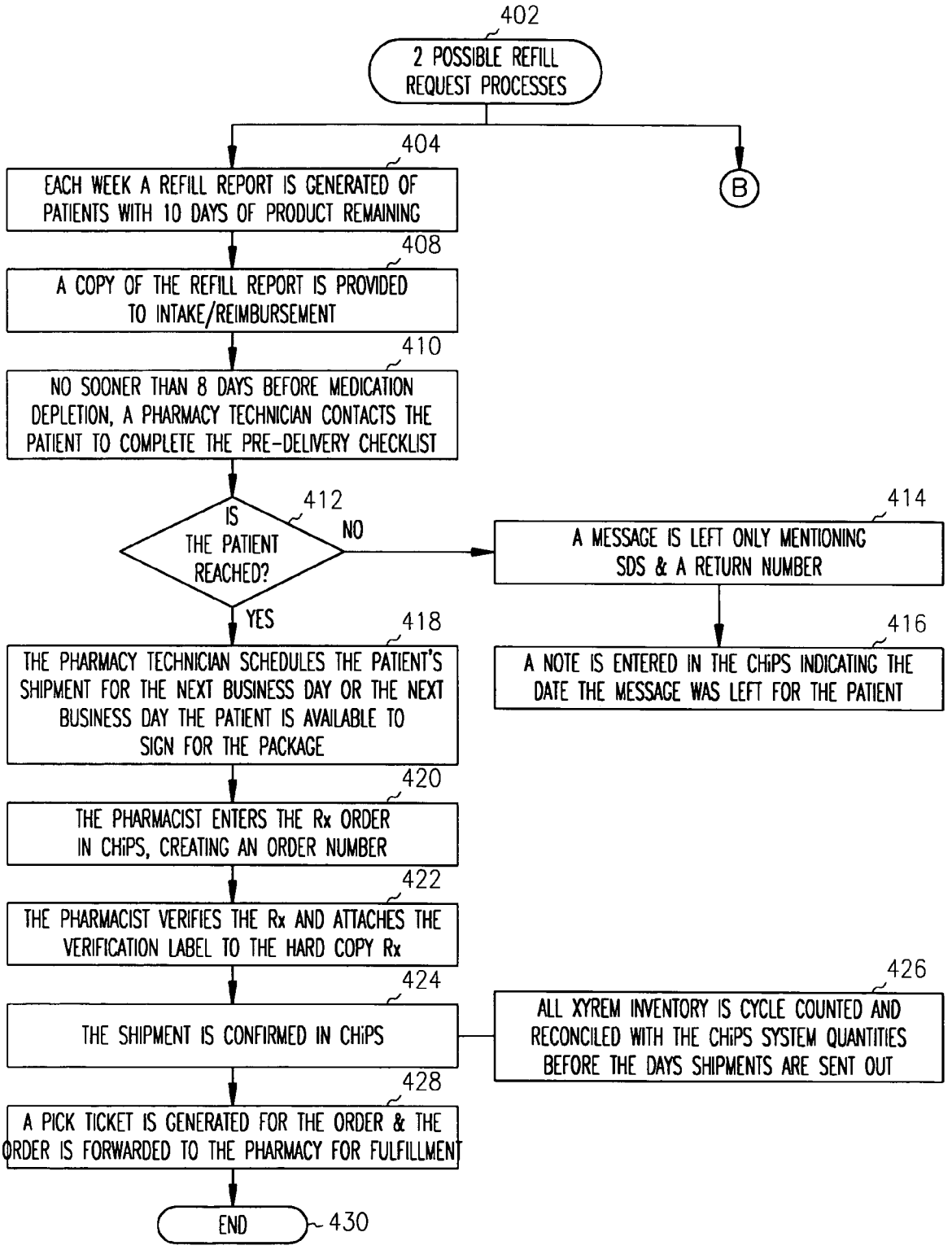

402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE 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

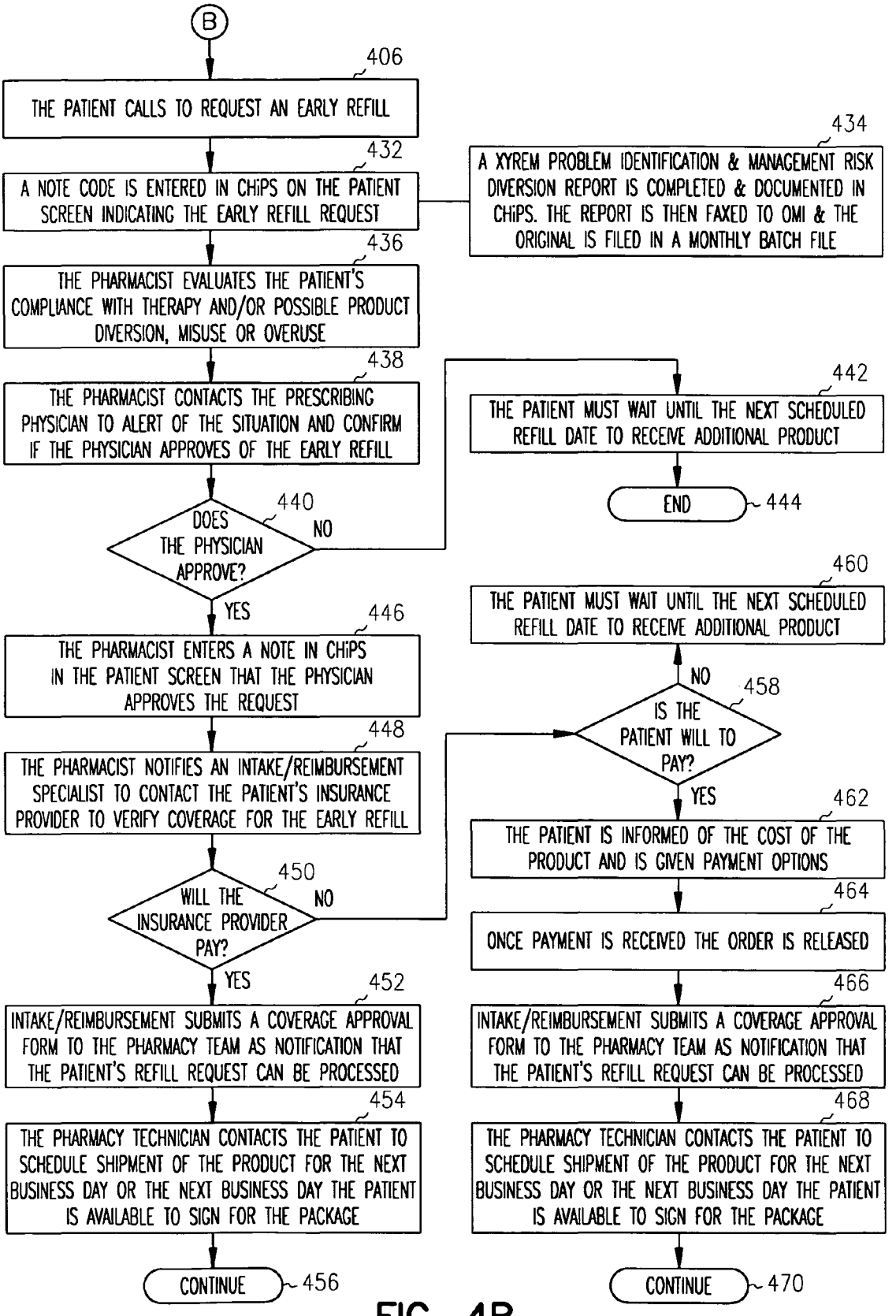

B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYREM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS 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

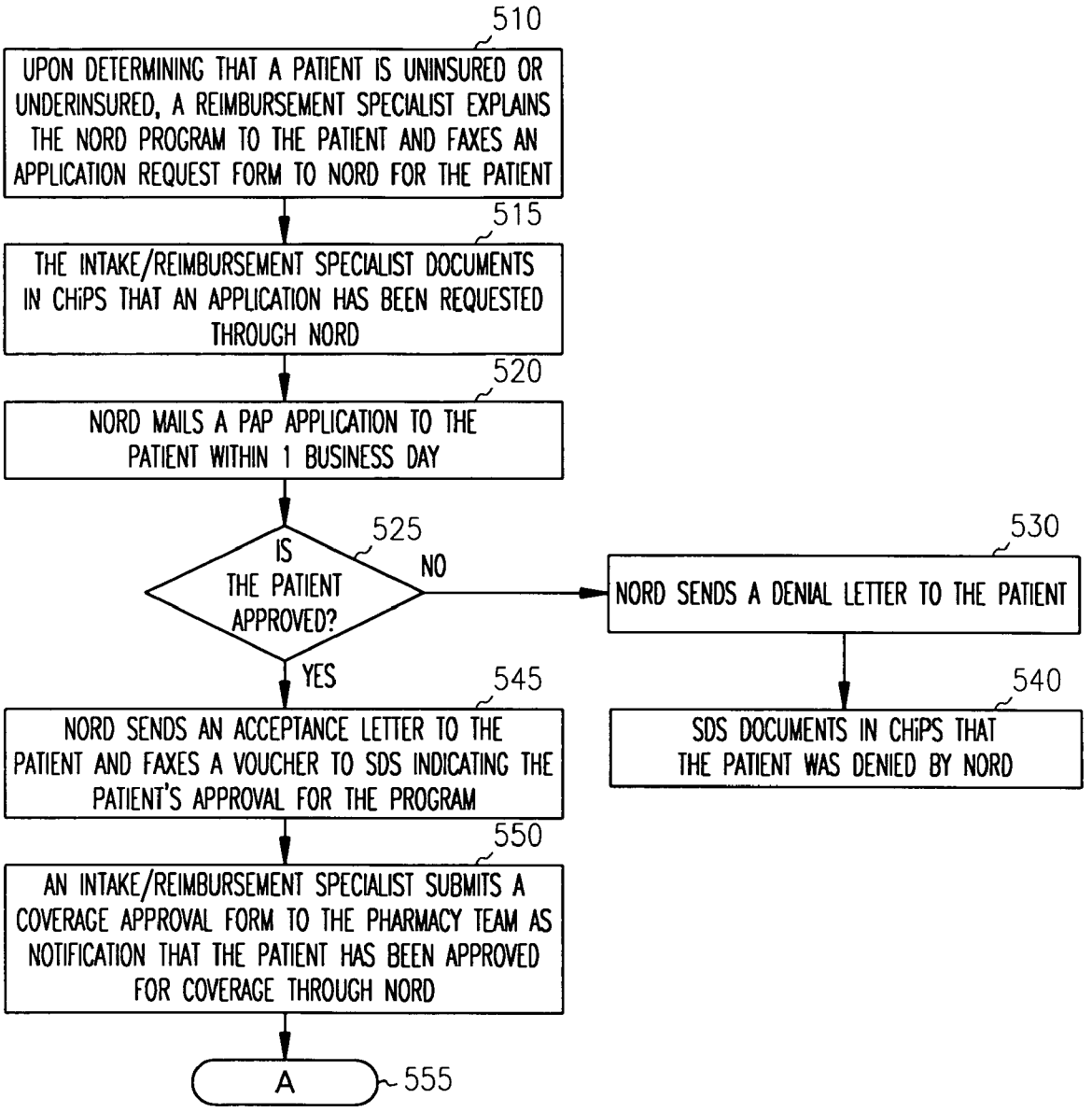

510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHiPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH 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

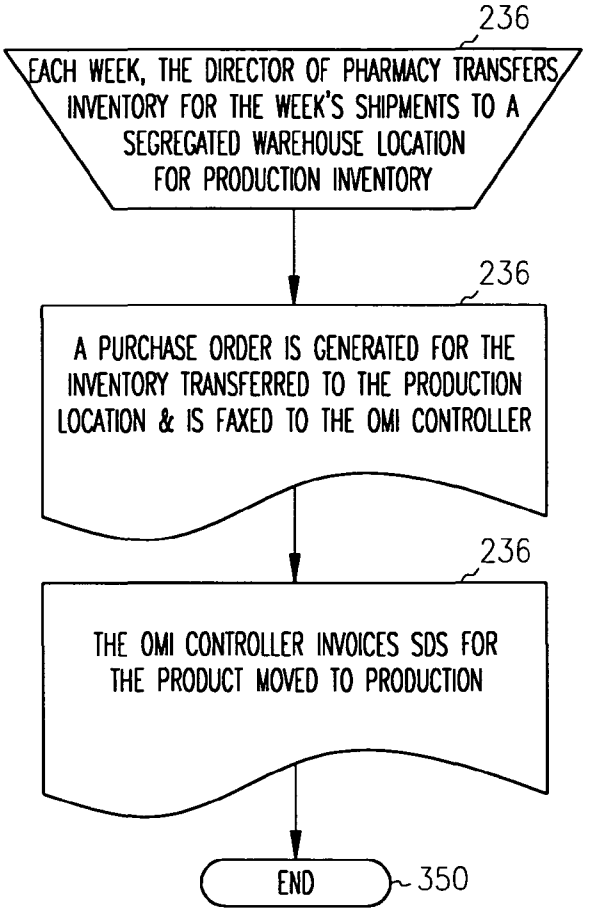


FIG. 6

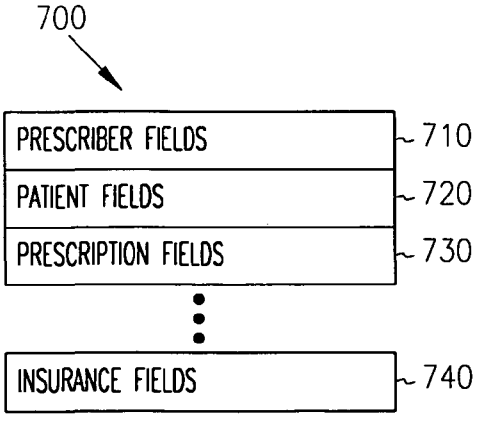


FIG. 7

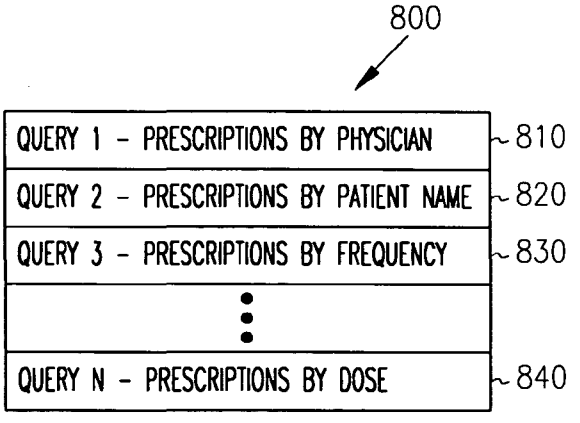


FIG. 8

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

1000

PATIENT ASSISTANCE APPLICATION REQUEST FORM

DATE:

TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS

FAX #: 203-798-2291

PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:

PATIENT NAME _____

ADDRESS _____

_____

_____

TELEPHONE: ( ) _____

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

_____ BOTTLES (THREE MONTHS SUPPLY)

BACKGROUND INFORMATION:

_____

_____

_____

_____

_____

_____

FIG. 10

1100

SENSITIVE DRUG PATIENT ASSISTANCE PROGRAM

VOUCHER REQUEST FOR MEDICATION

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

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

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

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml btl	1

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

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

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

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

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

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREM 180ml btl	1

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

APPROVED _____

PHARMACY USE

FIG. 11

1200

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE
OF MEDICAL NEED

PATIENT INFORMATION

DATE: _____

NAME: _____
LAST FIRST M

DATE OF BIRTH: _____

DRUG BEING PRESCRIBED: XYREM

DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: _____

ICD-9: _____

PHYSICIAN INFORMATION

PHYSICIAN'S NAME (PLEASE PRINT): _____

PHYSICIAN'S SIGNATURE: _____ DATE: _____

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

FIG. 12

ACTIVITY REPORTS

	REPORT FREQUENCY		
	WEEKLY	MONTHLY	QUARTERLY
SALES			
Rx BY ZIP (NEW AND TOTAL)	X	X	X
Rx BY PHYSICIAN BY ZIP	X	X	
$ BY ZIP	X	X	X
REGULATORY			
# OF PHYSICIAN REGISTRIES		X	
# OF DENIED PHYSICIAN REGISTRIES AND REASON		X	
# OF COMPLETED PATIENT REGISTRIES		X	
# OF PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORTS COMPLETED	X		
# OF CYCLE COUNTS PERFORMED & ACCURACY OF EACH		X	
QUALITY ASSURANCE			
# OF PRODUCT DEFECTS/COMPLAINTS REPORTED, TYPE AND LOT #		X	
CALL CENTER			
# OF CALLS RECEIVED		X	
# OF CALLS INITIATED		X	
# OF CALLS ANSWERED IN 30 SECONDS, ETC.		X	
PERCENTAGE OF CALLS ANSWERED IN 30 SECONDS		X	
# OF ABANDONED CALLS		X	
% OF ABANDONED CALLS		X	
AVERAGE CALL LENGTH		X	
PHARMACY			
# OF FAXED Rx/ENROLLMENT FORMS		X	
# OF MAILED Rx/ENROLLEMENT FORMS		X	
# OF 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		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 APPLICATIONS

This application is a divisional application of U.S. patent application Ser. No. 10/322,348, filed Dec. 17, 2002, now U.S. Pat. No. 7,668,730 which application is incorporated herein by reference.

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 ensure that they are not abuse and 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 theraputic 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 coveral 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 an reconciled with the database system quantities before shipments for the day are sent. This provides a very precise control of the inventor.

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 therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and from any and all doctors allowed to prescribe the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is prescribing the prescription drug;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using said exclusive central computer system, the controls selected

from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug.

2. The method of claim **1** , wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

3. A therapeutic method for treating a narcoleptic patient with sodium oxybate for daytime cataplexy comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed sodium oxybate and from any and all medical doctors allowed to prescribe sodium oxybate, the prescriptions containing information relating to the patient, sodium oxybate, and various credentials of the medical doctor who is prescribing the sodium oxybate;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion, such that all prescriptions for sodium oxybate are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of sodium oxybate using the exclusive central computer system that tracks all prescriptions of sodium oxybate and analyzes for the potential abuse, misuse, or diversion by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of sodium oxybate from periodic reports generated by the exclusive central computer system based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, sodium oxybate as the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using said exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe sodium oxybate by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for sodium oxybate that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the sodium oxybate to the patient in order to treat the patient with the sodium oxybate.

4. The method of claim **3**, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the

patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

5. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive computer database in a computer system, from any and all medical doctors allowed to prescribe the prescription drug and any and all patients being prescribed the prescription drug, all prescriptions for the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is prescribing the prescription drug;

requiring entering of the information into the exclusive computer database for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only via the exclusive computer database;

controlling the distribution of said prescription drug with the computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the computer system based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution of the prescription drug, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive computer database; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing the release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive computer database, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug.

6. The method of claim **5**, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive computer database; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

7. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and any and all medical doctors allowed to prescribed the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is writing the prescription;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using the exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information;

verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials;

verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug.

8. The method of claim **7**, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,765,106 B2
APPLICATION NO. : 10/979665
DATED : July 27, 2010
INVENTOR(S) : Dayton T. Reardan et al.

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

In column 12, lines 20-67, column 13, lines 1-20, column 14, lines 1-7, in Claim 7, delete "7. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and any and all medical doctors allowed to prescribed the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is writing the prescription;

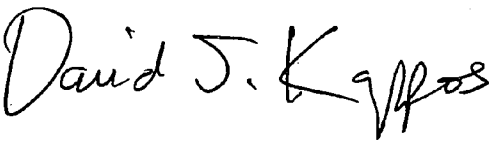
requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using the exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information;

verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug;

Signed and Sealed this

Twenty-third Day of November, 2010



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confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug." and

insert -- 7. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and any and all medical doctors allowed to prescribed the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is writing the prescription;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using the exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical 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. --, therefor.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,765,106 B2
APPLICATION NO. : 10/979665
DATED : July 27, 2010
INVENTOR(S) : Dayton T. Reardan et al.

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

Delete the Title Page showing an illustrative figure, and substitute the attached Title Page therefor.

Delete Sheet 2 of 16 showing Fig. 2A, and substitute the attached sheet therefor.

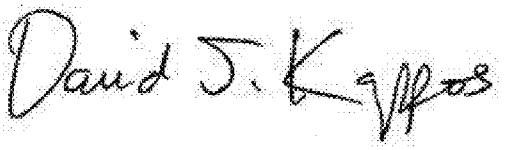
On Sheet 10 of 16, in Figure 9, line 23, after "ESTABLISHED" insert -- . --.

In column 1, line 27, delete "buterate" and insert -- butyrate --, therefor.

In column 1, line 28, delete "theraputic" and insert -- therapeutic --, therefor.

In column 4, line 65, delete "coveral" and insert -- coverage --, therefor.

Signed and Sealed this
Fifteenth Day of February, 2011



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

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

(10) **Patent No.: US 7,765,106 B2**
(45) **Date of Patent: *Jul. 27, 2010**

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

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

(73) Assignee: **JPI Commercial, LLC**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1645 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/979,665**

(22) Filed: **Nov. 2, 2004**

(65) **Prior Publication Data**

US 2005/0090425 A1 Apr. 28, 2005

Related U.S. Application Data

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

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

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

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

See application file for complete search history.

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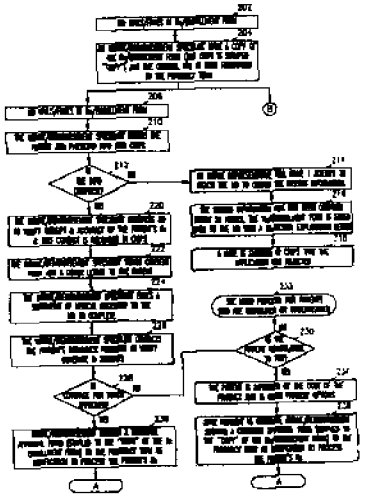
Primary Examiner—Gerald J. O'Connor
Assistant Examiner—Lena Najarian
(74) *Attorney, Agent, or Firm*— Schwegman, Lundberg & Woessner, P.A.

(57) **ABSTRACT**

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

8 Claims, 16 Drawing Sheets



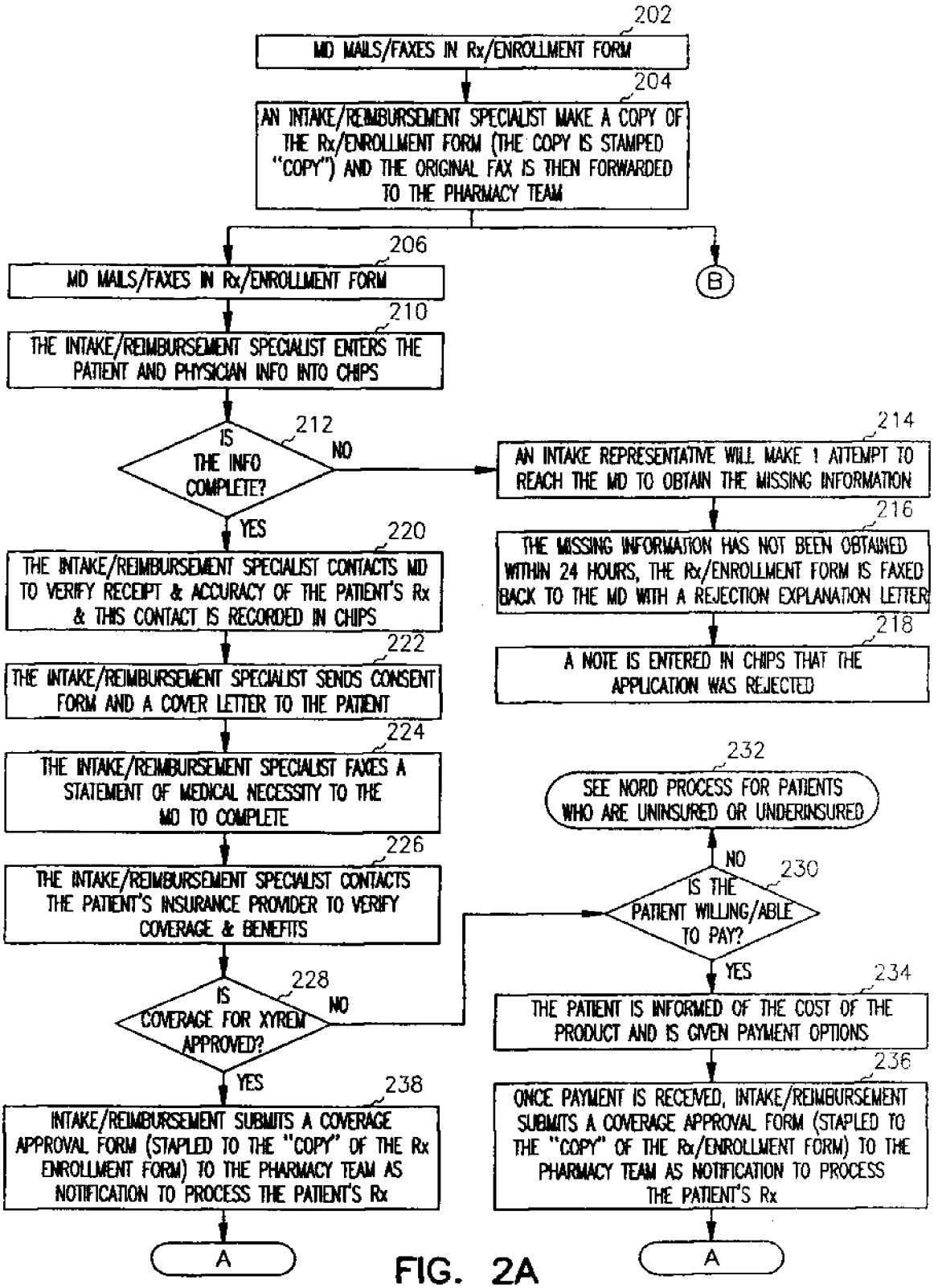

202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE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

FIG. 2A

EXHIBIT A

Attorney Docket No. JAZZ-043/02US 306882-2331 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	ALLPHIN, Clark et al.	Confirmation No.:	3698
Application No.:	16/025,487	Group Art Unit:	1619
Filed:	July 2, 2018	Examiner:	Gotfredson, Garen

FOR: CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES

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

Response to Accompany a Request for Continued Examination

This paper is filed in response to the Final Office Action mailed May 2, 2019. A Request for Continued Examination is being concurrently filed, and a three month extension of time is hereby requested. Accordingly, in light of the Notice of Appeal filed on November 1, 2019, this paper is timely filed. Reconsideration of this application is respectfully requested in view of the following amendments and remarks.

AMENDMENTS TO THE CLAIMS

Set forth below in ascending order, with status identifiers, is a complete listing of all claims currently under examination. Changes to any amended claims are indicated by strikethrough or underlining. This listing also reflects any cancellation and/or addition of claims.

1-108. (Canceled)

109. (Currently Amended) A ~~solid dosage~~ formulation comprising immediate release and ~~controlled~~ sustained release portions, each portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate ~~or a pharmaceutically acceptable salt thereof~~, wherein:

a. the ~~controlled~~ sustained release portion comprises a functional coating and a [[CR]] core, wherein the functional coating is ~~coated onto~~ deposited over the [[CR]] core, wherein the [[CR]] core comprises at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate ~~or a pharmaceutically acceptable salt thereof~~;, ~~and~~ wherein the functional coating comprises one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating; the sustained release portion comprises about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm;

b. the immediate release portion comprises ~~an amount of gamma-hydroxybutyrate or pharmaceutically acceptable salt thereof that is between~~ about 75% and about 98% by weight of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-

hydroxybutyrate, and the amount of gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the immediate release portion is about 10% to 50% by weight of the gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the formulation;

~~c. wherein a total gamma-hydroxybutyrate or pharmaceutically acceptable salt thereof in the solid dosage formulation is about 500 mg to about 12 g, and the amount of gamma-hydroxybutyrate or pharmaceutically acceptable salt thereof in the immediate release portion is about 10% to 50% by weight of the total gamma-hydroxybutyrate or pharmaceutically acceptable salt thereof in the solid dosage formulation;~~

~~d. the controlled release portion releases greater than about 40% of its gamma-hydroxybutyrate over about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm;~~

c[[e]]. the ~~solid dosage~~ formulation releases at least about 30% of its gamma-hydroxybutyrate by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm; and

d[[f]]. the ~~solid dosage~~ formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours ~~when tested in a dissolution apparatus 2~~ when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm.

110. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the ~~solid dosage~~ formulation releases greater than about 90% of its gamma-hydroxybutyrate by 7 hours when tested in a dissolution apparatus 2 when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm.

111. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the ~~solid dosage~~ formulation releases greater than about 90% of its gamma-hydroxybutyrate by 6

hours when tested in a dissolution apparatus 2 when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm.

112. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the ~~controlled~~ sustained release portion releases about 60% to about 90% of its gamma-hydroxybutyrate by about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm.

113. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the ~~controlled~~ sustained release portion comprises hydrogenated vegetable oil, hydrogenated castor oil, or mixtures thereof.

114. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 comprising a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.

115. (Currently Amended) The ~~solid dosage~~ formulation of claim 114 comprising a sodium salt of gamma-hydroxybutyrate.

116. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the immediate release portion comprises 50% by weight of the total gamma-hydroxybutyrate.

117. (Canceled)

118. (Currently Amended) The ~~solid dosage~~ formulation of claim 109, wherein the one or more methacrylic acid-methyl methacrylate co-polymers comprise from about 30% to about 45% by weight of the functional coating.

119. (Currently Amended) An oral ~~solid~~ dosage form comprising the ~~solid dosage~~ formulation of claim 109.

120. (New) The formulation of claim 109 wherein the sustained release portion releases about 10% or less of its gamma-hydroxybutyrate by about 1 hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm.

121 (New) A formulation of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, comprising immediate release and a solid sustained release portions:

a. wherein the immediate release portion comprises about 55 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate;

b. wherein the sustained release portion comprises from about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate and a functional coating deposited over a core comprising the at least one pharmaceutically active ingredient, wherein the functional coating comprises one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm;

c. the formulation releases at least about 30% of its gamma-hydroxybutyrate or salt thereof by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm; and

d. the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm.

EXHIBIT B

REMARKS

I. Status of the Claims

Upon the entry of the amendments, claims 109-116 and 118-121 are pending. Claims 109-116, 118, and 119 have been amended. Claims 120 and 121 are new. Support for these amendments and new claims can be found throughout the specification and in the claims as originally filed, particularly in Paragraphs [0027], [0037], [0038], [0055], [0069], and Figures 3-5.

Entry and consideration of these amendments are respectfully requested. No new matter is believed to have been added by way of these amendments.

II. Interview

Applicant thanks the Examiner and his Supervisor for the productive interview on January 23, 2019, with the co-inventor, Clark Allphin, and Applicant's representatives, Philip McGarrigle, Michael Tuscan, and the undersigned. Applicant also thanks the Examiner for the withdrawn of the 35 U.S.C. §112 (pre-AIA), second paragraph rejection, as well as the obvious-type double patenting rejection.

III. Rejections

A. 35 U.S.C. §112 (pre-AIA)

The Office rejected claims 109-119 under 35 U.S.C. §112 (pre-AIA), first paragraph as allegedly failing to comply with the written description requirement. The Office asserts that the specification fails to describe in sufficient detail that one skilled in the art can reasonably conclude that the inventor had actual possession of the claimed invention at the time of the invention.

Applicant respectfully disagrees and submits that the instant specification provides ample guidance for one skilled in the art to recognize that Applicant was in possession of the claimed dosage formulation at the time of filing. To establish that the claims are adequately described, the specification must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, [Applicant] was in possession [of] . . . whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1564 (Fed. Cir. 1991). A genus is adequately described if the

specification permits one of skill in the art to "visualize or recognize members of the genus." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997).

The specification teaches that that the dosage forms of the present invention release gamma-hydroxybutyrate (GHB) over a sustained period of time.[1] Figures 3-5 describe the claimed *in vitro* release rates, and the detailed description provides a discussion of how formulations of the presently claimed invention can be made. The inventors teach that "(i)n addition to adjusting the amount or nature of the pore former included in the functional coating composition, the release rate of drug provided by the controlled release dosage form disclosed herein may be adjusted by modifying the thickness or weight of the functional coating composition." [2] The application teaches that a pore-former, such as a methacrylic acid-methyl methacrylate co-polymer can be present at about 20% to about 50% by weight of the functional coating.[3] According to the MPEP, "if the art has established a strong correlation between structure and function, one skilled in the art would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function." [4] The examples, in concert with the general disclosure, provide enough guidance for one of skill in the art to conclude that Applicant was in possession of the claimed dosage formulation.

The Examiner states that the examples do not show an embodiment within the scope of the present claims. Respectfully, it is not necessary to disclose such an example order to meet the written description requirement. As explained in the MPEP by the Federal Circuit "examples are not necessary to support the adequacy of a written description, ... the written description standard may be met ... even where actual reduction to practice of an invention is absent."[5] Further, the numerous examples in the specification demonstrate a correlation between structure and function. Applicant therefore asserts that the examples show elements of the present invention and that the other support throughout the application is sufficient to prove written description for the present claims.

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[1] As-filed specification [0037] and [0038].
[2] As-filed specification [0056].
[3] As-filed specification [0051] and [0052].
[4] MPEP 2163 IIA3(a), quoting Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613, quoting the Written Description Guidelines, 66 Fed. Reg. at 1106, n. 49.
[5] MPEP 2163 IIA3(a), quoting Falkner v. Inglis, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006).

Therefore, Applicant respectfully requests withdrawal of this rejection.

B. 35 U.S.C. §103(a)

The Office rejected claims 109-119 under 35 U.S.C. §103(a) as unpatentable over Liang *et al.* (U.S. Pat. Pub. No. 2006/0210630, hereinafter "Liang.") Applicant respectfully disagrees. As discussed in more detail below, as well as in the accompanying declaration, the release profile of the claimed invention is distinct from that taught in Liang.

The presently claimed invention is directed to an oxybate formulation with a ***sustained release*** component. Liang however, teaches a ***delayed release*** formulation. These formulations are quite different structurally and functionally, and it would not be obvious to modify a delayed release formulation to make a sustained release formulation. Liang not only fails to teach or suggest the claimed sustained release profile, it fails to provide any motivation for a skilled artisan to modify its teachings of a delayed release formulation and arrive at a sustained release formulation as presently claimed.

1. Liang cannot support a case of *prima facie* obviousness

As an initial matter, the office has failed to establish a *prima facie* case of obviousness. To establish a case of *prima facie* obviousness, the combination of references must teach each and every element in the claims. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). As previously discussed, and as the Office states in the Final Action dated May 2, 2019, Liang does not teach the amount of GHB and methacrylic polymer coating, nor the claimed functional limitations regarding the *in vitro* release of GHB. However, the Office alleges that one of skill in the art would be motivated to modify Liang to arrive at the claimed invention.

Specifically, the Office asserts that the delayed release coatings of Liang could be modified to make a sustained release formulation. However, a skilled artisan would not consider modifying a delayed release formulation to make a sustained release formulation as they produce very different pK profiles.[6] Delayed release formulations quickly release the majority of the drug a certain amount of time after dosing. Essentially, a patient is given a delayed bolus dose. Sustained release formulations, in contrast, provide for a more gradual, but extended release of

[6] The Allphin Declaration, paragraph 12.

the drug over a period of time. Such a formulation could start releasing the drug shortly after dosing, or there could be a lag before the drug starts to release. This sustained release of the drug can then take place over a longer period of time than would typically occur in a delayed release formulation.

Since Liang is directed to *delayed* release, not sustained release, formulations of GHB. Liang's delayed-release coatings comprise about 87% by weight pH-sensitive enteric polymers, specifically pH-sensitive methacrylic acid-methyl methacrylate co-polymers.[7] As the coatings comprise a large percentage of pH-sensitive polymer, these dosage forms would release the majority of the drug relatively rapidly upon exposure to intestinal pH (e.g., about 6 and above), i.e., delayed release. As shown in Example 7 and Figures 1 and 2 of Liang, these "delayed release prototypes" release about 70%-100% of the drug within an hour at intestinal pH.[8]

In contrast, the presently claimed invention is directed to dosage forms comprising an immediate release portion and a *sustained* release portion. The claimed sustained release portion releases less than 10% of the drug within an hour in DI water and at least about 40% of the drug by about four to six hours in DI water, and the sustained release coating comprises about 20-50% by weight methacrylic acid-methyl methacrylate co-polymers. As discussed in the accompanying declaration from inventor Clark Allphin, the inventors were aware of Liang's teachings.[9] The light of these teachings, they conducted a regional GHB absorption study in humans in order to create an improved model of GHB delivery and used pharmacokinetic modeling to predict an *in vitro* release profile that would provide improved bioavailability.

The Office alleges that there is motivation for the skilled artisan to modify the Liang composition. However, the Office has failed to point out with any particularity where Liang provides the motivation to drastically alter its delayed release profile to an entirely different type of release profile. Rather, the Office alleges that modifying coatings is "routine optimization." Applicant disagrees, as there is no such motivation in Liang to change from one type of release profile to a very different type by modifying its delayed release coating to achieve a sustained release formulation as presently claimed. As discussed above, and in the attached declaration,

[7] Liang, Example 6.
[8] Liang, Fig 1-3 and [015]-[017].
[9] The Allphin Declaration, paragraph 5.

delayed release and sustained release are distinctly different types of release, and altering a formulation from delayed release to sustained release is not routine. Further, there is no motivation to modify Liang's coatings to achieve the particular *in vitro* release rate that is presently claimed. By saying one of skill, guided by Liang, would settle on the claimed release rate, the Office is relying on impermissible hindsight. Therefore, the Office has failed to establish a *prima facie* case of obviousness. As such, Applicant maintains that the claimed invention is not obvious in light of the cited art and respectfully requests that the rejection be withdrawn.

2. The claimed sustained release formulations provide superior bioavailability over Liang

As discussed in the Allphin Declaration, and as evidenced by the data in Liang, the delayed release formulations disclosed in Liang did not provide the desired bioavailability. [10] The formulation targeting the colon (DR-1) had about a quarter of the bioavailability of the immediate release dosage form, while the duodenum targeting formulation (DR-2) had about half the bioavailability of the immediate release dosage form.[11] Such a formulation would not provide sufficient GHB, and therefore would not be a useful once-nightly formulation.

The inventors, aware of the poor bioavailability of the Liang formulations, designed experiments to study the regional absorption of GHB in humans. The results of this study showed that substantial GHB absorption occurred in the upper intestinal tract, specifically, the ileum and jejunum.[12] The inventors modeled plasma pharmacokinetic (PK) simulations based on the data from these regional absorption studies, which allowed the inventors to predict a PK profile based on an *in vitro* release profile. As discussed in the Allphin Declaration, this modeling indicated that a sustained release formulation, where at least about 40% of the GHB is released by 4 to 6 hours when tested at a neutral pH (i.e., in DI water) would target the ileum and jejunum, and thereby provide improved absorption and better bioavailability. Additionally, the modeling showed that lag time of 1 hour results in a flatter PK profile, which is preferred. Therefore, the inventors focused on sustained release GHB formulations wherein less than 10%

[10] The Allphin Declaration, paragraph 7.
[11] Liang, Example 7, paragraph [0115], ad Table 3.
[12] The Allphin Declaration, paragraph 8.

of the drug is released within the first hour and a substantial portion of the drug (i.e., at least about 40%) is released by about 4 to 6 hours.

As the cited art teaches neither the presently claimed structural limitations, nor the presently claimed release profile, and one of skill in the art would have no motivation, based on the cited art, to develop a GHB formulation with the claimed *in vitro* release profile, the Office has failed to establish a case of *prima facie* obviousness. Further, as shown in the declaration, the inventors had discovered that the claimed *in vitro* release profile provides superior bioavailability as compared to the formulations in the cited art. As such, the Applicant respectfully requests the withdrawal of this rejection.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that no further impediments exist to the allowance of this application and, therefore, requests an indication of allowability. However, the Examiner is requested to call the undersigned if any questions or comments arise.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

Dated: March 6, 2020

Respectfully submitted,
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EXHIBIT C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	ALLPHIN, CLARK, et al.	Confirmation No.:	3698
Serial No.:	16/025,487	Group Art Unit:	1619
Filed:	July 2, 2018	Examiner:	GOTFREDSON, GAREN

DECLARATION OF CLARK ALLPHIN UNDER 37 C.F.R. §1.132

1. I am a co-inventor of the above-identified application. I am currently employed by Jazz Pharmaceuticals, Inc. as the Executive Director of Process and Product Science, New Product and Technology Integration and have worked at Jazz Pharmaceuticals for 13 years in various capacities in the Technical Operations group. At Jazz I have been working on gamma-hydroxybutyrate (GHB) related projects for more than 10 years and have 10 GHB-related U.S. patents. I have over 20 years of development experience in the field of pharmaceutical formulations. I received a Bachelor of Science degree in Chemical Engineering from the University of California, Berkeley. I am familiar with the above-identified application and reviewed the Final Office Action dated May 2, 2019.

Background on GHB and controlled release formulations

2 GHB is a prescription medication used to treat two symptoms of narcolepsy: sudden muscle weakness and excessive daytime sleepiness. XYREM®, the only FDA-approved GHB formulation, is an immediate release formulation and requires dosing of the drug twice during the night, specifically, a first dose at bedtime and a second dose 2.5 to 4 hours later, due to the short half-life of GHB. As some patients do not want to awake in the middle of the night for the second dose, a once-nightly dosage form would eliminate this need.

3. A formulator, looking to develop a dosage form suitable to replace two or more separately administered immediate release dosage forms, would understand that an effective release profile would depend on the various pharmacokinetic properties of the particular drug. Significant work would go in to both determining the desired release profile for a particular drug

and developing a formulation that provides said profile. As discussed in more detail below, we used regional absorption studies and pharmacokinetic modeling to develop a formulation that contained a sustained release portion of GHB. This sustained release formulation provides for a gradual, but extended release of GHB over a period of time. This sustained release is not taught in the cited prior art and provides improved bioavailability over the formulations taught in the cited art.

Liang's Teachings

4. It is my understanding that the Examiner believes that the pending claims are obvious in view of Liang *et al.* (US 2006/0210630). As discussed herein, the present invention would not have been obvious based on Liang to someone with an understanding of pharmaceutical formulations.

5. I have been familiar with the work described in Liang for at least 10 years. To the best of my knowledge, this work on GHB dosage forms began at Orphan Medical in 2002. Orphan Medical was later bought by Jazz Pharmaceuticals, Inc. in 2005. These formulations, however, failed to provide sufficient bioavailability for a once-nightly, dose.

6. Liang discloses delayed release formulations of GHB. Delayed release formulations are formulations that, after a certain delay after ingestion, release the majority of the drug in a relatively short period of time (i.e, less than an hour). One way to do this is with coatings of enteric polymers. Enteric polymers are pH-sensitive polymers that are insoluble in the acidic pH of the stomach, but highly soluble at the relatively higher pH of the intestine. Liang's GHB prototypes were GHB cores with coatings comprising about 87 % by weight pH-sensitive enteric polymers. These pH sensitive coatings would release GHB relatively rapidly, i.e, in about an hour, upon exposure to intestinal pH (e.g. about pH 6 in the duodenum and above pH 7 in the colon), as shown in Example 6 and Figures 1-3 of Liang. Specifically, the coating on DR-1 was designed to release GHB in the colon, while DR-2 was designed to release GHB in the duodenum (paragraphs [0104], [0106], and [0114] of Liang). Based on the data provided in Liang from canine studies with DR-1 and DR-2, these formulations had bioavailability that was about a fourth to a half that of the immediate release form, with higher bioavailability in the

duodenum (DR-2) as compared to the colon (DR-1) as shown in paragraph [0115] and Table 3 of Liang.

Development of the presently claimed formulations through regional absorption studies and PK simulations

7. Jazz conducted a regional GHB absorption study in humans in response to the failure of the Liang formulations to achieve suitable bioavailability and in order to create an improved model of GHB delivery. Specifically, this study was designed to show where GHB was absorbed in the intestine so that we could know how to optimally target the *in vitro* release profile. This study measured the plasma bioavailability upon oral delivery of 900mg GHB to the jejunum (Regimen "A"), ileum (Regimen "B"), and ascending colon (Regimen "C") through Enterion™ capsule delivery, which allows for targeted delivery via a radiolabeled capsule that releases its contents at the target site when activated by an electromagnetic signal. Regimen "D" consisted of 900 mg of an oral dosage of immediate release GHB (e.g., Xyrem) without the Enterion™ capsule. The results are summarized in Table 1 of the Appendix. The human regional absorption data indicated that substantial absorption occurs in the ileum as well as the jejunum. Thus, our aim was to develop GHB formulations that primarily targeted the ileum ***and*** jejunum, i.e., proved sustained release throughout the ileum and jejunum, rather than Liang's delayed release, which more rapidly releases GHB in a single part of the intestinal tract, e.g., DR-1 was designed to release in the colon and DR-2 was designed to release in the duodenum.

8. While the human regional absorption data gave us a better understanding of what part of the intestine to target to maximize bioavailability of GHB, we still had to determine how long this sustained release should be and how soon after ingestion sustained release should start. Based on the human regional absorption data obtained above, my co-inventor on the present application, James Pfeiffer, performed plasma PK simulations. These simulations were intended to correlate an *in vitro* profile, a release rate that could be tested in a lab, with the plasma levels of the drug.

9. The results of these plasma PK simulations indicated that a sustained release formulation would provide improved bioavailability. Specifically, that sustained plasma levels can be reached with a formulation that has an *in vitro* release profile wherein a significant amount of

drug is released within 4-6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm. Additionally, we found that a 1 hour lag in release in yields a substantially flatter plasma PK profile as compared to a similar formulation without the lag time. Relatively flatter PK profiles are preferred, as the levels of drug in the blood vary less, thereby providing a more consistent therapeutic effect.

10. Based on these results, we targeted a sustained release formulation comprising an immediate release portion and a sustained release portion, wherein the sustained release portion releases less than 10% of its GHB within the first hour and at least about 40% of its GHB by 4 to 6 hours when it is tested at a neutral pH (i.e., in DI water) in order to target the ileum and jejunum, i.e., ***sustained release*** over a period of time.

11. In contrast, as discussed above, Liang proposed a different approach, with delayed release formulations. Liang's delayed release formulations provide rapid release of the drug in the duodenum or colon, as discussed above and shown in as shown in Example 6 and Figures 1-3 of Liang, and therefore would provide a significantly different *in vitro* release profile in DI water than is presently claimed, as well as a different, less preferred, PK profile.

12. Without additional information, one of skill in the art would not be motivated to modify a delayed release formulation to a sustained release formulation. If we had relied solely on Liang's teachings of delayed release formulations, we would not have arrived at the presently claimed sustained release formulations. Rather, it was only after conducting the regional absorption studies and the pharmacokinetic modeling that we were able to develop the claimed formulation and *in vitro* release profile.

13. Figure A of the Appendix shows that the dissolution profile of a sustained release portion of a GHB formulation meeting the limitations of the claims. The sustained release portion contains GHB (as sodium oxybate) coated with 28% (w/w) Eudragit L100 (methacrylic acid-methyl methacrylate copolymer), 55% (w/w) ethylcellulose, and 17% (w/w) poloxamer 188. Its dissolution profile was tested in a dissolution apparatus in deionized water at a temperature of 37° C, a dip rate of 30/min, and intervals of 30 minutes until 2 hours, then hourly thereafter. As shown in Figure A, the sustained release portion releases less than 10% of its GHB at 1 hour, about 45% of its GHB at 4 hours, and about 80% of its GHB at about 8 hours.

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

5 March 2020

Clark Allphin

Date

EXHIBIT D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SENSORMATIC ELECTRONICS, LLC, Plaintiff, v. GENETEC (USA) INC. and GENETEC INC., Defendants.	)	C.A. No. 20-760 (MN)

MEMORANDUM ORDER

At Wilmington this 29th day of September 2021:

As announced at the hearing on August 10, 2021, IT IS HEREBY ORDERED that the disputed claim terms of U.S. Patent Nos. 9,463,954 ("the '954 Patent") and 7,307,652 ("the '652 Patent") are construed as follows:

1. "one or more landing matrices that define access to the floors, the access control system providing the landing matrices to the elevator controller" / "one or more landing matrices defining access to floors by one or more elevators" means "data structure(s) provided to an elevator controller that define(s) access to the floors of a building" ('954 Patent, claims 1 & 15)

2. "the landing matrices" shall be given its plain and ordinary meaning ('954 Patent, claims 1, 5, 7, 8, 9, 15, 18 & 20-25)

3. "landing matrix object" does not require construction ('954 Patent, claims 1, 4, 10-13, 15, 17, 24 & 26)

4. "landing matrix application programing interface (API)" does not require construction ('954 Patent, claims 1 & 15)[1]

[1] The only dispute over the meaning of the terms "landing matrix object" and "landing matrix application programming interface (API)" from the '954 Patent was whether the terms were indefinite. That is, Plaintiff proposed no construction necessary and Defendants argued the terms were indefinite. The Court found that indefiniteness had not been proven at this stage, leaving no further claim construction dispute for these terms.

5. "detecting moving objects [within said / in the] selected monitoring area" means "performing detection of moving objects only within/in said selected monitoring area" ('652 Patent, claims 1, 3 & 22)

6. Claims 9, 12 and 13 of the '652 Patent are not invalid as indefinite for improperly mixing apparatus and method limitations under *IPXL Holdings*

The parties briefed the issues (*see* D.I. 43) and submitted an appendix containing intrinsic and extrinsic evidence, including expert declarations (*see* D.I. 44). Each side provided a tutorial describing the relevant technology. (*See* D.I. 41 & 42). The Court carefully reviewed all submissions in connection with the parties' contentions regarding the disputed claim term, heard oral argument (*see* D.I. 60) and applied the following legal standards in reaching its decision.

I. LEGAL STANDARDS

A. Claim Construction

"[T]he ultimate question of the proper construction of the patent [is] a question of law," although subsidiary fact-finding is sometimes necessary. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 837-38 (2015). "[T]he words of a claim are generally given their ordinary and customary meaning [which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc) (internal citations and quotation marks omitted). Although "the claims themselves provide substantial guidance as to the meaning of particular claim terms," the context of the surrounding words of the claim also must be considered. *Id.* at 1314. "[T]he ordinary meaning of a claim term is its meaning to the ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted).

The patent specification "is always highly relevant to the claim construction analysis . . . [as] it is the single best guide to the meaning of a disputed term." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). It is also possible that "the specification may reveal a

special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316. "Even when the specification describes only a single embodiment, [however,] the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction." *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1372 (Fed. Cir. 2014) (internal quotation marks omitted) (quoting *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004)).

In addition to the specification, a court "should also consider the patent's prosecution history, if it is in evidence." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). The prosecution history, which is "intrinsic evidence, . . . consists of the complete record of the proceedings before the PTO [Patent and Trademark Office] and includes the prior art cited during the examination of the patent." *Phillips*, 415 F.3d at 1317. "[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id.*

In some cases, courts "will need to look beyond the patent's intrinsic evidence and to consult extrinsic evidence in order to understand, for example, the background science or the meaning of a term in the relevant art during the relevant time period." *Teva*, 135 S. Ct. at 841. Extrinsic evidence "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Markman*, 52 F.3d at 980. Expert testimony can be useful "to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field."

Phillips, 415 F.3d at 1318. Nonetheless, courts must not lose sight of the fact that "expert reports and testimony [are] generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence." *Id.* Overall, although extrinsic evidence "may be useful to the court," it is "less reliable" than intrinsic evidence, and its consideration "is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." *Id.* at 1318-19. Where the intrinsic record unambiguously describes the scope of the patented invention, reliance on any extrinsic evidence is improper. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1308 (Fed. Cir. 1999) (citing *Vitronics*, 90 F.3d at 1583).

B. Indefiniteness

Section 112 of the Patent Act requires a patent applicant to "particularly point[] out and distinctly claim[] the subject matter" regarded as the applicant's invention. 35 U.S.C. § 112 ¶ 2. "The primary purpose of the definiteness requirement is to ensure that the claims are written in such a way that they give notice to the public of the extent of the legal protection afforded by the patent, so that interested members of the public, *e.g.*, competitors of the patent owner, can determine whether or not they infringe." *All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779-80 (Fed. Cir. 2002) (citing *Warner-Jenkinson Co. v. Hilton-Davis Chem. Co.*, 520 U.S. 17, 28-29 (1997)). Put another way, "[a] patent holder should know what he owns, and the public should know what he does not." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 731 (2002).

A patent claim is indefinite if, "viewed in light of the specification and prosecution history, [it fails to] inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 910 (2014). Definiteness is a question of law, but the Court must sometimes render factual findings based on extrinsic evidence to resolve the ultimate issue of definiteness. *See, e.g., Sonix Tech. Co. v. Publ'ns Int'l, Ltd.*, 844

F.3d 1370, 1376 (Fed. Cir. 2017); *see also Teva*, 135 S. Ct. 842-43. "Any fact critical to a holding on indefiniteness . . . must be proven by the challenger by clear and convincing evidence." *Intel Corp. v. VIA Techs., Inc.*, 319 F.3d 1357, 1366 (Fed. Cir. 2003); *see also Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1338 (Fed. Cir. 2008).

II. THE COURT'S RULING

The Court's ruling regarding the six disputed claim terms of '954 and '652 Patents was announced from the bench at the conclusion of the hearing as follows:

> . . . At issue we have two patents and [six][2] disputed claim terms.
>
> I am prepared to rule on … the disputes. I will not be issuing a written opinion, but I will issue an order stating my rulings. I want to emphasize before I announce my decisions that although I am not issuing a written opinion, we have followed a full and thorough process before making the decisions I am about to state. I have reviewed the patents in dispute. I have also reviewed the portions of the prosecution histories, dictionaries, and expert declarations included in the Joint Appendix. There was full briefing on each of the disputed terms and a technology tutorial submitted by each of the parties. We have also had argument here today. All of that has been carefully considered.
>
> As to my rulings, I am not going to read into the record my understanding of claim construction law and definiteness. I have a legal standard section that I have included in earlier opinions, including recently in *Roche Diabetes Care, Inc. v. Insulet Corp.*, C.A. No. 20-825. I incorporate that law and adopt it into my ruling today and will also set it out in the order that I issue.
>
> The parties have suggested slightly different definitions of the person of ordinary skill in the art for each of the patents, but no party suggests that the differences are relevant to the issues currently before me.
>
> Now the disputed terms.
>
> The first term is actually two terms. First, what I will call term 1A, is "one or more landing matrices that define access to the

[2] The parties originally had disputes about ten claim terms. After the hearing, Plaintiff informed the Court that it had withdrawn the claims containing four of the disputed terms (D.I. 64), leaving six disputes.

floors, the access control system providing the landing matrices to the elevator controller" in claim 1 of the '954 Patent and second, term 1B, is "one or more landing matrices defining access to floors by one or more elevators" in claim 15 of that patent. Plaintiff argues that the terms require no construction as their meaning is readily apparent to a person of ordinary skill in the art. Today, when pressed on what the ordinary meaning is, Plaintiff offered "data structure(s) provided to an elevator controller that define(s) access to the floors of a building." Defendants mostly agree with Plaintiff but would add that the "data structures" are "proprietary to the elevator vendor" in that definition.

I do not, however, find support in the intrinsic evidence for reading "proprietary" into these terms. The portion of the intrinsic evidence cited to me discusses proprietary mechanisms for configuring and defining the access to the floors but that does not say anything about landing matrices. Therefore, I will construe the terms to mean "data structure(s) provided to an elevator controller that define(s) access to the floors of a building."

The second term is "the landing matrices" in various claims of the '954 Patent. Plaintiff again argues that no construction is necessary, and Defendants argue that the term should be construed to mean "the same one or more landing matrices previously stored by the access control system." I am not entirely sure what the dispute is here. During the hearing, Plaintiff agreed that "the landing matrices" that are overridden in both claims 1 and 15 are the same landing matrices that had been stored on the access control system. And Plaintiff agrees with that because other language in claims 1 and 15 requires it. I agree. And as such I do not believe that Defendants' proposal is necessary or helpful. So I think that the plain meaning is clear from the words themselves.

The third term in dispute is "landing matrix object" in a number of claims of the '954 Patent. The fourth term is "landing matrix application programing interface (API)" in claims 1 and 15 of that patent. The only dispute between the parties on these two terms is whether the term is indefinite. That is, Plaintiff argues that no construction is necessary, and Defendants argue that the terms are indefinite relying on an expert declaration. A finding of indefiniteness requires clear and convincing evidence, which I do not believe exists on the present record. Thus, I decline to reach the merits of Defendants' indefiniteness arguments at this time and Defendants may raise the issue again in connection with summary judgment to the extent that they wish to continue pursuing indefiniteness.

The fifth term is "detecting moving objects [within said / in the] selected monitoring area" from claims 1, 3 and 22 of the '652 Patent. Both sides agree that "detecting" means "performing detection of" and, further, that "the selected monitoring" area is the previously recited "selected monitoring area" in the claims. The dispute here is whether the detection of moving objects must occur only within the selected monitoring area, as Defendants propose, or whether there is no such limitation. In Plaintiff's view, there is no support for limiting the claims to exclude scenarios where detection also occurs outside the selected monitoring area as long as there is also detection in the monitoring area. Defendants, on the other hand, argue that the '652 Patent applicant disclaimed this claim scope during prosecution, effectively limiting the claims to detecting objects only within the selected monitoring area (which is smaller than the full field of view).[3]

I will get to the prosecution history in a moment. I first want to look at the claims and specification. In claims 1 and 3, the terms at issue recite that detecting moving objects occurs either "within said selected monitoring area" or "in the selected monitoring area." To a person of skill, this suggests that the moving objects must be detected in the selected monitoring area that was previously indicated by the user in a prior step. Tracking these claims, there is an embodiment disclosed in the specification where "only objects falling within a predefined area of the camera's 12 field of view are detected." There are also embodiments that are not so limited – *i.e.*, embodiments where the user does not have to indicate a selected monitoring area and instead objects are detected without that limitation. These embodiments seem to track with independent claims other than claims 1 and 3. For example, claim 9 – which does not contain the disputed term – relies on objects meeting previously selected "object qualifying parameters" to detect moving objects. Similarly, claim 12 – which also omits the disputed term – detects moving objects in the whole field of view of the motion video camera. This intrinsic evidence suggests that there are some embodiments where object movement detection is based upon a selected monitoring area that is smaller than the entire field of view. This, in turn, suggests that the "detecting moving objects [within said / in the] selected monitoring area" language is a limitation where moving object detection does only occur in a monitoring area selected previously by a user.[4]

---

3 (D.I. 58 at 23-24).

4 (*Id.* at 4:63-67).

As I noted, this language was added to the claims during prosecution. The fundamental dispute over this term is whether, in amending the claims to overcome a prior art rejection, the Applicant disavowed claim scope that would cover detection of moving objects outside of the selected monitoring area. Prior to the rejection, the claims at issue only recited "detecting moving objects" without requiring that detection be in "the selected monitoring area." In fact, there was no "selected monitoring area" recited at all in the claims at issue. The Examiner rejected the claims as anticipated over the Crabtree reference, which disclosed detecting moving objects in the camera's field of view. In response, the Applicant amended the claims to recite an additional limitation that required indication of a selected monitoring area within the camera's field of view. Additionally, in that same amendment, the Applicant also amended the detecting limitations to read as "detecting moving objects [within said / in the] selected monitoring area." That is, the claims were amended to require that the detecting of moving objects occur within the selected monitoring area indicated by the user in a previous step. In remarks accompanying that amendment, the Applicant argued that Crabtree did not anticipate the amended claims because it did not "describe or suggest receiving an indication of a selected monitoring area in a field of view of the video frame and detecting moving objects only within the selected monitoring area." In Defendants' view, these amendments and accompanying remarks constitute clear and unmistakable disavowal of claim scope that permits detection of moving objects outside of that selected monitoring area. Plaintiff argues that the point of distinction over Crabtree was the indication of a selected monitoring area, not the detection of moving objects only within said area.

Here, I agree with Defendants. In response to the § 102 rejection, the Applicant amended its claims to recite not only (1) that an indication of a selected monitoring area is required but also (2) that detection of moving objects occurs within that selected monitoring area. Indeed, in explaining the amendment and how it overcame the Crabtree rejection, the Applicant made clear that Crabtree was different than the amended claims because Crabtree did not disclose receiving an indication of a selected monitoring area and because it did not disclose detecting moving objects only within that selected monitoring area. A person of skill viewing the amendments alongside the Applicant's remarks would understand that the invention claimed in the amended claims was different than Crabtree because it involved "detecting moving objects only within the selected monitoring area" previously indicated by the user. To Plaintiff's argument that the point of distinction over Crabtree was the addition of indicating a selected monitoring area, I am unpersuaded. To a person of skill, the addition of that claim element means little in isolation – rather, that indication of a selected

monitoring area is tied to the detection of moving objects in that very same area. Moreover, if moving object detection could occur both within and outside of the selected monitoring area, "[within said / in the] selected monitoring area" would no longer have meaning.

Therefore, by adding the step of indicating a selected monitoring area and revising the detecting step to require "detecting moving objects [within said / in the] selected monitoring area" to overcome a prior art rejection, the '652 Patent Applicant disclaimed detection of moving objects outside of that selected monitoring area. A person of skill viewing these amendments and accompanying remarks would understand that the Applicant clearly and unmistakably disavowed claim scope that would cover moving object detection outside of the selected monitoring area indicated by the user in a prior step.

* * *

Finally, the [remaining] term is not really a claim term. Instead, it is simply referred to as "claims 9, 12 and 14," all of which Defendants contend are invalid. Each of the three claims is directed to a "computer-readable medium having stored thereon computer-executable instructions" – *i.e.*, these are all apparatus claims. Focusing on the "performing the steps of" limitation in each of the claims, Defendants argue this element is a method step that must be performed to practice the claim. In Defendants' view, under *IPXL Holdings*, the claims improperly mix apparatus and method limitations, rendering it unclear whether infringement turns upon the characteristics of the device or whether a particular use is necessary to practice the claimed invention. Therefore, according to Defendants, the claims are invalid. Plaintiff argues that a person of ordinary skill would understand the "performing" limitation indicates the steps a computer is to perform once the instructions are executed.[5]

Here, I agree with Plaintiff. I think that the reach of *IPXL Holdings* is limited. In that case, the claim at issue was directed to an electronic financial transaction system where one of the limitations provided that "the user uses the input means to either change the predicted transaction information or accept the displayed transaction type and transaction parameters." Although the claim at issue was clearly an apparatus claim, this limitation added a method step, performance of which was necessary to practice the claimed invention. As a result, the mixed nature of the claim rendered it unclear whether infringement arose from the manufacture of the apparatus or from the user's use of the apparatus. These claims are

5 (*Id.* at 5:36-39).

of a different nature. They all recite a computer-readable medium with instructions stored thereon, and I think a person of ordinary skill would understand that the "performing" limitation indicates the steps that a computer is to perform once it executes the claim instructions. That is, the claims are effectively reciting capability rather than required method steps.

Therefore, I decline to find claims 9, 12 and 13 invalid under *IPXL Holdings* for improperly mixing apparatus and method limitations.

Maryellen Noreika

The Honorable Maryellen Noreika
United States District Judge

EXHIBIT E

CAMBRIDGE DICTIONARY of AMERICAN ENGLISH

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•

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•

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buttonhole /'bʌt·ᵊn,hoʊl/ *v* [T] to stop (someone) and make them listen to you • *They took out newspaper ads and buttonholed politicians to lobby for the change.*

buttress /'bʌ·trəs/ *v* [T] to give support to or strengthen (something) • *He looked for things that would buttress the prosecution case and win a conviction.*

buttress /'bʌ·trəs/ *n* [C] *specialized* a structure made of stone or brick that sticks out from and supports a wall of a building

buxom /'bʌk·səm/ *adj* (of a woman) having large breasts

buy PAY FOR /baɪ/ *v* [T] *past* **bought** /bɔːt/ to obtain (something) by paying money for it • *She was saving to buy a car.* ◦ *He bought some flowers for his girlfriend.* ◦ *They bought into a software company* (= bought a part of it in order to have some control over it). • If you buy someone off, you get their help, esp. in a matter that may not be legal, by giving them money. [M] • To buy up something is to buy large amounts of it, or all that is available: *He bought up all the land in the surrounding area.* [M] • *He tried to* **buy time** (= be allowed more time) *by saying he hadn't been well.*

buy /baɪ/ *n* [C] an occasion in which you pay less for something than what it is worth, and are therefore pleased • *The rug turned out to be quite a buy.*

buyer /'baɪ·ər/ *n* [C] a person who pays money for something, or a person whose job is to decide what goods will be brought into a store for sale • *He's still looking for a buyer for his house.*

buy BELIEVE /baɪ/ *v* [T] *past* **bought** /bɔːt/ *infml* to believe that something is true • *She'll never buy that story about having to take care of your sick grandmother.*

▫ **buy out** /'-'-/ *v adv* [M] (of a person) to give (someone) money so that you own the part of a business that previously belonged to them • *She bought out her partner and now she owns the whole company.*

buyout /'baɪ·aʊt/ *n* [C] • *The law firm was active in management buyouts, mergers, and acquisitions.*

buzz MAKE SOUND /bʌz/ *v* [I/T] to make a continuous, low sound such as the sound some insects make, or to move quickly while making this sound • *Something was buzzing around me as I tried to sleep.* [I] • To buzz someone is to call them by using a device that makes a low, continuous sound: *All were expected to run, literally, into McLaughlin's office whenever he buzzed them.* [T]

buzz /bʌz/ *n* [C usually sing] • *the buzz of conversation* • (*infml*) A buzz is also a telephone call: *I'll give you a buzz early next week.*

buzzer /'bʌz·ər/ *n* [C] a device that makes a low, continuous sound

buzz BE FILLED WITH /bʌz/ *v* [I] to be filled with excitement, activity, or sounds • *The place was buzzing with excitement.*

buzzard /'bʌz·ərd/ *n* [C] a large North American bird that eats the flesh of dead animals; a VULTURE

buzz word /'bʌz·wɜrd/ *n* [C] a word or expression that is very often used, esp. in public discussions, because it represents opinions that are popular • *"Listening to the people" was the buzz word among politicians.*

by CAUSE /baɪ/ *prep* used to show the person or thing that causes something to happen or to exist • *The car was driven by a short, bald man.* ◦ *I'm reading some short stories by Chekhov.* ◦ *I took her umbrella by mistake.* • A **byline** is a line giving a writer's name at the top of a newspaper or magazine article.

by METHOD /baɪ/ *prep* used to show how something is done • *They thought about flying to Boston but decided to go by car.* ◦ *She did the repair work by herself* (= without help). ◦ *Do you want to be paid in cash or by check?* ◦ *He learned English by listening to the radio.* • **By and large** means speaking generally: *By and large, you're better off making reservations well in advance.*

by ACCORDING TO /baɪ/ *prep* according to • *By my watch, it's 2 o'clock.* ◦ *The students were listed by name.*

by NOT LATER THAN /baɪ/ *prep* not later than; at or before • *She promised to be back by 10 p.m.*

by MEASUREMENT /baɪ/ *prep* used to show measurements or amounts • *Their wages increased by 12%.* ◦ *The room measures 15 feet by 20 feet.*

by DURING /baɪ/ *prep* during • *We traveled by night and rested by day.*

by NEAR /baɪ/ *prep, adv* [not gradable] near, beside, or (in distance or time) past • *A small child stood quietly by her side.* ◦ *Claire waved as she drove by.* ◦ *As time went by, she became more attached to him.*

bye /baɪ/ *exclamation short form of* GOODBYE

bye–bye /baɪ'baɪ/ *exclamation* GOODBYE

bygone /'baɪ·gɔːn/ *adj* [not gradable] belonging to or happening in a past time • *The empty factories are relics of a bygone era.*

bypass /'baɪ·pæs/ *v* [T] to avoid (something) by going around it • *Take the highway that bypasses Richmond to avoid heavy traffic.* ◦ (*fig.*) *Posting news on the Internet bypasses traditional news sources such as radio and TV.*

bypass /'baɪ·pæs/ *n* [C] a road built around a city to take traffic around the edge of it rather than through it • A **bypass (operation)** is a medical operation in which the path of a person's blood esp. in the heart is changed to improve the flow of blood.

by–product, byproduct /'baɪ,prɑd·əkt, -,ʌkt/ *n* [C] something that is produced as a result

EXHIBIT F

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CIRBA INC. (d/b/a DENSIFY) and CIRBA IP, INC.,	:	
Plaintiffs,	:	
v.	:	C.A. No. 19-742-LPS
VMWARE, INC.,	:	
Defendant.	:	

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MEMORANDUM OPINION

February 24, 2022
Wilmington, Delaware

STARK, U.S. District Judge:

This consolidated action involves 11 patents. Plaintiffs Cirba Inc. (d/b/a Densify) and Cirba IP, Inc. (collectively, "Plaintiffs" or "Densify") assert U.S. Patent Nos. 8,209,687 (the "'687 patent"), 9,654,367 (the "'367 patent"), 10,523,492 (the "'492 patent"), and 10,951,459 (the "'459 patent") against Defendant VMware, Inc. ("Defendant" or "VMware"). Densify's patents relate to virtualization technology and management of virtual environments. VMware counterclaims for infringement of its U.S. Patent Nos. 8,875,266 (the "'266 patent"), 8,336,049 (the "'049 patent"), 9,521,151 (the "'151 patent"), 9,379,995 (the "'995 patent"), 9,766,945 (the "'945 patent"), 10,025,638 (the "'638 patent"), and 10,261,842 (the "'842 patent").[1]

Following a nine-day trial in January 2020 on Densify's '687 and '367 patents, a jury found that VMware infringed the asserted claims of both patents. Post-trial, the Court dismissed Cirba Inc. for lack of standing, vacated the jury's verdict, and ordered a new trial.

Presently before the Court is the issue of claim construction. The parties dispute terms found in Densify's '687, '492, and '459 patents as well as in VMware's '995, '945, '638, and '842 patents. The parties submitted technology tutorials (*see* D.I. 1091, 1093), objections to the tutorials (D.I. 1099, 1100), a joint claim construction brief (D.I. 1094), and exhibits (D.I. 1095-1 & -2; D.I. 1096-1 to -35), including expert declarations (D.I. 1095-1 Exs. A-19 to A-21; D.I. 1095-2 Exs. B-2, B-13 & -14). The Court held a claim construction hearing on December 22, 2021, at which both sides presented oral argument. (D.I. 1114) ("Tr.") After the hearing, the parties submitted supplemental briefing relating to two of the disputed terms. (*See* D.I. 1142)

[1] VMware asserted infringement of eight patents; however, the Court previously found the asserted claims of VMware's U.S. Patent No. 10,069,752 (the "'752 patent") invalid. (*See* D.I. 839 at 25-28; D.I. 840)

I. LEGAL STANDARDS

The ultimate question of the proper construction of a patent is a question of law. *See Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 321 (2015) (citing *Markman v. Westview Instruments, Inc.* ("*Markman II*"), 517 U.S. 370, 388-91 (1996)). "It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted). "[T]here is no magic formula or catechism for conducting claim construction." *Id.* at 1324. The Court is free to attach the appropriate weight to appropriate sources "in light of the statutes and policies that inform patent law." *Id.*

"[T]he words of a claim are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art [("POSA")] in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1312-13 (internal quotation marks omitted). "[T]he ordinary meaning of a claim term is its meaning to the ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted). The patent "specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

While "the claims themselves provide substantial guidance as to the meaning of particular claim terms," the context of the surrounding words of the claim also must be considered. *Phillips*, 415 F.3d at 1314. Furthermore, "[o]ther claims of the patent in question, both asserted and unasserted, can also be valuable sources of enlightenment" because "claim terms are normally used consistently throughout the patent." *Id.*

It is likewise true that "[d]ifferences among claims can also be a useful guide." *Id.* "For example, the presence of a dependent claim that adds a particular limitation gives rise to a

presumption that the limitation in question is not present in the independent claim." *Id.* at 1314-15. This presumption of claim differentiation is "especially strong when the limitation in dispute is the only meaningful difference between an independent and dependent claim, and one party is urging that the limitation in the dependent claim should be read into the independent claim." *SunRace Roots Enter. Co. v. SRAM Corp.*, 336 F.3d 1298, 1303 (Fed. Cir. 2003).

It is also possible that "the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316. It bears emphasis that "[e]ven when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction." *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1372 (Fed. Cir. 2014) (internal quotation marks omitted).

In addition to the specification, a court should "consider the patent's prosecution history, if it is in evidence." *Markman v. Westview Instruments, Inc.* ("*Markman I*"), 52 F.3d 967, 980 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). The prosecution history, which is "intrinsic evidence," "consists of the complete record of the proceedings before the [U.S. Patent and Trademark Office] and includes the prior art cited during the examination of the patent." *Phillips*, 415 F.3d at 1317. "[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id.*

Sometimes, "the district court will need to look beyond the patent's intrinsic evidence and to consult extrinsic evidence in order to understand, for example, the background science or

the meaning of a term in the relevant art during the relevant time period." *Teva*, 574 U.S. at 331. "Extrinsic evidence consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Markman I*, 52 F.3d at 980. For instance, technical dictionaries can assist the court in determining the ordinary and customary meaning of a term because such dictionaries "endeavor to collect the accepted meanings of terms used in various fields of science and technology." *Phillips*, 415 F.3d at 1318. In addition, expert testimony can be useful "to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field." *Id.* Nonetheless, courts must not lose sight of the fact that "expert reports and testimony [are] generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence." *Id.* Overall, while extrinsic evidence "may be useful to the court," it is "less reliable" than intrinsic evidence, and its consideration "is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." *Id.* at 1318-19. Where the intrinsic record unambiguously describes the scope of the patented invention, reliance on any extrinsic evidence is improper. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1308 (Fed. Cir. 1999) (citing *Vitronics*, 90 F.3d at 1583).

Finally, "[t]he construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Renishaw PLC v. Marposs SpA*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). It follows that "a claim interpretation that would exclude the inventor's device is rarely the correct interpretation." *Osram GmbH v. Int'l Trade Comm'n*, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (internal quotation marks omitted).

II. CONSTRUCTION OF DISPUTED TERMS FOUND IN DENSIFY'S PATENTS

A. '687 Patent

1. "evaluating each virtual guest against each virtual host and other virtual guests using one or more rule sets pertaining to said technical, business and workload constraints"[2]

Densify This limitation has already been fully construed by the Court (*see* D.I. 356) as: "evaluating each virtual machine against each virtual host and other virtual machines using one or more rule sets pertaining to said technical, business and workload constraints" No further construction is necessary or appropriate.
VMware "evaluating each virtual machine against each virtual host and each virtual machine against other virtual machines, in each case using one or more rules pertaining to each of technical, business and workload constraints associated with the corresponding virtual machine"
Court "evaluating each virtual machine against each virtual host and other virtual machines, in each case using one or more rule sets pertaining to each of technical, business and workload constraints"

In November 2019, in connection with the first trial, the Court construed the term "evaluating each virtual guest against each virtual host and other virtual guests" found in claims 2, 3, and 7 of the '687 patent. (*See* D.I. 356 at 4-6) The Court adopted VMware's construction, concluding that the claim term required each virtual machine ("VM") to be evaluated against each virtual host in the virtualized environment.[3] (*See id.*) During post-trial briefing, however, a

[2] This term appears in claims 3 and 7 of the '687 patent.

The parties' attempt to reach a post-hearing resolution with respect to this term failed, so they submitted supplemental claim construction briefing. (*See* D.I. 1142) While Densify complains that VMware's responsive letter brief "includes new arguments and material" (D.I. 1146), the Court agrees with VMware that Densify has had ample opportunity to respond, and Densify's "vague reference to alleged 'new arguments and material' in VMware's one-page responsive brief neither warrants delaying the proceedings nor justifies giving [it] yet another chance to reargue its position" (D.I. 1148).

[3] Densify does not dispute the requirement that all VMs be evaluated. (*See* D.I. 1094 at 28-29; Tr. at 11-12)

new dispute relating to this term emerged involving whether each VM must be evaluated using rules for all three constraints.[4] (*See* D.I. 761 at 2-5; *see also* D.I. 754 at 7) Accordingly, the Court ordered further claim construction to resolve this dispute before the upcoming trial. (*See* D.I. 1003 ¶ 13) The Court has not previously construed the precise term the parties have now put before it,[5] and doing so is necessary to resolve the parties' "fundamental dispute" as to claim scope. *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1362 (Fed. Cir. 2008). In this context, contrary to Densify's contention (*see* D.I. 1094 at 7), the Court does not view VMware's proposal as a motion for reconsideration and does not require a demonstration of good cause.

VMware argues that, in the absence of claim construction, the jury will not know (1) whether each VM requires an association with ***all three*** of the claimed constraints (i.e., technical, business, and workload) and (2) whether ***each*** evaluation between a VM and host or a VM and

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[4] Densify contends that the issue it raised in supplemental post-trial briefing was narrow and singular. (*See* D.I. 1142 at 6) In Densify's view, the only claim construction dispute the Court's Scheduling Order permitted to be briefed was whether every VM must have a business rule. (*See id.*) Accordingly, Densify continues, there is no further dispute to be decided, since VMware has made clear it is ***not*** arguing each VM must have a business rule, "disclaim[ing] the only position that was to be briefed." (*Id.*) (citing Tr. at 30) The Court disagrees with Densify. The Scheduling Order contemplates further construction in relation to the "dispute for the '687 patent that [Densify] first raised in the parties' supplemental post-trial briefing." (D.I. 1003 ¶ 13) The "post-trial claim construction dispute" reasonably encompasses more than the narrow issue of whether every VM must have a business rule. For instance, in opposing VMware's post-trial position, Densify argued that "VMware's interpretation [of the claim language] ignores the 'evaluating' and 'one or more rules sets' language," suggesting the parties' dispute implicated these broader questions of claim scope. (D.I. 761 at 3) Regardless, it is clear from the parties' claim construction briefing and supplemental briefing that the parties have a genuine, material dispute as to the scope of this claim term. In the Court's view, construction is necessary.

[5] By contrast, in *Nuance Communications, Inc. v. ABBYY USA Software House, Inc.*, 813 F.3d 1368, 1372-73 (Fed. Cir. 2016), a case relied on by Densify for its position that the Court should not further construe this term (*see* D.I. 1094 at 29), the plaintiff sought a new construction of the exact same claim term that had already been construed.

another VM (as opposed to all evaluations in the aggregate) must use one or more rule sets for each of the three constraints. (*See id.* at 31) The Court agrees with VMware that Densify's "non-construction leaves these issues uncertain," which would be improper in the circumstances presented here. (*Id.*)

VMware contends that each of the three constraints must be associated with each VM, such that a VM with just two associated constraints would not meet the claim limitation.[6] (*Id.*) In support, VMware points to the language of claim 7, describing its "obtaining" limitation as element 7A and its "evaluating" limitation as element 7B. (*Id.* at 13-14) VMware argues that the phrase "associated with a corresponding virtual machine" in element 7A modifies the three constraints, rather than the "data set," noting that "'[m]odifiers should be placed next to the words they modify.'" (*Id.* at 14) (quoting *HTC Corp. v. IPCom GmbH & Co., KG*, 667 F.3d 1270, 1274 (Fed. Cir. 2012)) Further, since element 7A already describes "a data set for each of said plurality of virtual machines," it would be redundant to note again that each data set is "associated with a corresponding virtual machine." (*Id.*) Plaintiffs, however, suggest that it is the information (pertaining to the constraints) contained in the data sets that is associated with a corresponding VM, not the "constraints" themselves.[7] (*Id.* at 24, 28)

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[6] Densify argues that VMware's construction requires that every VM be associated with "rules" pertaining to each of the three constraints. (*See, e.g.*, D.I. 1094 at 3, 23-24). VMware clarified, however, that its proposed construction requires that every VM be associated with all three "constraints," not with the "rules" or "rule sets" pertaining to those constraints. (*Id.* at 13, 19) Densify also contends that VMware's construction improperly reads "rule sets" out of the claim, replacing it with "rules." (*Id.* at 3) VMware responds that the distinction between "rules" and "rule sets" is not significant (*see* Tr. at 41) and, in any event, ultimately agreed to Densify's preferred "rule sets" in VMware's supplemental claim construction briefing (*see* D.I. 1142 at 8 & Ex. B-1). Accordingly, the Court's construction uses "rule sets."

[7] Densify offers an analogy involving a rule providing that everyone with a dietary restriction be seated at the same table. (*See* Tr. at 48-49) By applying this rule to a data set (i.e., a group of people), one could obtain information pertaining to dietary restrictions, which could include that

The Court finds Plaintiffs' position more persuasive. As Plaintiffs explain, the first step of the method recited in claim 7 is to obtain information (i.e., a data set) about each VM. (*Id.* at 23) The parties appear to agree that "said data sets" referenced in element 7B refers back to the data set referenced in element 7A. (*See id.* at 15) The second step is to evaluate those data sets using the "rule sets" recited in element 7B. (*Id.* at 23) Notwithstanding the close proximity of the phrase "associated with a corresponding virtual machine" to the three constraints, the Court is not persuaded that a person of ordinary skill in the art (POSA) would read the plain language of element 7A to require that the data set associated with each VM must contain information pertaining to all three constraints. Nor is the Court persuaded that the highlights on Densify's Dr. Madisetti's trial demonstrative (*see id.* at 14-15) or the specification compels that conclusion. Accordingly, the Court's construction omits Defendant's proposed addition of the phrase "associated with the corresponding virtual machine" imported from element 7A.[8]

Turning to the second issue, VMware argues that each evaluation must use one or more rules for each of the three constraints, such that the claim limitation would not be met where an evaluation skips a rule pertaining to even one of the three constraints. (*Id.* at 31) In support, VMware points to the specification, which describes evaluations that account for all three constraints and does not describe rules being skipped for any evaluation. (*See id.* at 16-17)

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a person has ***no*** dietary restrictions. (*See id.*) In such an instance, what is obtained is information pertaining to a constraint, but not a constraint itself.

[8] This conclusion is further supported by the absence of any "obtaining" (i.e., element 7A) limitation in claim 3 of the '687 patent, in which the disputed claim term is also found. VMware does not specifically address the distinction between claims 3 and 7, or whether the rationale underlying its proposed construction would require the term to have a different meaning in claims 3 and 7.

At the claim construction hearing, Densify conceded this point, stating that, "[o]f course, each and every evaluation must have rules pertaining to each of the three constraints." (Tr. at 43) It further clarified its position that the claim limitation is not met if there is simply one or more rule sets "in the cloud" or in the aggregate that pertain to each of the three constraints; rather, ***each evaluation*** requires one or more rule sets for each of the three constraints. (*Id.* at 48; *see also id.* at 50 (reiterating same)) Resolving any remaining doubt about its position, Densify stated that it agreed with Dr. Madisetti's testimony at trial that an evaluation lacking even one constraint would not infringe. (*See id.* at 43-44 (referring to D.I. 590 at 618; D.I. 511 at DDX-3.3 ("spiderweb" graphic)); *see also* D.I. 1142 at 6)

For those reasons, the Court is persuaded that a POSA would understand ***each*** required evaluation must use one or more rule sets pertaining to all three constraints in order to satisfy the claim.[9] The phrase "in each case" in the Court's construction reflects this understanding.

B. Terms Common to the '459 and '492 Patents

1. "source system" / "source computer system"[10]

Densify "a physical, virtual, or hypothetical system from which applications and/or data are moved or are to be moved"
VMware "a system from which applications and/or data are to be moved"

[9] VMware clarifies that it is not arguing that ***all*** rule sets used in each evaluation must pertain to all three constraints. (*See* D.I. 1094 at 32) Nor should the Court's construction be read to require this. VMware further notes that its position applies only to "the evaluations on which [Densify] relies to show infringement." (D.I. 1142 at 8-9) VMware recognizes that the claims at issue are "comprising" claims, which allow for additional evaluations apart from the claimed "evaluations." (*Id.*; *see also* Tr. at 32) The Court's construction incorporates this understanding as well.

[10] This term appears in claims 1, 12, and 23 of the '492 patent and claims 1-3, 9-10, 16-17, 22-23, 26-34, 40-41, 47-48, 53-54, and 57-63 of the '459 patent. The '459 patent is a continuation of the '492 patent and shares a common specification.

Court
"a physical, virtual, or hypothetical system from which applications and/or data are moved or are to be moved"

The parties have two disputes with respect to this claim term: (1) whether the term encompasses physical, virtual, or hypothetical systems, and (2) whether the term is subject to a temporal limit. As to both issues, the Court agrees with Densify.

The parties agree that the patentees acted as their own lexicographer for this term, pointing to the common specification's definition of a "source system" as "a system from which applications and/or data are to be moved." ('492 patent at 5:56-57) Densify described this definition as an express definition of "source system" during both IPR proceedings and at a Section 101 hearing on the '492 patent; the construction VMware now proposes is the same one the PTAB adopted when instituting the IPR. (*See* D.I. 1094 at 35-36) The parties agree that the Court's construction should have this express definition as its foundation.

With respect to the first issue, the specification explains that "systems may be physical systems, virtual systems or hypothetical models." ('492 patent at 5:64-65) Despite this disclosure, VMware argues that Densify's proposed construction improperly narrows the disputed term's scope. (*See* D.I. 1094 at 36) Somewhat incongruously, VMware also criticizes Densify for including hypothetical systems within the claim scope. (*See id.* at 42) ("[Densify] now argues 'system' includes 'hypothetical systems.'") Although VMware appeared to concede at the hearing that the systems ***can*** be hypothetical (*see* Tr. at 70-72), the Court agrees with Densify that – particularly given the seeming inconsistencies in VMware's position – there is a need at this stage to explicitly define what the systems can be. (*See id.* at 57) In the Court's view, the specification's disclosure that the systems may be physical, virtual, or hypothetical is "consistent with the express definition while providing more specificity." (D.I. 1094 at 38)

Moreover, while VMware suggests that Densify's construction is unduly narrowing, it does not provide any examples of systems that may be improperly excluded under Densify's proposal.

As to the second issue, VMware argues its construction is consistent with the specification's express definition and reflects the patent's disclosure of only forward-looking "analysis" activity. (*Id.* at 36-37) Densify concedes that the compatibility ***analysis*** is forward-looking, but notes that the term to be construed is "source system," not analysis. (*See* Tr. at 59) The Court agrees with Densify that the patent does not place a temporal limit on the claimed "source system" – that is, it does not exclude systems that have already been moved or are currently being moved. (*See id.* at 59-60)

Finally, the Court agrees with Densify that ***components*** are not excluded from the scope of "source system," as the specification does not limit "source systems" to entire systems. (*See, e.g.*, '492 patent at 6:28-32) ("[A] 'system' . . . can encompass any entity [capable of being analyzed] for any type of compatibility and should not be considered limited to existing or hypothetical physical or virtual systems.")

2. "target system" / "target computer system"[11]

Densify "a physical, virtual, or hypothetical system to which applications and/or data are moved or are to be moved"
VMware "a system to which applications and/or data from a source system are to be moved"
Court "a physical, virtual, or hypothetical system to which applications and/or data are moved or are to be moved"

[11] This term appears in claims 1, 4-6, 9, 11-12, 15-17, 20, 22-23, 26-28, 31, and 33 of the '492 patent and claims 1-3, 9-10, 16-17, 22-23, 26-34, 40-41, 47-48, 53-54, and 57-63 of the '459 patent.

The parties assert nearly identical arguments in support of their construction of "target system" / "target computer system" as for "source system" / "source computer system." (*See* D.I. 1094 at 42-44) The same reasoning underlying the Court's construction of "source system" applies to this term.

3. "*place*" terms

Term	Densify	VMware	Court
'492 patent terms[12]			
"for placing the source systems on target systems" "to determine whether the systems can or can not be placed together on a specific target system" "placing the source systems onto the target systems"	Plain and ordinary meaning	"for moving applications and/or data from source systems onto target systems" "to determine whether applications and/or data can or can not be moved from the systems together onto a specific target system" "moving applications and/or data from the source systems onto the target systems"	Plain and ordinary meaning. No construction is necessary.
'459 patent terms[13]			
"determining a placement of source computer systems on target computer systems" "determine a placement of at least one source system from the collection of computer systems on at least one target system from the collection of computer systems"	Plain and ordinary meaning	"determining movement of applications and/or data from source computer systems onto target computer systems" "determine a movement of applications and/or data from at least one source system from the collection of computer systems onto at least one target system from the collection of computer systems"	Plain and ordinary meaning. No construction is necessary.

[12] These terms appear in claims 1, 12, and 23 of the '492 patent.

[13] These terms appear in claims 1, 32, and 63 of the '459 patent.

"one or more other source systems[,] either already placed on the specific target system, or being evaluated for placement onto the specific target system"		"one or more source systems from which applications and/or data[,] have either already moved onto the specific target system or are being evaluated for movement onto the specific target system"	
"to determine if the specific source system can be placed with those other source systems on the specific target system"		"to determine if applications and/or data can be moved from the specific source system, with applications and/or data from those other source systems, onto the specific target system"	
"placing the specific source system on the specific target system"		"moving applications and/or data from the specific source system onto the specific target system"	
"issue instructions to place the at least one source system on the at least one target system in accordance with the determined placement"		"issue instructions to move applications and/or data from the at least one source system onto the at least one target system in accordance with the determined movement"	

The parties dispute the meaning of the "place" terms used in the '492 and '459 patents, which are directed to the placement of source systems on target systems.

First, the parties disagree as to whether the word "placement" should be limited to "movement." The Court agrees with Densify that the specification does not limit the scope of the "place" terms to exclude all other actions aside from "moving," as it additionally includes references to, for example, "consolidating," "stacking," and "transferring." (*See* D.I. 1094 at 45-46) (citing '459 patent at 2:5-7, 18-20, 13:37-40) That some of these actions ***involve*** moving applications and/or data does not compel the narrowing construction VMware seeks. (*See id.* at 47-49) Instead, the Court agrees with Densify that "place" should be given its plain and ordinary

meaning in this context, which is broader than "move," and may include, as Densify argues, "put[ting] in a particular position" or "a suitable place." (*Id.* at 45) (citing D.I. 1095-2 Ex. B-1)

Second, the parties dispute whether the "source systems" being placed should be limited to the "applications and/or data" within those source systems. A POSA would not read the specification as teaching that a "source system" is merely the applications and/or data within it. (*See id.* at 50-51) Similarly, the claim language does not foreclose placing an entire source system (and not merely its contents) on a target system. (*See id.*)

C. '492 Patent

1. "the systems" / "the source systems" / "the target systems"[14]

Densify Not indefinite and no construction necessary; antecedent basis is reasonably certain.
VMware Indefinite for lack of a reasonably certain antecedent basis.
Court Not indefinite.

VMware argues "the systems," "the source systems," and "the target systems" each lack a reasonably certain antecedent basis and are thus indefinite. The Court disagrees.

As to "the systems," VMware points to the following language:

> evaluating [1] one or more source systems against [2] other source systems and against [3] one or more target systems using at least one rule set that evaluates parameters of ***the systems*** to determine whether ***the systems*** can or can not be placed together on a specific target system . . . ;

('492 patent cl. 1) (emphasis added)

[14] These terms appear in claims 1, 12, and 23 of the '492 patent.

Densify contends that the '492 patent makes clear that both bolded "the systems" terms encompass both "the source systems [1] and [2]" and "the target systems [3]," arguing that the preamble and claim language provide the antecedent basis for "the systems" and pointing to several instances in which the specification describes both the source systems and target systems as "systems." (D.I. 1094 at 54)

VMware responds that a target system cannot be "placed" on another target system (a point which Densify concedes). (*Id.* at 56, 59) In VMware's view, then, the second bolded "the systems" term cannot encompass "the target systems [3]." (*Id.* at 56) Densify counters that, while indeed a target system cannot be "placed" on another target system, the specification teaches that, when stacking multiple source entities onto a target, the source entities and targets coexist in the same operating system environment. (*Id.* at 59) Thus, a POSA would understand that determining compatibility between source entities and targets would require determining whether source systems and a specific target system can be placed together on that target system or in its environment. (*See id.*; *see also* Tr. at 90)

The Court agrees with Densify that a POSA would understand from the specification that a target system cannot be "placed" on another target system. (*See* Tr. at 99) ("You have to try really hard not to understand the claim in light of what the specification teaches.") Accordingly, despite the existence of some ambiguity as to whether the second bolded "the systems" term encompasses "the target systems [3]," VMware has not shown that this claim is indefinite. *See generally Phillips*, 415 F.3d at 1327 ("[A]mbiguity in . . . claim language should . . . be resolved in a manner that would preserve the patent's validity.").

As to "the source systems," VMware points to the following language:

> A computer implemented method for placing [1] source systems on target systems, the method comprising:

> evaluating [2] one or more source systems against [3] other source systems and against one or more target systems using at least one rule set that evaluates parameters of the systems to determine whether the systems can or can not be placed together on a specific target system . . . ; and
>
> placing ***the source systems*** onto the target systems . . . .

('492 patent cl. 1) (emphasis added)

VMware argues it is impossible to determine which "source systems" must be placed in order to infringe, citing several possibilities, such as the preamble's "[1] source systems," all of the "[2] one or more source systems," or each of the "[3] other source systems" as possible contenders. (*See* D.I. 1094 at 57) Densify responds that it is clear from the claim language that the bolded "source systems" refers to the "[2] one or more source systems" and the "[3] other source systems" that are evaluated against each another. (*Id.* at 60)

The Court agrees with Densify that VMware has not met its burden to show this term is indefinite. As Densify explained at the hearing, "there is really only one plausible way to look at this," which is "that the source systems are the ones that get placed, and the target systems are the ones on which the source systems are placed." (Tr. at 92) A POSA would understand that the source systems being placed are the "one or more source systems" and the "other source systems."

Finally, as to "the target systems," VMware points to the following language:

> A computer implemented method for placing source systems on [1] target systems, the method comprising:
>
> evaluating one or more source systems against other source systems and against [2] one or more target systems using at least one rule set that evaluates parameters of the systems to determine whether the

> systems can or can not be placed together on [3] a specific target system . . . ; and
>
> placing the source systems onto ***the target systems*** . . . .

('492 patent cl. 1) (emphasis added)

VMware asserts it is not clear if infringement requires placement on one or all target systems, arguing that the most reasonable antecedent for the bolded "target systems" is the singular "[3] a specific target system." (D.I. 1094 at 58) Densify counters that the only reasonable antecedent of the plural "the target systems" is the also plural "[2] one or more target systems." (*Id.* at 60-61) Here, too, the Court agrees with Densify. VMware has not met its burden to show this term is indefinite.

2. "at least one of a compatibility score, and a number of transfers"[15]

Densify Plain and ordinary meaning. Alternatively: "a compatibility score and/or a number of transfers"
VMware "at least one compatibility score and at least one of a number of transfers"
Court "at least one compatibility score and at least one of a number of transfers"

The parties dispute what "at least one of" modifies here. Densify argues the plain and ordinary meaning of the phrase makes clear that the "one or more criteria" used to select the placement solution can be at least one of ***either*** a compatibility score, a number of transfers, or both. (D.I. 1094 at 63) In support, it points to instances in which the specification contemplates some, but not all, of the criteria being selected. (*See id.* at 63-64)

[15] This term appears in claims 3, 14, and 25 of the '492 patent.

By contrast, VMware contends that the claims require at least one compatibility score and at least one of a number of transfers. (*Id.* at 64) In support, it relies on *SuperGuide Corp. v. DirecTV Enterprises, Inc.*, 358 F.3d 870, 885-86 (Fed. Cir. 2004), in which the Federal Circuit applied grammatical and stylistic principles to conclude that "at least one of" followed by elements joined by "and" (rather than "or") requires at least one element of ***each type***. *See also SIMO Holdings Inc. v. Hong Kong uCloudlink Network Tech. Ltd.*, 983 F.3d 1367, 1377 (Fed. Cir. 2021) ("When there is a straightforward, parallel construction that involves all nouns or verbs in a series, a prepositive or postpositive modifier normally applies to the entire series," and this principle "has particular force when the term joining the items in a series is 'and'").

As Densify notes, the *SuperGuide* presumption is rebuttable. (*See* Tr. at 103) In *Rex Medical, L.P. v. Intuitive Surgical, Inc.*, 2020 WL 2128795, at *6 (D. Del. May 5, 2020), for example, the Court found the presumption inapplicable because "at least one of" in that case modified a list of two, rather than three items, and because interpreting the disputed phrase in the conjunctive would have rendered "at least one of" superfluous in that context. Significantly, however, the Court in *Rex Medical* also explained that a "disjunctive construction is ***required*** in order for the plain words of [the claim] to make sense." *Id.* at *7 (emphasis added). There, the parties disputed the meaning of "at least one of the first jaw and the second jaw," and the Court reasoned that a conjunctive construction would nonsensically permit more than one "first jaw" and more than one "second jaw." *Id.* Further, the Court found "nothing in the specification that supports an apparatus with more than one set of jaws." *Id.*

By contrast, here, embodiments in the specification support a conjunctive construction by allowing for selection of a workload placement solution based on ***both*** a compatibility score and a number of transfers. (*See* D.I. 1094 at 64-65) (citing, e.g., '492 patent at 35:41-46) Moreover,

as VMware explains, a conjunctive construction would not render "at least one of" superfluous in this context. (*See* Tr. at 109-10) The specification provides examples involving multiple compatibility scores and varying numbers of transfer sets, and the "at least one of" helpfully indicates that there may be more than one of either of those items. (*See id.*)

Accordingly, in the Court's view, neither the claim language nor the specification "rebuts the presumption that the . . . patentee intended the plain and ordinary meaning of this language." *SuperGuide*, 358 F.3d at 887. Thus, the Court adopts VMware's proposed construction.

3. "determining at least one optimal combination of applications operable independently on the target system"[16]

Densify Not indefinite. Plain and ordinary meaning. Alternatively, "capable of operating independently from one another." (D.I. 1142 Ex. A-1 at 8)
VMware Indefinite.
Court Not indefinite. "Capable of operating independently from one another."

VMware contends this term is indefinite because a POSA would not be able to determine with reasonable certainty what it means for applications to be "operable independently" or what they must operate independently of. (D.I. 1094 at 68) The Court disagrees.

VMware suggests the applications could perhaps operate independently of ***each other*** or of ***the source systems*** on which they are running, but the intrinsic record does not make clear which of these interpretations applies. (*See id.* at 68-69) Densify counters that the specification supports only one possible meaning: that the applications are capable of operating independently from one another. (D.I. 1142 at 12; *id.* Ex. A-1 at 8) VMware argues this position is

[16] This term appears in claims 9, 20, and 31 of the '492 patent.

inconsistent with the position Densify took in its reply brief and at the hearing, in which Densify asserted that a POSA would understand the applications are "operable independently on the target system." (D.I. 1142 at 10) But these positions are not incompatible; they are, in fact, not really even two separate positions. Instead, as Densify explains, it has asserted all along that the applications must be "able to be operated independently of each other on the target system." (*Id.* at 12 (emphasis omitted); D.I. 1094 at 67)

In support, Densify points to a passage in the specification describing "multi-dimensional rule-based compatibility analysis," which describes assessing the compatibility of transferring multiple source entities to a target system. (D.I. 1094 at 70) There, the patent discloses two types of target systems: "concrete" and "malleable." ('492 patent at 30:10-23) Where a target system is "concrete," the source entities are "assumed to be required to conform to the target," while where a target is "malleable" it is "generally adaptable in accommodating source entities." (*Id.*) Densify argues a POSA would understand that when a target system is "concrete," the target may not be able to accommodate each of the applications' individual requirements. (D.I. 1094 at 70) Therefore, the applications must be "operable independently on the target system" – that is, they would not require or rely on individual target system accommodations to be able to operate on the target system. (*Id.*)

While VMware is correct that the specification excerpt upon which Densify relies – which never uses the words "operable" or "independent" – does not provide robust guidance as to this claim term (*see id.* at 71), the Court is nonetheless persuaded that (as Dr. Madisetti testified) a POSA would understand with reasonable certainty the claim scope here. (*See* D.I. 1095-2 Ex. B-13 ¶¶ 36-40) VMware has not shown by clear and convincing evidence that the

term is indefinite. *See BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1365 (Fed. Cir. 2017).

4. "a 1-to-1 compatibility analysis"[17]

Densify "an analysis that evaluates the compatibility of every possible source-target pair combination in a collection of systems on a 1-to-1 basis"
VMware "an analysis that evaluates the compatibility of every system in a collection of systems as a source system against every system in the collection of systems as a target system on a 1-to-1 basis"
Court "an analysis that evaluates the compatibility of every system in a collection of systems as a source system against every system in the collection of systems as a target system on a 1-to-1 basis"

The patentees acted as their own lexicographer for this term, indicating in the specification that "[t]he 1-to-1 compatibility analysis evaluates the compatibility of every possible source-target pair combination in the collection of systems . . . on a 1-to-1 basis." ('492 patent at 7:19-21) Both parties' proposed constructions reflect this express definition. However, VMware argues its construction provides further clarity to the meaning of "every possible source-target pair combination." (D.I. 1094 at 72)

At the claim construction hearing, Densify described VMware's construction as "a more detailed recitation of what they believe 'every possible' means," but added that Densify did not discern any meaningful difference in the parties' constructions. (Tr. at 122-23) Indeed, the parties appear to agree that the 1-to-1 compatibility analysis produces a score for each source-target system pairing that exists in a collection of systems. (*See* D.I. 1094 at 71-72) In VMware's view, however, the further detail in its proposed construction reflects that the phrase

[17] This term appears in claims 1, 12, and 23 of the '492 patent.

"every possible" requires an exhaustive analysis. (Tr. at 124) Since the specification reflects this understanding, and Densify does not dispute it, the Court will adopt VMware's construction to resolve any ambiguity VMware contends may otherwise exist. (*See id.* at 125)

5. "an N-to-1 compatibility analysis"[18]

Densify "an analysis that evaluates the compatibility of each of N source systems separately and individually against a common target system"
VMware "an analysis that evaluates the compatibility of each of N source systems against a common target system"
Court "an analysis that evaluates the compatibility of each of N source systems separately and individually against a common target system"

The parties agree the specification teaches that a goal of the claimed "N-to-1 compatibility analysis" is to determine whether multiple source systems can operate together on the same target system, and that the outcome of such an analysis is a single compatibility score for the transfer set as a whole. (*See* D.I. 1094 at 75-77) (citing '492 patent at 7:26-31)

Densify argues, however, that its construction is necessary to clarify that the N-to-1 compatibility analysis does not involve evaluating the ***combination*** of N source systems against the common target system. (*Id.* at 78) VMware responds that Densify does not explain how "separate" and "individual" evaluations could determine if the N source systems could operate ***together*** on the same target. (*Id.* at 76-77) It notes further that its proposed construction is supported by the specification, and is the same construction Densify proposed in the '492 patent IPR proceedings. (*Id.* at 76)

[18] This term appears in claims 1, 12, and 23 of the '492 patent.

VMware's proposal, however, does not appear to resolve the parties' dispute. The Court finds it appropriate, therefore, to look more closely at the specification for further guidance. *See Phillips*, 415 F.3d at 1315 (specification is "the single best guide to the meaning of a disputed term").

In Densify's view, the specification teaches that the N-to-1 compatibility analysis involves ***separate*** evaluations of each ***individual*** source system against the common target. (D.I. 1094 at 75-76) In support, it points to the specification's description of how the N-to-1 compatibility score is calculated. (*Id.*) (citing '492 patent at 30:46-60) That portion of the specification teaches that determining the compatibility between N source entities and a single target involves "***[s]eparately*** evaluat[ing] each source entity against the target." ('492 patent at 30:50) (emphasis added) This description is followed by examples in which source systems (s1, s2, and s3) are evaluated separately and individually against a common target system (s16); that is, the specification describes three separate evaluations of (1) "s1 against S16," (2) "s2 against s16," and (3) "s3 against s16," rather than one evaluation of the combination of s1 + s2 + s3 against s16. (*Id.* at 30:62-65; *see also id.* fig. 24(c) (separately evaluating each source entity against target))

The Court finds Densify's citations to the specification persuasive and, accordingly, adopts Densify's proposed construction.

D. '459 Patent

1. "the source systems"[19]

Densify Not indefinite. Plain and ordinary meaning. Alternatively: "the specific source system and those other source systems"
VMware Indefinite for lack of a reasonably certain antecedent basis.
Court "the specific source system and one or more other source systems"

VMware argues the term "the source systems" claimed in the '459 patent lacks a reasonably certain antecedent basis and is indefinite. The Court disagrees.

VMware points to the following language:

> evaluate compatibility between [1] the specific source system from [2] the plurality of source systems and [3] one or more other source systems either already placed on the specific target system, or being evaluated for placement onto the specific target system, to determine if the specific source system can be placed with those other source systems on the specific target system, by evaluating one or more rules that operate against attributes or data relating to ***the source systems***;

('459 patent cl. 1) (emphasis added)

Densify argues that a POSA would be reasonably certain that the bolded "the source systems" term above refers to "[1] the specific source system from [2] the plurality of source systems" ***and*** the "[3] one or more other source systems."[20] (D.I. 1094

[19] This term appears in claims 1, 31, and 63 of the '459 patent. Densify has agreed that claim 63 should read "the source systems," consistent with claims 1 and 31, rather than "the two or more source systems." (D.I. 1094 at 82 n.17)

[20] Although Densify took a different position in its opening brief, it conceded at the claim construction hearing that, "[c]andidly, [its] opening position was a mistake." (Tr. at 143)

at 83; Tr. at 141, 144) In VMware's view, however, the term is susceptible to multiple interpretations. (*See* D.I. 1094 at 82)

Despite the ambiguity suggested by VMware, the Court agrees with Densify that the plain language of the claims and the specification provide a POSA with enough information to understand what "the source systems" refers to in this context. (*See* Tr. at 144) As Densify explained at the hearing, it would be unreasonable for "the source systems" to refer to "[2] the plurality of source systems," as such a reading would include those source systems that are not being evaluated. (*Id.*) VMware has not shown by clear and convincing evidence that this term is indefinite.

III. CONSTRUCTION OF DISPUTED TERMS FOUND IN VMWARE'S PATENTS

A. '995 Patent

1. "snapshot"[21]

Densify "data that contains configuration and resource usage information of a distributed computer system at a particular moment in time"
VMware "data at a particular moment in time"
Court "data that contains configuration and resource usage information of a distributed computer system at a particular moment in time"

The parties agree that a "snapshot" is data "at a particular moment in time." (*See* D.I. 1094 at 85)

VMware argues, however, that the additional language in Densify's proposed construction renders superfluous the claims' "wherein" clause, which states: "wherein the

[21] This term appears in claims 1, 9, and 17 of the '995 patent.

snapshot includes configurations and resource usage information of at least some components of the distributed computer system." ('995 patent cls. 1, 9, 17)

Densify responds that its proposed construction simply reflects the express definition in the specification, namely: "[a]s used herein a snapshot of a distributed computer system contains at least configuration and resource usage information of the distributed computer system at a particular moment in time." (*Id.* at 7:53-56) Densify argues that its construction does not render the claims' "wherein" clause superfluous, as here the term "snapshot" appears in the same limitation as the "wherein" clause, with the phrase as a whole operating as a single limitation, mutually reinforcing that the claimed "snapshot" must contain ***at least*** a configuration and resource usage information, as distinguished from other types of data. (*See* D.I. 1094 at 86-87)

The Court will adopt Densify's construction, which incorporates the specification's express definition. VMware does not dispute that the language on which Densify relies is an express definition for "snapshot." Moreover, unlike in *IpLearn, LLC v. Kenexa Corp.*, 2013 WL 5730610 (D. Del. Oct. 22, 2013), this case does not involve a suggestion that the Court import a different limitation from a ***dependent*** claim into an independent claim such that the language in the dependent claim may be rendered superfluous. Instead, here the terms are part of the same limitation of the same claim, and Densify's construction serves to reinforce the patentee's express definition for "snapshot" (which the parties appear to agree controls).

2. "iteratively traversing a resource hierarchy"[22]

Densify Indefinite for failure to point out with particularity and distinctly claim the subject matter such that one of ordinary skill in the art would be reasonably apprised of the bounds of the asserted claims.
VMware Not indefinite. This term should not be construed as it takes its plain and ordinary meaning. Alternatively, this term should be construed as "repeatedly moving along resources that are organized in a hierarchy, such as in ranks, layers, or a tree structure."
Court Not indefinite. "Repeatedly moving along resources that are organized in a hierarchy, such as in ranks, layers, or a tree structure."[23]

Densify contends that the disputed term is indefinite, arguing a POSA would understand the patent to teach three possible meanings for "iteratively traversing" without being able to reasonably ascertain which one applies. (*See* D.I. 1094 at 95) In Densify's view, the patent teaches that "iteratively traversing" could mean (1) simply repeatedly "moving" along the hierarchy (by moving among nodes); (2) repeatedly "adjusting" operations at nodes on the hierarchy (which would require only a ***single*** movement from a first to a second node); or (3) repeatedly moving along the hierarchy ***and*** performing the adjustment operation at each node. (*See id.* at 92-95)

VMware agrees with Densify that the patent teaches the first of these three meanings of "iteratively traversing;" it argues, however, that Densify's proposed second and third possible meanings are based on improper importations of limitations into the claims. (*See id.* at 99-100) The Court agrees with VMware that the two other "possible meanings" Densify identifies are not supported by the plain language of the claims or the specification. VMware notes correctly that

[22] This term appears in claims 1, 9, and 17 of the '995 patent.

[23] The parties agree that "resource hierarchy" means "resources organized in ranks, layers, or a tree structure." (D.I. 1094 at 92)

the claims recite "iteratively traversing," not "iteratively ***adjusting***." (*Id.*) The specification does not equate "traversing" and "adjusting," nor mandate that "traversing" include adjusting. (*See id.*) Moreover, while certain embodiments may illustrate "iteratively traversing" by starting from the bottom layer in the resource hierarchy and moving up (*see, e.g.*,'995 patent at 13:6-10), the patent does not limit "iteratively traversing" to "moving higher in the hierarchy or moving laterally after first moving higher," as Densify argues. (D.I. 1094 at 98)

The parties appear to generally agree that the plain meaning of iteratively is "repeatedly" and that "traversing" means moving. Accordingly, the Court adopts VMware's alternative construction.

3. "target resource allocation"[24]

Densify "desired resource allocation"
VMware This term should not be construed as it takes its plain and ordinary meaning.
Court Plain and ordinary meaning. No construction is necessary.

The parties appear to agree that the term "target" connotes a goal or an objective. They disagree as to whether the Court's construction should involve some measure of a person's subjective intentions. (*See* D.I. 1094 at 101-03)

Densify points to the patent's Background, which states that "[r]esource allocation techniques . . . are important to ensure that the clients are operating at ***desired*** or ***target*** levels." ('995 patent at 1:14-17) (emphasis added) The Court agrees with VMware, however, that a POSA would not read the Background as equating "target" with "desired." (*See* D.I. 1094 at

[24] This term appears in claims 1, 9, and 17 of the '995 patent.

102) The word "target" in this context could be understood either to reiterate the "desired" modifier or (if the "or" is disjunctive) indicate another type of level that is distinct from "desired."

Besides its lack of specification support, Densify's proposed "desired" could confusingly suggest to the jury that it must assess subjective intentions. (*See id.*) Densify's contention that the jury will be confused without a construction, a conclusion Densify reaches based on reference to meanings of "target" that plainly do not apply (e.g., "a mark or point at which someone fires or aims"), is unpersuasive. (*See id.*) Instead, as VMware notes, the specification supports an understanding that the plain and ordinary meaning of "target" as used in the patent is a "goal" or "objective." (*Id.* at 101) (citing '995 patent at 11:43-48 (describing exemplary target resource allocation as "resource allocation goal")) Accordingly, no construction is necessary.

4. "resource configuration action"[25]

Densify "action relating to resource configuration in accordance with resource allocation recommendation"
VMware This term should not be construed as it takes its plain and ordinary meaning.
Court Plain and ordinary meaning. No construction is necessary.

Densify provides no persuasive reason to recast the claimed phrase "resource configuration action" to an "action relating to resource configuration." (D.I. 1094 at 103)

Densify further contends that the resource configuration action must be "in accordance with" the resource allocation recommendation. (*See id.* at 104) The claims state that "the resource allocation recommendation specifies at least one resource configuration action . . . ."

[25] This term appears in claims 1, 9, and 17 of the '995 patent.

('995 patent cls. 1, 9, 17) The Court agrees with VMware that an action "in accordance with" a recommendation is vaguer than an action ***specified*** by the recommendation. (*See* D.I. 1094 at 104) Hence, Densify's proposed substitution may confuse a jury by implying that performing the specified "resource configuration action" depends on other unidentified requirements in the recommendation. (*See id.*)

Nor does the specification support Densify's construction. While the specification identifies exemplary actions that can be specified by the resource allocation recommendation (*see* '995 patent at 9:4-18), it does not require that the claimed resource configuration action be "in accordance with" that recommendation (*see* D.I. 1094 at 105).

The plain language of the claims makes clear that the resource configuration actions are tied to the resource allocation recommendation, which "specifies" those actions.

5. "capacity expansion action"[26]

Densify "action relating to capacity expansion in accordance with resource allocation recommendation"
VMware This term should not be construed as it takes its plain and ordinary meaning.
Court Plain and ordinary meaning. No construction is necessary.

The parties assert the same arguments with respect to this claim term as with the "resource configuration action" term. For the same reasons, the Court concludes that construction is not necessary.

[26] This term appears in claims 1, 9, and 17 of the '995 patent.

B. '945 Patent

1. "calculating a target resource configuration"[27]

Densify "calculating a desired resource configuration"
VMware This term should not be construed as it takes its plain and ordinary meaning.
Court Plain and ordinary meaning. No construction is necessary.

As with the term "target resource allocation" found in the '995 patent, Densify proposes exchanging the ordinary word "target" for the more subjective word "desired." (*See* D.I. 1094 at 110) For the same reasons discussed with respect to the '995 patent, the Court finds VMware's position more persuasive.

Further support for the Court's conclusion is found in the fact that, unlike with the '995 patent, the term "desired" does not even appear in the '945 patent. While the specification describes the calculation of an "ideal" resource configuration, Densify does not explain how this description compels the construction it seeks. (*See id.* at 109) (citing '945 patent at 6:43-58)

C. '638 Patent

1. "operationally distinct cloud computing facilities"[28]

Densify Indefinite for failure to point out with particularity and distinctly claim the subject matter such that one of ordinary skill in the art would be reasonably apprised of the bounds of the asserted claims.
VMware Not indefinite. This term should not be construed as it takes its plain and ordinary meaning.
Court Not indefinite. Plain and ordinary meaning.

[27] This term appears in claims 1, 8, and 15 of the '945 patent.

[28] This term appears in claims 10 and 19 of the '638 patent.

Densify argues the intrinsic record provides insufficient guidance as to what it means for a cloud computing facility to be "operationally distinct." (*See* D.I. 1094 at 116) VMware counters that a POSA would understand that "operationally distinct" cloud computing facilities "function separately from one another." (*See id.* at 111) It notes that "operationally" ordinarily means "functionally" and "distinct" ordinarily means "separate." (*Id.* at 117; *see also* Tr. at 159)

The specification uses the term "operationally distinct" only once – in connection with Figure 10 – and states that the cloud-computing facilities "are geographically and operationally distinct." ('638 patent at 12:56-13:2) VMware argues this supports its construction, as it describes distinct cloud-computing facilities that function separately from one another while being centrally managed. (*See* D.I. 1094 at 111-12) In the Court's view, the specification does not provide such clarity.

The prosecution history reveals that the Examiner expressed confusion as to the meaning of "operationally distinct," noting that the claim language does not shed light on the term's meaning and adding that the specification suggests "it is only necessary that the node[s] operate independent of each other in some way." (D.I. 1095-2 Ex. B-3 at 10) In response, the applicant explained that the facilities are "operationally distinct" because "the virtual data centers are themselves large distributed systems that include interfaces and abstraction layers that provide access to well-defined sets of services that are carried out entirely within the virtual data centers." (D.I. 1032-13 Ex. T at 24)

Densify argues the applicant's response provides little guidance, leaving it unclear (among other things) whether facilities must be "geographically distinct." (*See* D.I. 1094 at 115-16) VMware responds that the patent discusses "geographically distinct" and "operationally distinct" as separate concepts, and the claims only require that the cloud computing facilities be

"operationally" distinct. (*Id.* at 118; Tr. at 161, 169) A POSA would understand that the applicant's response reiterates that "operationally distinct" cloud computing facilities "function separately from one another."

The Court's conclusion that VMware's plain and ordinary meaning construction provides sufficient guidance as to the term's meaning, and that this term is not indefinite, is further supported by the fact that, although the PTAB did not ultimately decide the issue of what qualifies as "operationally distinct," it was nonetheless able to analyze the term in relation to the prior art. *See generally Sonix Tech. Co. v. Publ'ns Int'l, Ltd.*, 844 F.3d 1370, 1379-80 (Fed. Cir. 2017).

2. "cloud-connector server"[29]

Densify "a dedicated server computer or virtual machine running within a server computer that interfaces to users on a remote computer and that interfaces to remote cloud-connector nodes"
VMware This term should not be construed as it takes its plain and ordinary meaning. Alternatively, this term should be construed as "a dedicated server computer or virtual machine running within a server computer."
Court "a dedicated server computer or virtual machine running within a server computer that interfaces to users on a remote computer and that interfaces to remote cloud-connector nodes"

Densify argues the term "cloud-connector server" has no plain and ordinary meaning, pointing to the patentee's representation during prosecution that "'cloud-connector server' . . . do[es] not have [a] well-known or accepted meaning[] within the computing arts." (D.I. 1094 at 122) (citing D.I. 1095-2 Ex. B-4 at 12) The patentee further stated that the phrase was "developed for the current application" and should be understood according to the definitions provided in the application. (D.I. 1095-2 Ex. B-4 at 12) The patentee provided an express

[29] This term appears in claims 10 and 19 of the '638 patent.

definition for "cloud-connector server" as "a dedicated server computer or virtual machine running within a server computer that interfaces to users on a remote computer and that interfaces to remote cloud-connector nodes." (*Id.* at 11) Densify proposes that the Court adopt this definition as its construction.

The Court agrees with Densify that "'the patentee acted as his own lexicographer and clearly set forth a definition of the disputed claim term in . . . [the] prosecution history.'" (D.I. 1094 at 125) (quoting *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002)) VMware offers no persuasive intrinsic evidence casting doubt on that definition, and concedes that the patentee's definition should inform the Court's understanding of the term. (*See id.* at 121) VMware also agrees with Densify that, as disclosed in the specification, the cloud-connector server can be a physical server computer or a virtual machine. (*See id.*) (citing '638 patent at 13:5-8, 12:51-57) Accordingly, the Court will adopt Densify's construction, which is consistent with both the plain language of the claims and the specification, as well as the express definition given during prosecution.

3. "cloud-connector node"[30]

Densify "an application or set of applications running within a virtual machine installed within each computing-facility of the multiple cloud-computing-facility aggregation, in a virtual data center management server, cloud director, or management system"
VMware "an application or set of applications that connects the cloud-computing server with a cloud-computing facility"
Court "an application or set of applications that connects the cloud-computing server with a cloud-computing facility"

[30] This term appears in claims 10 and 19 of the '638 patent.

As with "cloud-connector server," the patentee stated during prosecution that "cloud-connector node" does not have a well-known meaning in the art. (*See* D.I. 1095-2 Ex. B-4 at 12) Densify notes that the patentee also represented that a cloud-connector node "is generally implemented as an application or set of applications running within a virtual machine." (*Id.*) Additionally, the patentee described the claimed cloud-connector nodes as being "installed in a virtual data center management server, cloud director, or management system within a cloud-computing facility of the multiple cloud-computing facility." (D.I. 1032-13 Ex. T at 26)

The Court agrees with VMware, however, that the patentee's use of "generally" to describe the way in which "a cloud-connector node" is implemented suggests that other examples (beyond applications "running within a virtual machine") are possible and detracts from Densify's argument that the statement relied on by Densify should be read as an express definition. (*See* D.I. 1094 at 128) Nor is that statement a clear disavowal of claim scope. (*See id.* at 130)

Absent lexicography or a clear disavowal of claim scope, the fact that dependent claims 14 and 23 expressly limit the cloud-connector node to a "virtual appliance" (i.e., an application or set of applications running within a virtual machine) provides another reason – under the doctrine of claim differentiation – not to limit independent claims 10 and 19 in a manner that would result in their scope being no broader than that of the dependent claims. (*See id.* at 128) Moreover, the specification provides support for VMware's construction, describing the "cloud-connector node" as a means to connect the cloud-computing server with a cloud-computing facility. (*See, e.g.*, '638 patent at 12:33-38, 51-55, 13:15-36)

For similar reasons, the prosecution history also does not support requiring the nodes to be installed "in a virtual data center management server, cloud director, or management system."

These limitations are not persuasively supported by the evidence Densify cites and would render express claim language superfluous. (*See* D.I. 1094 at 129)

D. '842 Patent

1. "distributed resource scheduling module"[31]

Densify This is a means-plus-function term subject to § 112, ¶ 6. The term is indefinite for lack of sufficiently definite corresponding structure. ***Functions*:** - receiving a recommended change to a virtual architecture of the virtual computing environment at a distributed resource scheduling module; - determining, by the distributed resource scheduling module, an impact on current workload in the virtual computing environment if the recommended change is performed; - determining, by the distributed resource scheduling module, an impact on future workload in the virtual computing environment if the recommended change is performed; - calculating, by the distributed resource scheduling module, a combined impact on current and future workload from the determined impact on current workload in the virtual computing environment if the recommended change is performed and from the determined impact on future workload in the virtual computing environment if the recommended change is performed; - determining, by the distributed resource scheduling module, that the combined impact is above a threshold; and - in response to determining that the combined impact on current and future workload is above the threshold, performing the recommended change to the virtual architecture of the virtual computing environment. ***Structure*:** Insufficient.
VMware Not a means-plus-function term subject to §112, ¶ 6 and not indefinite. This term should not be construed as it takes its plain and ordinary meaning. That plain and ordinary meaning is "distributed resource scheduler" (D.I. 1094 at 133). If this limitation is subject to § 112, ¶ 6: ***Function*:** receiving a recommended change

[31] This term appears in claim 1 of the '842 patent.

***Structure*:** conventional software modules for receiving recommended changes to virtual environments for evaluation ***Function*:** determining . . . an impact on current workload ***Structure*:** conventional software for scoring recommended changes, e.g., "based on [their] improvement in the cluster imbalance metric and on its risk-adjusted costs and benefits" before the "imbalance metric is recomputed incorporating that move" ***Function*:** determining . . . an impact on future workload ***Structure*:** conventional software for scoring recommended changes based on a "predicted load," such as one based on a "pattern matching predictor," "'polyfit' prediction" or "simple step prediction" ***Function*:** calculating . . . a combined impact on current and future workload ***Structure*:** conventional software for "sum[ming]" impact scores, such as "scor[ing] as the sum of current and future impact, weighted by confidence in the future prediction" ***Function*:** determining . . . that the combined impact is above a threshold ***Structure*:** conventional software for comparing scores to thresholds, such as by cost benefit analysis (D.I. 1109 at 159)
Court Not a means-plus-function term subject to §112, ¶ 6 and not indefinite. The plain and ordinary meaning of this term is "distributed resource scheduler."

Densify argues the term "distributed resource scheduling module" ("DRS module") is subject to 35 U.S.C. § 112, ¶ 6 and is indefinite because the specification does not disclose adequate corresponding structure. (D.I. 1094 at 133-36) The Court must first evaluate whether means-plus-function claiming applies. If it applies, the Court then identifies the function and determines whether the specification discloses sufficient structure to perform the function.

Where, as here, a claim does not use the word "means," there is a rebuttable presumption that means-plus-function claiming does ***not*** apply, although that presumption is not a "strong" one. *Williamson v. Citrix Online, LLC*, 792 F.3d 1339, 1349 (Fed. Cir. 2015); *see also Zeroclick, LLC v. Apple Inc.*, 891 F.3d 1003, 1007 (Fed. Cir. 2018). "Module," however, is a

"well-known nonce word that can operate as a substitute for 'means.'" *Williamson*, 792 F.3d at 1350. Densify argues, as a consequence, that means-plus-function claiming applies.

"When evaluating whether a claim limitation invokes § 112, ¶ 6, the essential inquiry remains whether the words of the claim are understood by persons of ordinary skill in the art to have a sufficiently definite meaning as the name for structure." *Zeroclick*, 891 F.3d at 1007 (internal quotation marks omitted); *see also Greenberg v. Ethicon Endo-Surgery, Inc.*, 91 F.3d 1580, 1583 (Fed. Cir. 1996) ("What is important is . . . that the term, as the name for structure, has a reasonably well understood meaning in the art."). VMware argues that DRS modules were well-known in the art as of the '842 patent's filing date. (D.I. 1094 at 131) In support, it points to testimony from earlier in this case from both Densify's Dr. Madisetti and VMware's Dr. Menascé recognizing that distributed resource schedulers, and their resource allocation function, were well-known in the art. (*Id.* at 131-32 (citing D.I. 789-2 Ex. B-1 ¶¶ 25, 30; D.I. 789-1 Ex. A-1 ¶¶ 10-13; *id.* Ex. A-2 ¶¶ 35-36); *see also* Tr. at 173 ("There is no dispute between the parties or their experts . . . that [DRS] modules were well known in the art."))

In VMware's view, the background of the '842 patent's specification provides further support, describing "[c]onventional techniques for [DRS]." (D.I. 1094 at 132) (citing '842 patent at 1:47-51) During prosecution, the applicant similarly described "conventional techniques for [DRS]." (*Id.* at 138) (citing D.I. 1032-14 Ex. U at 17304)

Densify responds that there is no discussion of what these allegedly "conventional techniques" are, and that, unlike in *M2M Solutions LLC v. Sierra Wireless America, Inc.*, 2016 WL 1298961 (D. Del. Mar. 31, 2016), upon which VMware relies, the claim here does not describe in detail how the limitation (i.e., the DRS module) works. (*See* D.I. 1094 at 136) The Court, however, is persuaded that there is sufficient evidence – including intrinsic evidence and

testimony from both parties' experts – showing that DRS modules were well-known structures in the art at the time of the '842 patent's filing. Accordingly, the patent's use of this conventional class of structures does not invoke § 112, ¶ 6, and the disputed term is not indefinite.

2. "a non-transitory computer-readable storage medium comprising instructions that, when executed in a computing device, causes the computing device to carry out the steps of"[32]

Densify This is a means-plus-function term subject to § 112, ¶ 6. The term is indefinite for lack of sufficiently definite corresponding structure. ***Functions***: the steps listed in the claim ***Structure***: Insufficient.
VMware Not a means-plus-function term subject to §112, ¶ 6 and not indefinite. As preambles, these terms are not limiting, merely identify well-known claim forms (non-transitory computer-readable storage media and computer systems), and should not be construed. If this limitation is subject to § 112, ¶ 6: ***Function***: receiving a recommended change ***Structure***: conventional software modules for receiving recommended changes to virtual environments for evaluation ***Function***: determining . . . an impact on current workload ***Structure***: conventional software for scoring recommended changes, e.g., "based on [their] improvement in the cluster imbalance metric and on its risk-adjusted costs and benefits" before the "imbalance metric is recomputed incorporating that move" ***Function***: determining . . . an impact on future workload ***Structure***: conventional software for scoring recommended changes based on a "predicted load," such as one based on a "pattern matching predictor," "'polyfit' prediction" or "simple step prediction" ***Function***: calculating . . . a combined impact on current and future workload ***Structure***: conventional software for "sum[ming]" impact scores, such as "scor[ing] as the sum of current and future impact, weighted by confidence in the future prediction" ***Function***: determining . . . that the combined impact is above a threshold

[32] This term appears in claim 12 of the '842 patent.

Structure: conventional software for comparing scores to thresholds, such as by cost benefit analysis ***Function***: perform[ing] the recommended change ***Structure***: conventional software for implementing recommended changes in a virtual environment (D.I. 1109 at 169)
Court Not a means-plus-function term subject to §112, ¶ 6 and not indefinite.

The parties agree that claim 12's preamble is limiting in that it specifies "instructions that, when executed in a computing device, cause[] the computing device to carry out the steps of" the recited method. (D.I. 1094 at 149) Densify argues that, absent the preamble's recitation of "computer-readable storage medium comprising instructions," the claim would have no structure that enables the steps set forth in the body of the claim. (*Id.* at 146) In Densify's view, this structure is insufficiently detailed such that a POSA would not have an adequate indication of the structure claimed. (*See id.*) Accordingly, despite the term's lack of the word "means," Densify believes it has overcome the presumption that § 112, ¶ 6 does not apply. (*See id.*)

The Court disagrees. This case can be distinguished from *Arendi S.A.R.L. v. LG Electronics, Inc.*, 2019 WL 3891150, at *12-13 (D. Del. Aug. 19, 2019), in which the claims provided little or no detail regarding the claimed algorithm, and "the specification include[d] no specific protocols, no flow-charts, and no other description of how the claimed 'inserting' function is to be implemented." Here, by contrast, the claim outlines a specific, detailed, multi-step set of instructions informing a POSA as to how those instructions are executed and how they interact. (*See* D.I. 1094 at 150; Tr. at 184 ("Critically, the steps are specific. The operations and objectives of the instructions are clear within the language of the claims. The inputs and outputs are also clear. . . . And each step follows from the next. It's clear from the claim language itself how they interact.")) Moreover, VMware points out that Densify has no expert support for its

position that the term lacks structure, as Densify's expert, Dr. Madisetti, was instructed to simply assume the preamble here was a means-plus-function term. (*See* D.I. 1094 at 150)

Accordingly, the Court concludes that § 112, ¶ 6 does not apply, and the disputed term is not indefinite.

3. "a virtual management computer configured to"[33]

Densify This is a means-plus-function term subject to § 112, ¶ 6. The term is indefinite for lack of sufficiently definite corresponding structure. ***Functions***: the steps listed in the claim ***Structure***: Insufficient.
VMware Not a means-plus-function term subject to §112, ¶ 6 and not indefinite. As preambles, these terms are not limiting, merely identify well-known claim forms (non-transitory computer-readable storage media and computer systems), and should not be construed. If this limitation is subject to § 112, ¶ 6: ***Function***: receiving a recommended change ***Structure***: conventional software modules for receiving recommended changes to virtual environments for evaluation ***Function***: determining . . . an impact on current workload ***Structure***: conventional software for scoring recommended changes, e.g., "based on [their] improvement in the cluster imbalance metric and on its risk-adjusted costs and benefits" before the "imbalance metric is recomputed incorporating that move" ***Function***: determining . . . an impact on future workload ***Structure***: conventional software for scoring recommended changes based on a "predicted load," such as one based on a "pattern matching predictor," "'polyfit' prediction" or "simple step prediction" ***Function***: calculating . . . a combined impact on current and future workload ***Structure***: conventional software for "sum[ming]" impact scores, such as "scor[ing] as the sum of current and future impact, weighted by confidence in the future prediction" ***Function***: determining . . . that the combined impact is above a threshold

[33] This term appears in claim 17 of the '842 patent.

***Structure*:** conventional software for comparing scores to thresholds, such as by cost benefit analysis ***Function*:** perform[ing] the recommended change ***Structure*:** conventional software for implementing recommended changes in a virtual environment (D.I. 1109 at 181)
Court Not a means-plus-function term subject to §112, ¶ 6 and not indefinite.

Densify acknowledges that the "issues with this term mirror th[ose]" of the previous term, as "a virtual management computer configured to" appears in the preamble of claim 17 and precedes identical instructions. (D.I. 1094 at 153) Accordingly, the Court reaches the same conclusion here. Section 112, ¶ 6 does not apply, and the disputed term is not indefinite.

4. "a combined impact on current and future workload"[34]

Densify Indefinite for failure to point out with particularity and distinctly claim the subject matter such that one of ordinary skill in the art would be reasonably apprised of the bounds of the asserted claims.
VMware Not indefinite. These terms should not be construed as they take their plain and ordinary meaning.
Court Not indefinite. Plain and ordinary meaning.

In response to Densify's indefiniteness arguments (*see, e.g.*, D.I. 1094 at 156), VMware points out that this claim term uses ordinary English words – "impact," "current," "future," "combined," and "workload" – and should take its plain meaning, consistent with the claim language and specification. (*See id.* at 155, 157) The claims, for example, explain what is needed to calculate the "combined impact" – the determined "impact on current workload" from

[34] This term appears in claims 1, 12, and 17 of the '842 patent.

performing a recommended change and the determined "impact on future workload" from performing a recommended change – and require that the result must be an "impact" comparable to a threshold. (*Id.* at 157-58; '842 patent cls. 1, 12, 17) Figure 5 of the patent discloses an example of this process, and the specification describes exemplary "impacts," including "improvement in the cluster imbalance metric" and "improved performance" resulting from performing a recommended change. (*See* '842 patent fig. 5, 9:15-17, 10:17-19)

In Densify's view, however, the disclosures regarding how to combine impacts in cases in which one or both workloads are negatively impacted are "opaque and inconsistent." (D.I. 1094 at 157) For example, the patent discloses embodiments in which the performed change would "improve current, but hurt future cluster imbalance" or "hurt current but improve future cluster imbalance." ('842 patent at 9:59-67) In such scenarios, the patent teaches that consideration of the combined impact may involve a "cost-benefit analysis" or may be "challenging to analyze." (*Id.*)

The Court agrees with VMware that the examples in the specification on which Densify relies "simply address different ways in which the impacts on current and future workloads might be considered." (D.I. 1094 at 158) The existence of some imprecision or variation in the specification relating to the ways in which "combined impact" is calculated does not compel a finding of indefiniteness. Instead, the plain meaning of the term, which is consistent with the claim language and specification, provides a POSA with reasonable certainty as to the bounds of the asserted claims at issue. (*See* D.I. 1095-1 Ex. A-20 ¶¶ 55-59) Densify has not proven indefiniteness by clear and convincing evidence.

IV. CONCLUSION

An appropriate Order follows.

EXHIBIT G

WILEY ELECTRICAL AND ELECTRONICS ENGINEERING DICTIONARY

Steven M. Kaplan
Lexicographer

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WILEY-INTERSCIENCE
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10 9 8 7 6 5 4 3 2 1

synchroscope A device or instrument which indicates whether two values, magnitudes, voltages, frequencies, phases, or the like, are synchronized. An oscilloscope, for instance, may indicate the synchronization, or any difference in phases, frequencies, or the like which are being monitored. Used, for instance, to verify that two or more generators are in phase.

synchrotron A particle accelerator similar to a cyclotron, and in which the frequency of the field is adjusted so as to compensate for the increased mass of the particles as their speed approaches that of light. A proton synchrotron accelerates protons, an electron synchrotron accelerates electrons, and there are specialized variations, such as tevatrons, which can generate energies in excess of 1 TeV.

synchrotron radiation The electromagnetic radiation emitted by charged particles which are moving within a magnetic field at speeds approaching that of light. This is observed, for instance, in a synchrotron.

syntax **1.** In a natural language, the rules which describe how words and phrases are combined to form expressions and sentences. Such rules are taken into account, for instance, in voice-recognition programs. **2.** The rules which determine how statements are formed, so as to be understood by a given computer program.

syntax error An error in a computer program arising from the improper use **syntax (2)**.

synthesis The proper combination of elements, components, substances, and so on, to form a given whole. Examples include the synthesis of digital speech, musical sounds, circuits with a given response, or chemical compounds.

synthesis telescope A computer-controlled telescope which utilizes two or more pairs of antennas which sequentially cover sections of the total aperture, in order to gather the information equivalent to that obtained by a much larger single telescope. Also called **aperture synthesis telescope**.

synthesize To unite the proper combination of elements, components, substances, and so on, to form a given whole.

synthesizer **1.** That which serves to **synthesize**. **2.** A circuit or device which generates precise frequency signals. Such a device usually utilizes one or more crystal oscillators, and can generate equally-spaced frequencies within a given band through the use of frequency multipliers, dividers, mixers, and so on. Also called **frequency synthesizer**. **3.** A device which electronically generates or reproduces sounds that emulate musical instruments and voices, and which can be utilized to compose, play, and record music. A keyboard, real or virtual, is usually used, and two common techniques for generating sounds are FM synthesis and wavetable synthesis. Also called **music synthesizer**.

synthetic **1.** Pertaining to, characteristic of, involving, or arising from **synthesis**. **2.** Produced by synthesis, especially that which is artificial. Examples include synthetic radioactive chemical elements, resins, plastics, crystals, fibers, rubbers, polymers, and so on.

synthetic aperture radar An airborne radar that emits microwave energy along a given path, and which utilizes the Doppler effect to process the phase of the returned radar signals. Such a radar effectively synthesizes the equivalent of a very long aperture, and is used, for instance, for ground mapping. Its abbreviation is **SAR**.

synthetic voice Simulation of a human voice through the use of a device which incorporates a loudspeaker and a computer. Used, for example, in robotics, or to assist those with reduced speech abilities.

syntonic Pertaining to two oscillating circuits which have the same resonant frequency.

syntony The circumstance of two oscillating circuits having the same resonant frequency.

sysadmin Acronym for **system administrator**.

sysop Acronym for **system operator**.

SysReq Same as **SysRq**.

SysReq key Same as **SysRq**. Abbreviation of **System Request key**. Also spelled **SysRq key**.

SysRq Abbreviation of **System Request**. On many computer keyboards, a key intended to access specific operating system functions. Such a key is sometimes programmed to perform special functions within a given operating system environment or application. Also spelled **SysReq**. Also called **SysRq key**.

SysRq key Same as **SysRq**. Abbreviation of **System Request key**. Also spelled **SysReq key**.

system **1.** A set of interrelated and/or interdependent components which form a complex whole serving for one or more purposes or functions. There are countless examples, including control, sound, expert, radar, alarm, computer, carrier, biometric, and satellite systems. **2.** A **system (1)** incorporating components which are mechanical, electrical, electronic, magnetic, optical, and so on, or any combination of these. For instance, electromechanical, optoelectronic, or magnetohydrodynamic systems. **3.** A set of objects, entities, characteristics, phenomena, or rules, utilized to describe, classify, organize, compare, or analyze. For example, a system which enables the precise specification and comparison of colors, a scale which allows the classification of materials according to their resistance to scratching or denting, a coordinate system, or a quantum system. **4.** A set of related objects, entities, characteristics, or phenomena, which occur naturally, such as a solar system. **5.** A set of components, including equipment, media, and channels, which incorporate all that is necessary for any form of communication from one or more points to others. For example, telephone, TV, or radio systems, computer networks, and so on. **6.** The complete complement of components required for a computer to function. These include the CPU, keyboard, mouse, monitor, memory, storage mediums, cables, and so on, which comprise the hardware of the computer itself, plus any necessary peripheral devices. In addition, a computer system incorporates the operating system. Also called **computer system**.

system administration The functions performed by a **system administrator**. These include the allocation of resources, security, maintenance, improvements, and the like.

system administrator A person who is responsible for, supervises, and/or manages a computer or communications network. Its acronym is **sysadmin**.

system analysis Same as **systems analysis**.

system analysis and design Same as **systems analysis**.

system-area network A high-speed network which serves to link processors, I/O systems, or servers. Its acronym is **SAN**.

system basic input/output system Same as **system BIOS**.

system BIOS Acronym for **system basic input/output system**. **1.** A set of indispensable software routines that enable a computer to boot itself. It has the code necessary to control all peripherals and perform other functions, such as testing, and is generally stored on a ROM chip so that disk failures do not disable it. Currently, it is usually contained in a flash-memory chip, and is typically copied to the RAM at startup, as RAM is faster. Also called **BIOS**. **2.** The **system BIOS (1)** of a computer which is contained in the motherboard, as opposed to that contained in a peripheral.

system board The main circuit board of a computer, containing the connectors necessary to attach additional boards. It contains most of the key components of the system, and incorporates the CPU, bus, memory, controllers, expansion slots, and so on. Memory chips may be added to it, and some motherboards allow for the CPU to be replaced. Also called **motherboard**, **mainboard**, or **backplane (2)**.

EXHIBIT H

US007765106B2

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

(10) **Patent No.: US 7,765,106 B2**
(45) **Date of Patent: *Jul. 27, 2010**

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

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

(73) Assignee: **JPI Commercial, LLC**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1645 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/979,665**

(22) Filed: **Nov. 2, 2004**

(65) **Prior Publication Data**

US 2005/0090425 A1 Apr. 28, 2005

Related U.S. Application Data

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

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

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

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

See application file for complete search history.

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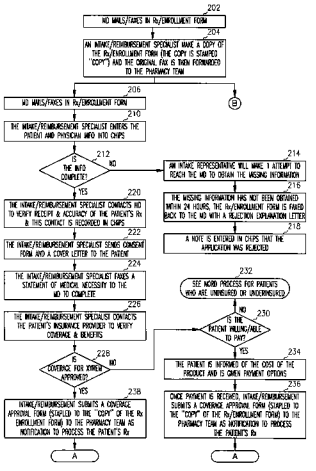
Primary Examiner—Gerald J. O'Connor
Assistant Examiner—Lena Najarian
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg & Woessner, P.A.

(57) **ABSTRACT**

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

8 Claims, 16 Drawing Sheets



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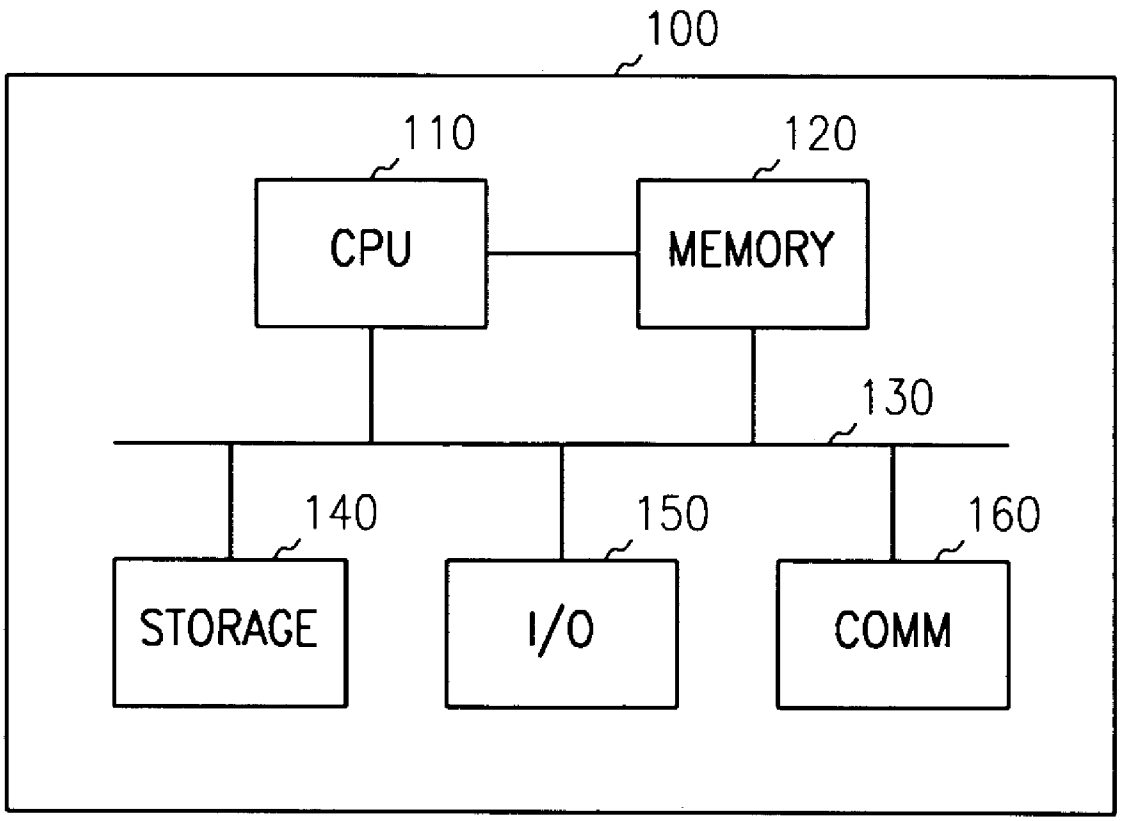


FIG. 1

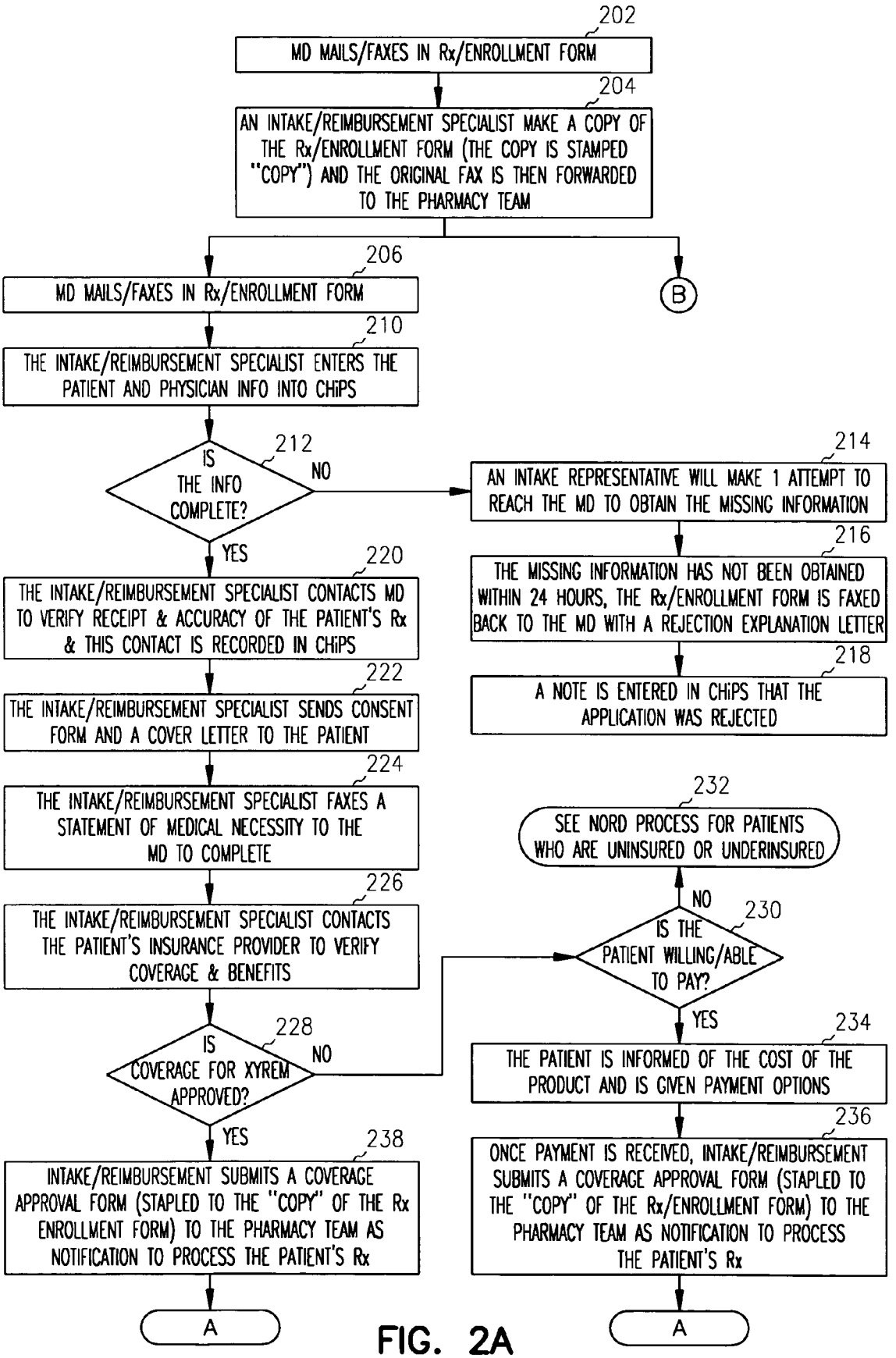

202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHiPS
212
IS THE INFO COMPLETE?
NO
YES
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
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

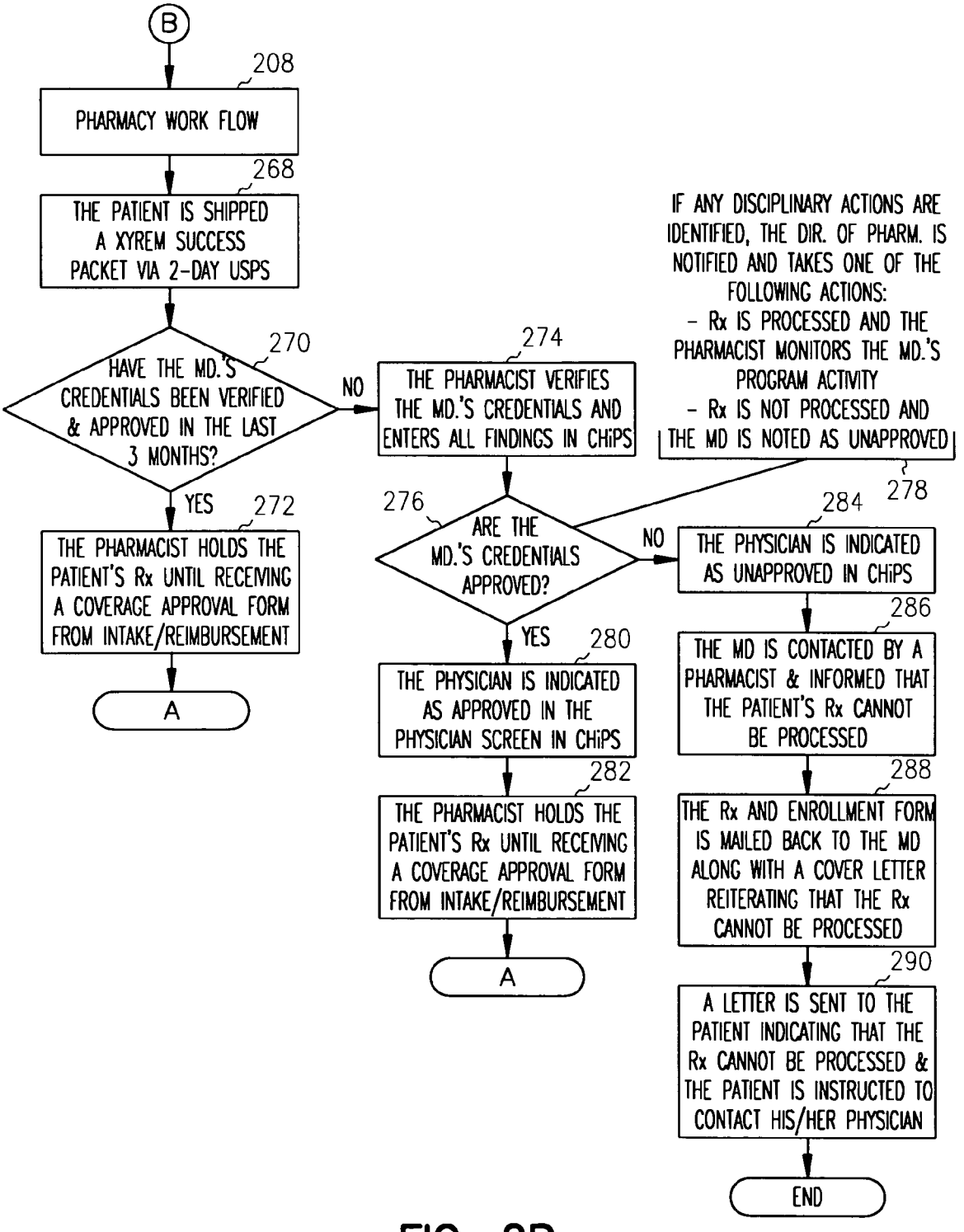

B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHiPS
276
ARE THE MD.'S CREDENTIALS APPROVED?
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
NO
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

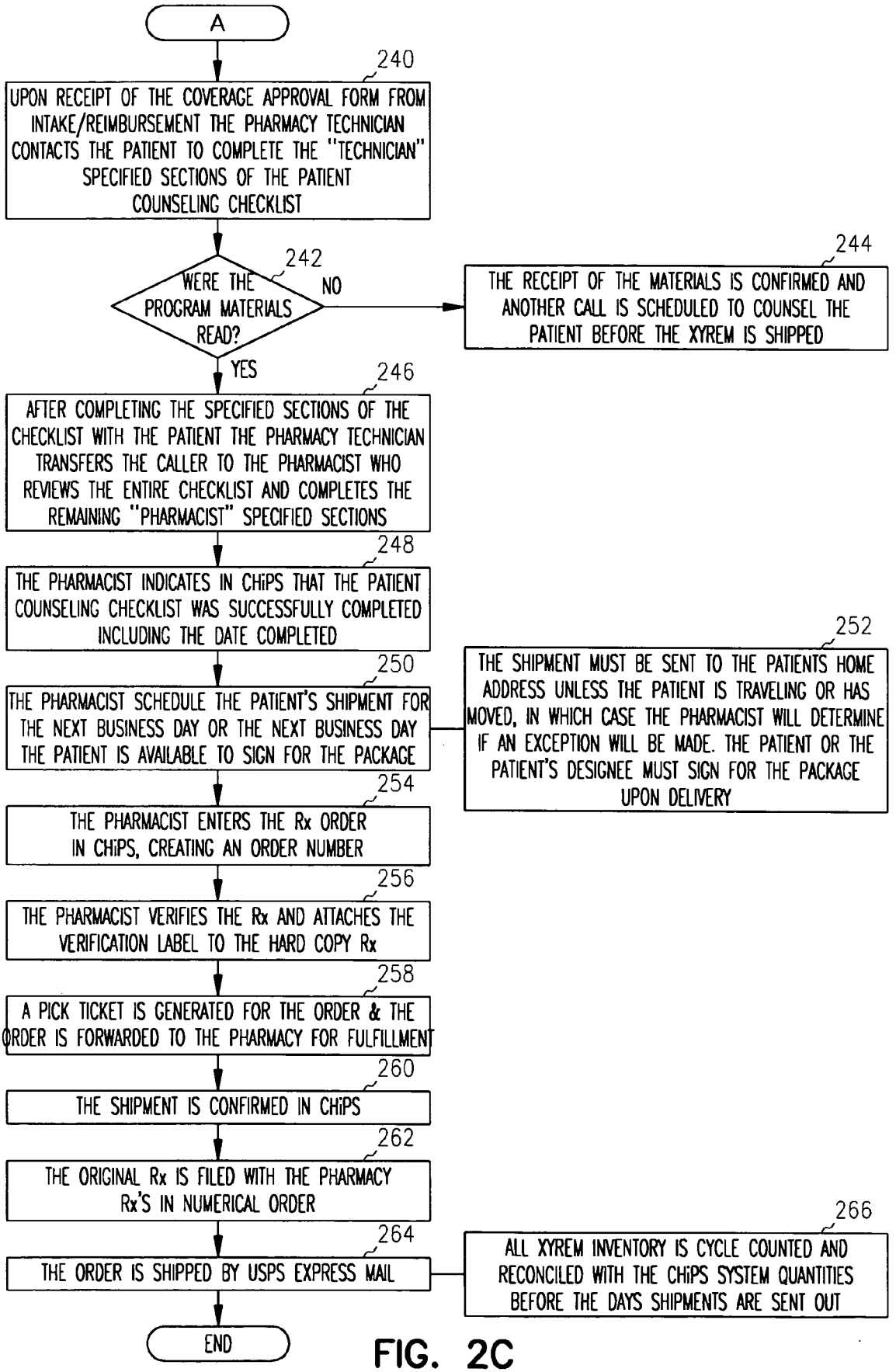

A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER 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

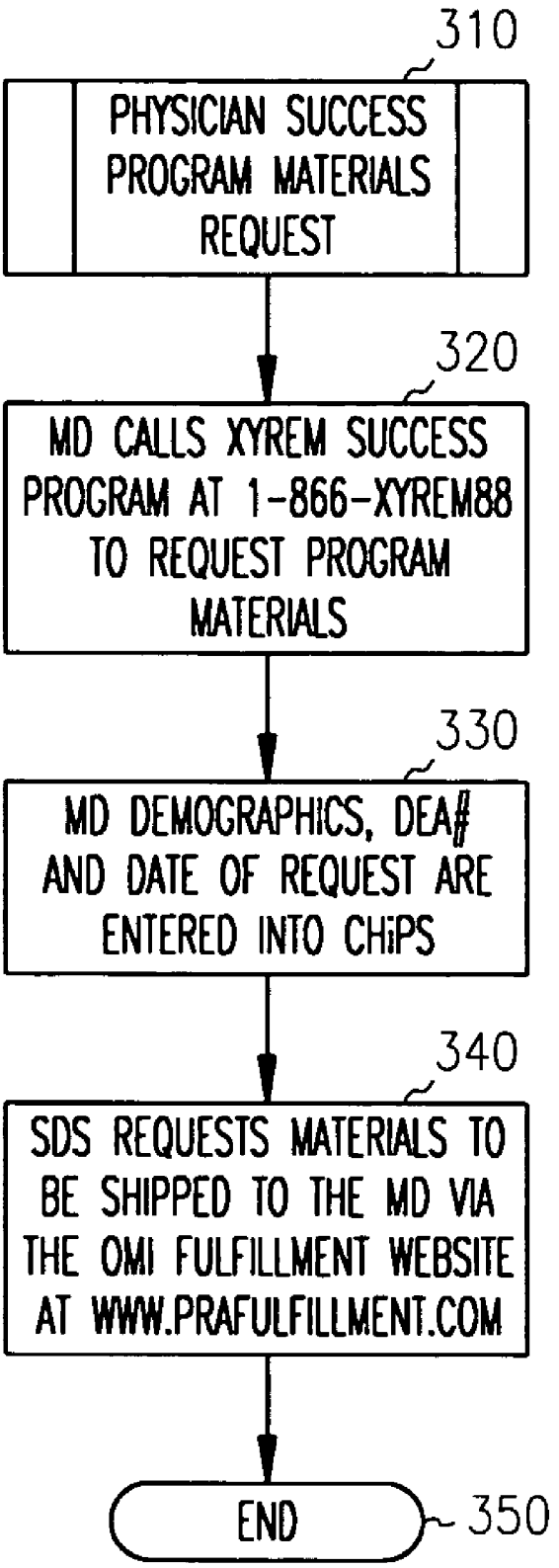

310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHiPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM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

FIG. 3

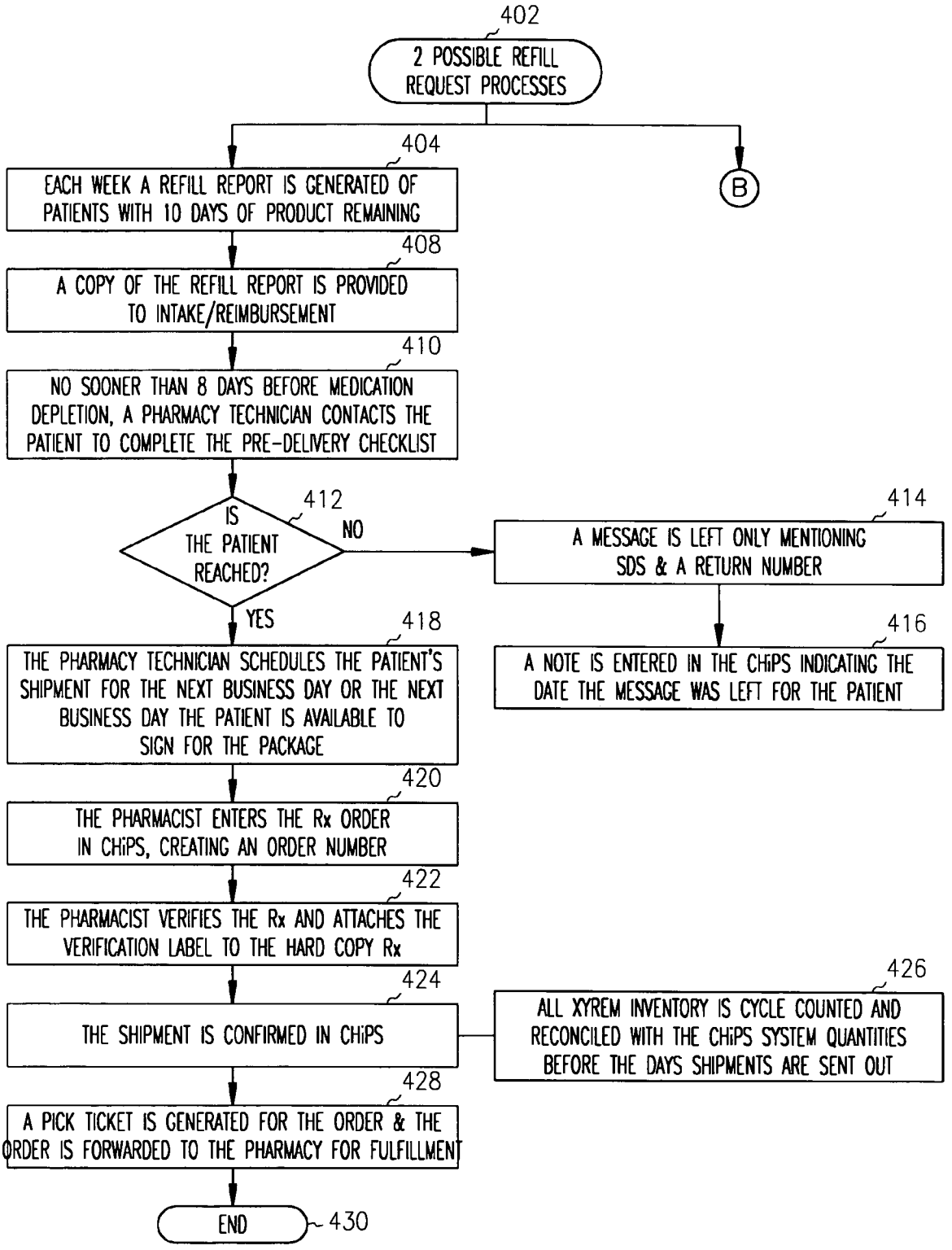

402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE 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

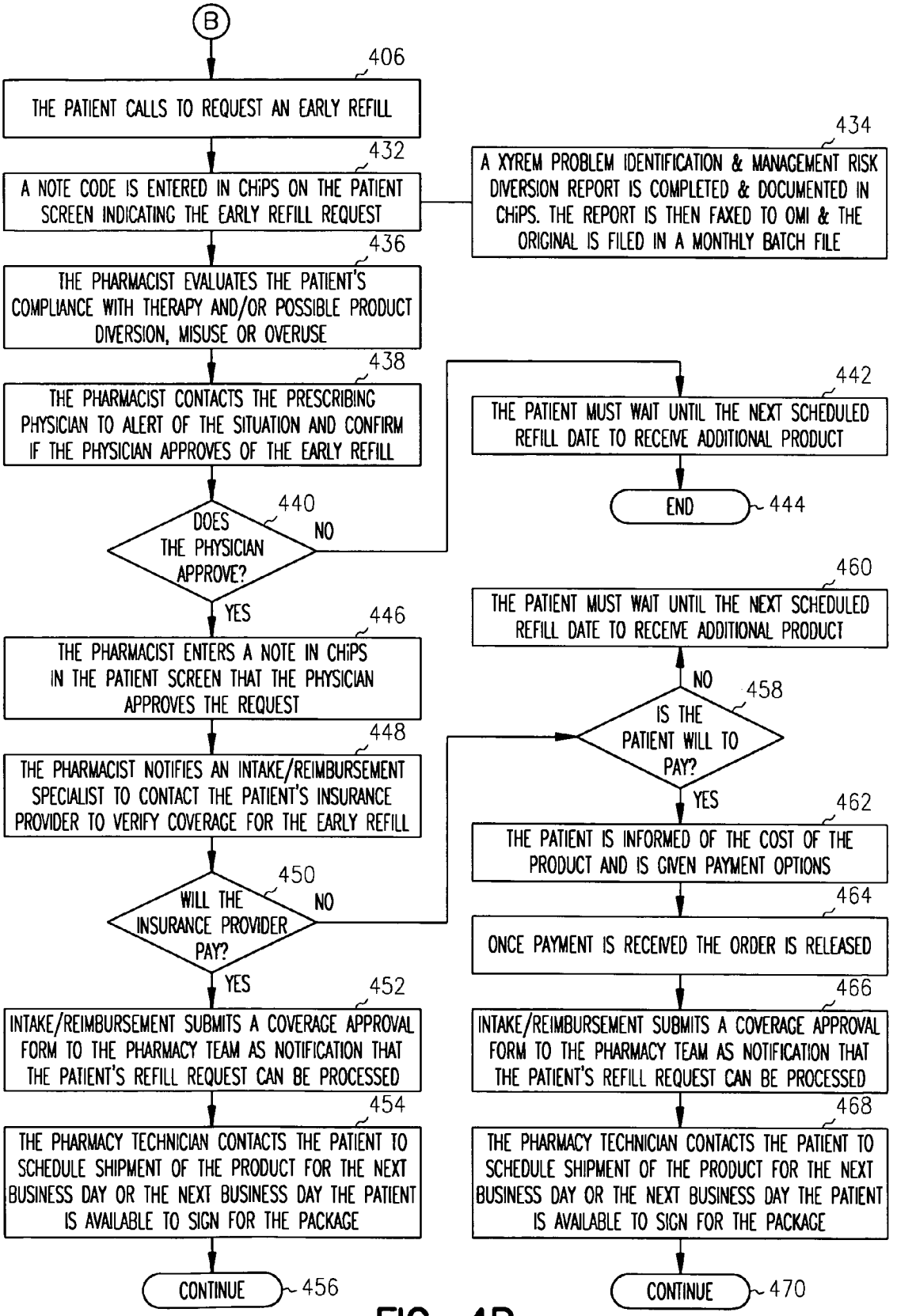

B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYREM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS 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
YES
452
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
464
ONCE PAYMENT IS RECEIVED THE ORDER IS RELEASED
466
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
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

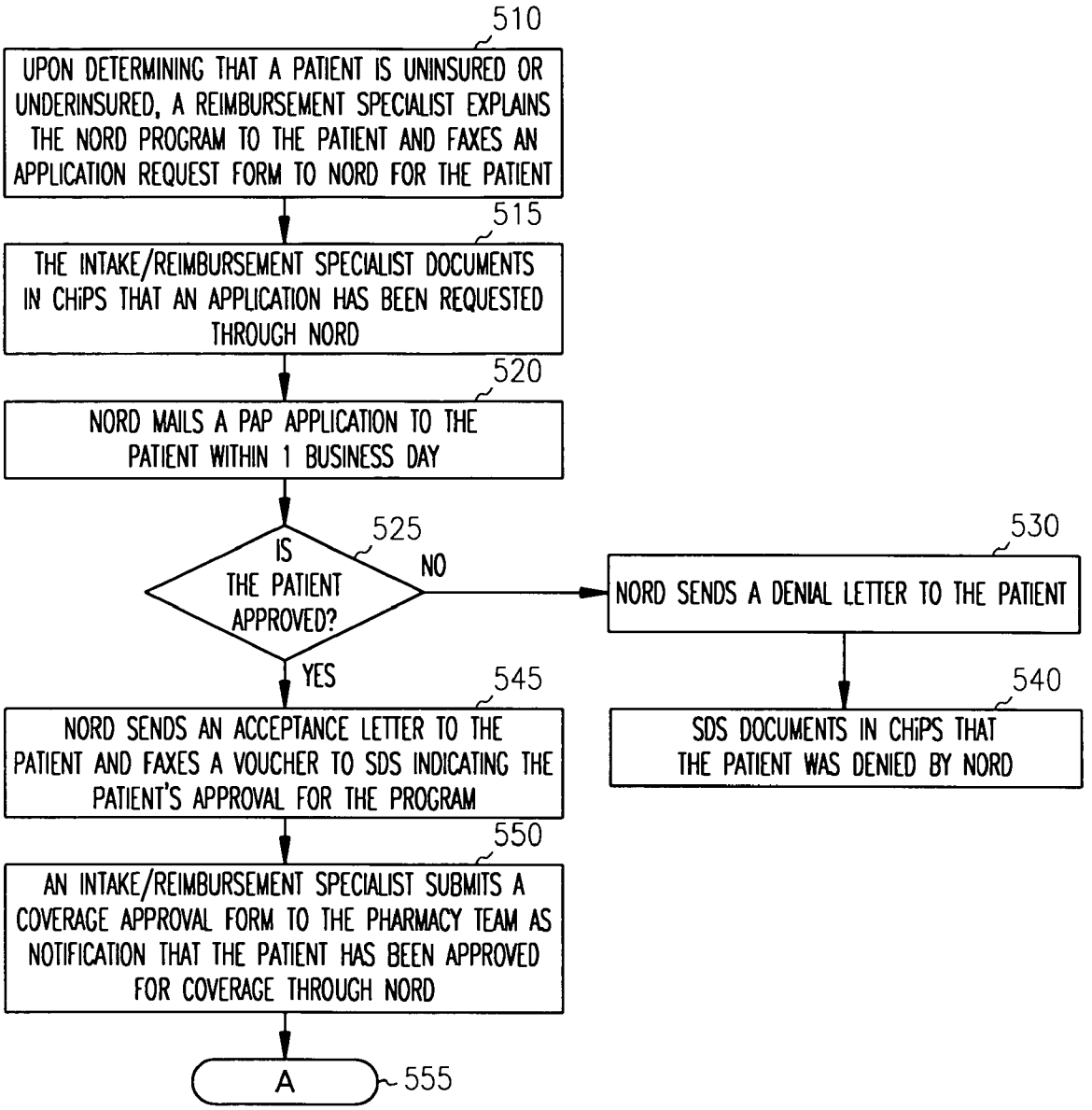

510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHiPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH 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

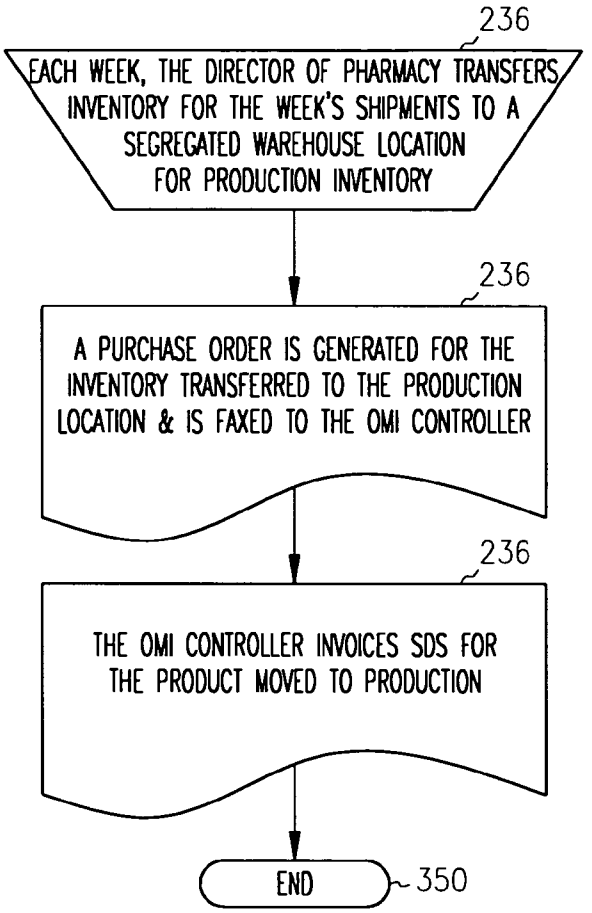


FIG. 6

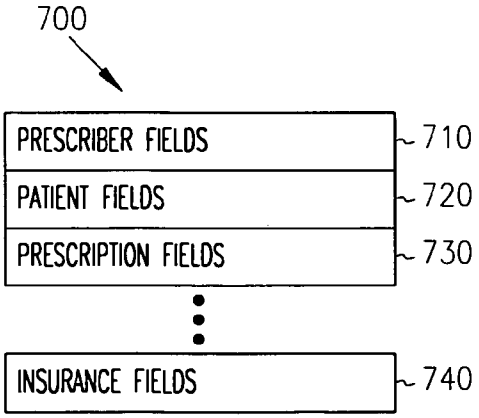


FIG. 7

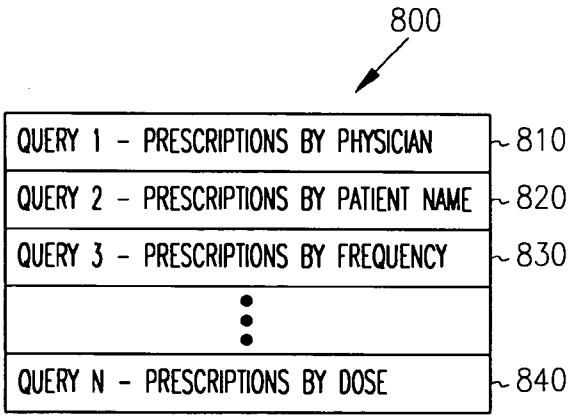


FIG. 8

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
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

CASE CODE: ********

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

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml btl	1

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

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

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

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

CASE CODE: ********

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

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

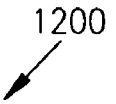
DRUG	QUANTITY
XYREM 180ml btl	1

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

APPROVED _____

PHARMACY USE

FIG. 11



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		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 APPLICATIONS

This application is a divisional application of U.S. patent application Ser. No. 10/322,348, filed Dec. 17, 2002, now U.S. Pat. No. 7,668,730 which application is incorporated herein by reference.

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 ensure that they are not abuse and 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 theraputic 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 coveral 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 an reconciled with the database system quantities before shipments for the day are sent. This provides a very precise control of the inventor.

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 therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and from any and all doctors allowed to prescribe the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is prescribing the prescription drug;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using said exclusive central computer system, the controls selected

from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug.

2. The method of claim **1** , wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

3. A therapeutic method for treating a narcoleptic patient with sodium oxybate for daytime cataplexy comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed sodium oxybate and from any and all medical doctors allowed to prescribe sodium oxybate, the prescriptions containing information relating to the patient, sodium oxybate, and various credentials of the medical doctor who is prescribing the sodium oxybate;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion, such that all prescriptions for sodium oxybate are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of sodium oxybate using the exclusive central computer system that tracks all prescriptions of sodium oxybate and analyzes for the potential abuse, misuse, or diversion by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of sodium oxybate from periodic reports generated by the exclusive central computer system based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, sodium oxybate as the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using said exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe sodium oxybate by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for sodium oxybate that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the sodium oxybate to the patient in order to treat the patient with the sodium oxybate.

4. The method of claim **3**, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the

patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

5. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive computer database in a computer system, from any and all medical doctors allowed to prescribe the prescription drug and any and all patients being prescribed the prescription drug, all prescriptions for the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is prescribing the prescription drug;

requiring entering of the information into the exclusive computer database for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only via the exclusive computer database;

controlling the distribution of said prescription drug with the computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the computer system based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution of the prescription drug, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive computer database; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing the release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive computer database, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug.

6. The method of claim **5**, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive computer database; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

7. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and any and all medical doctors allowed to prescribed the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is writing the prescription;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using the exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information;

verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials;

verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug.

8. The method of claim **7**, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,765,106 B2
APPLICATION NO. : 10/979665
DATED : July 27, 2010
INVENTOR(S) : Dayton T. Reardan et al.

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

In column 12, lines 20-67, column 13, lines 1-20, column 14, lines 1-7, in Claim 7, delete "7. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and any and all medical doctors allowed to prescribed the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is writing the prescription;

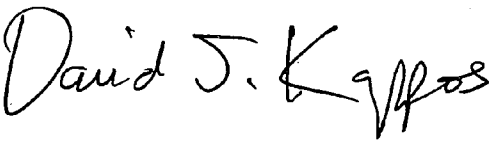
requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using the exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information;

verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug;

Signed and Sealed this

Twenty-third Day of November, 2010



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

confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug." and

insert -- 7. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and any and all medical doctors allowed to prescribed the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is writing the prescription;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using the exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical 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. --, therefor.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,765,106 B2
APPLICATION NO. : 10/979665
DATED : July 27, 2010
INVENTOR(S) : Dayton T. Reardan et al.

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

Delete the Title Page showing an illustrative figure, and substitute the attached Title Page therefor.

Delete Sheet 2 of 16 showing Fig. 2A, and substitute the attached sheet therefor.

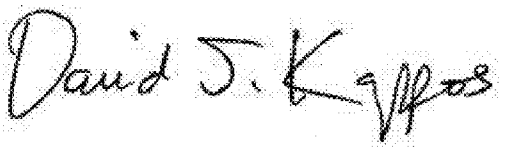
On Sheet 10 of 16, in Figure 9, line 23, after "ESTABLISHED" insert -- . --.

In column 1, line 27, delete "buterate" and insert -- butyrate --, therefor.

In column 1, line 28, delete "theraputic" and insert -- therapeutic --, therefor.

In column 4, line 65, delete "coveral" and insert -- coverage --, therefor.

Signed and Sealed this
Fifteenth Day of February, 2011



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

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

(10) **Patent No.: US 7,765,106 B2**
(45) **Date of Patent: *Jul. 27, 2010**

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

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

(73) Assignee: **JPI Commercial, LLC**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1645 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/979,665**

(22) Filed: **Nov. 2, 2004**

(65) **Prior Publication Data**

US 2005/0090425 A1 Apr. 28, 2005

Related U.S. Application Data

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

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

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

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

See application file for complete search history.

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6,347,329	B1	2/2002	Evans	
6,564,121	B1	5/2003	Wallace et al.	
6,687,676	B1	2/2004	Denny	
6,755,784	B2	6/2004	Williams et al.	
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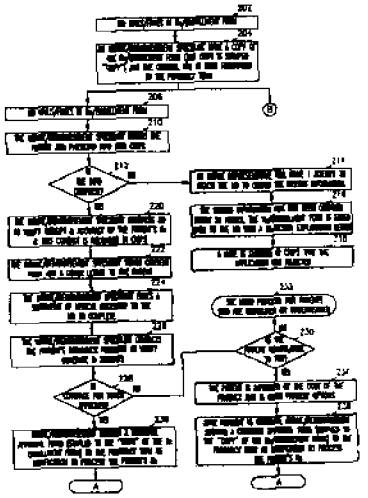
Primary Examiner—Gerald J. O'Connor
Assistant Examiner—Lena Najarian
(74) *Attorney, Agent, or Firm*— Schwegman, Lundberg & Woessner, P.A.

(57) **ABSTRACT**

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

8 Claims, 16 Drawing Sheets



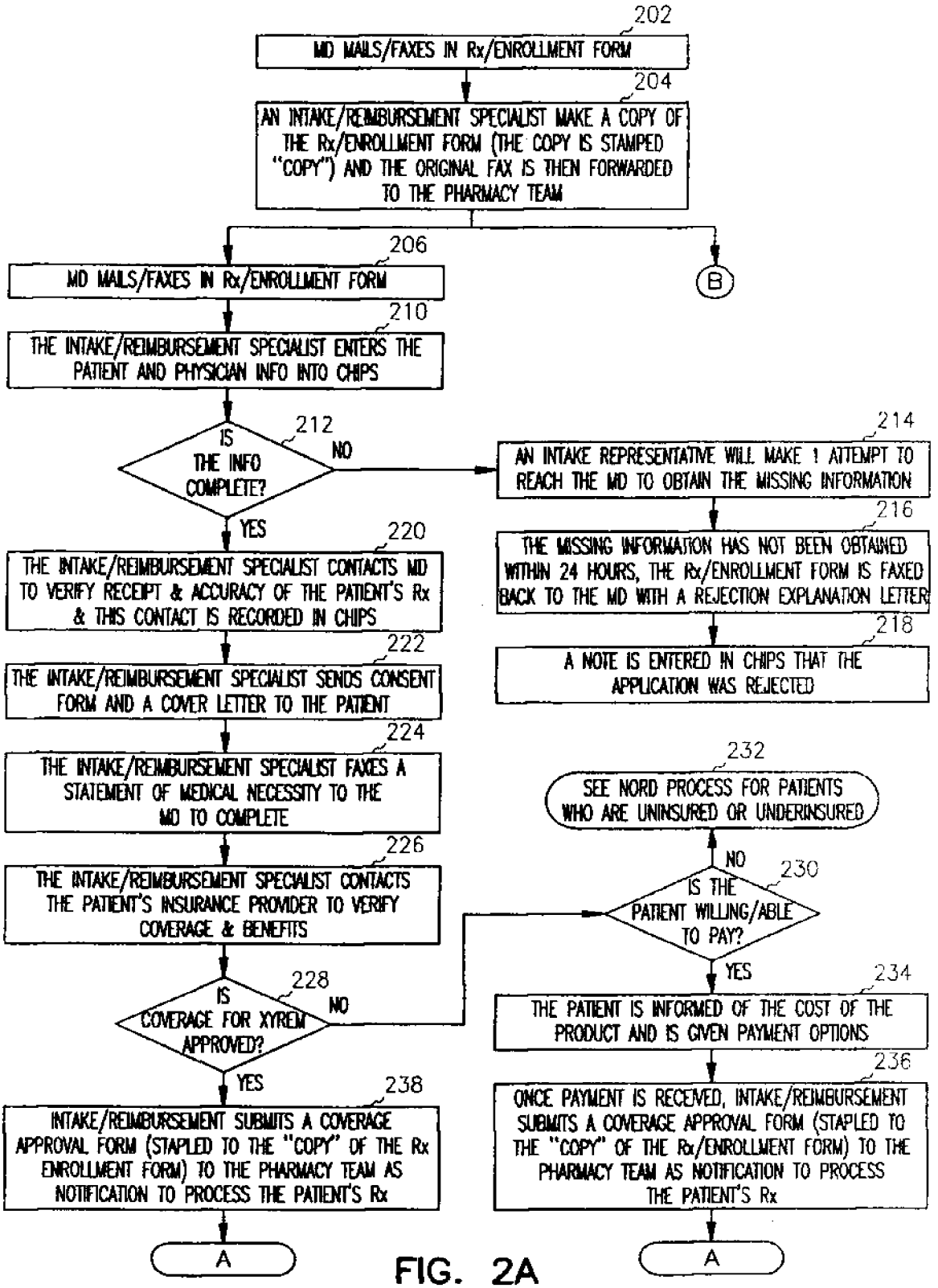

202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHIPS
212
IS THE INFO COMPLETE?
NO
214
AN INTAKE REPRESENTATIVE WILL MAKE 1 ATTEMPT TO REACH THE MD TO OBTAIN THE MISSING INFORMATION
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
YES
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
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
A

FIG. 2A

EXHIBIT I

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.

(56) **References Cited**

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5,737,539	A	4/1998	Edelson et al.
5,845,255	A	12/1998	Mayaud
5,924,074	A	7/1999	Evans
6,021,392	A	2/2000	Lester et al.
6,045,501	A	4/2000	Elsayed et al.
6,055,507	A	4/2000	Cunningham
6,112,182	A	8/2000	Akers et al.
6,315,720	B1	11/2001	Williams et al.
6,347,329	B1	2/2002	Evans
6,561,977	B2	5/2003	Williams et al.
6,564,121	B1	5/2003	Wallace et al.
6,755,784	B2	6/2004	Williams et al.
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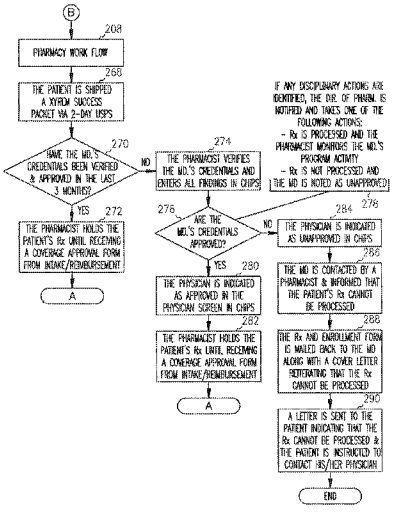
Primary Examiner — Lena Najarian
(74) *Attorney, Agent, or Firm* — Schwegman Lundberg & Woessner, P.A.

(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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"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)), (Dec. 5, 2011), 37 pgs.
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"U.S. Appl. No. 13/592,202, Restriction Requirement mailed Jan. 16, 2013", 6 pgs.
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"Civil Cover Sheet", *Jazz Pharmaceuticals, Inc.* v. *Amneal Pharmaceuticals, LLC*, (United States District Court, District of New Jersey, (Jan. 18, 2013), 2 pgs.
"Complaint for Patent Infringement", *Jazz Pharmaceuticals, Inc.* v. *Amneal Pharmaceuticals, LLC*, (United States District Court, District of New Jersey, (Jan. 18, 2013), 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, (Dec. 12, 2012), 3 pgs.
"Detailed Factual and Legal Basis of Non-Infringement and/or Invalidity", Amneal Pharmaceuticals, LLC, (Dec. 7, 2012), 6 pgs.
"Exhibits A-D", *Jazz Pharmaceuticals* v *Amneal Pharmaceuticals, LLC*, (Jan. 18, 2013), 151 pgs.
"Exhibits D-G", *Jazz Pharmaceuticals* v *Amneal Pharmaceuticals, LLC*, (Jan. 18, 2013), 123 pgs.
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"Making Good in Your Own Mail-Order Business", Changing Times—The Kiplinger Magazine, (Oct. 1980), 66-68.
"Markman Opinion, filed Sep. 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)", (Sep. 14, 2012), 43 pgs.
"Notice of Electronic Filing: Civil Inital Pleadings (Attorney/Credit Card) USE CASE 33-1", US District Court, District of new Jersey [LIVE], (Jan. 18, 2013), 2 pgs.
"Notice of Paragraph IV Certification Concerning ANDA 203631 for Sodiium Oxybate Oral Solution, 500 mg/mL", Amneal Pharmaceuticals, LLC, (Dec. 7, 2012), 4 pgs.
"Notice of Paragraph IV Certification Concerning ANDA 203631 for Sodiium Oxybate Oral Solution. 500 mg/mL", Amneal Pharmaceuticals, LLC, (Dec. 12, 2012), 4 pgs.
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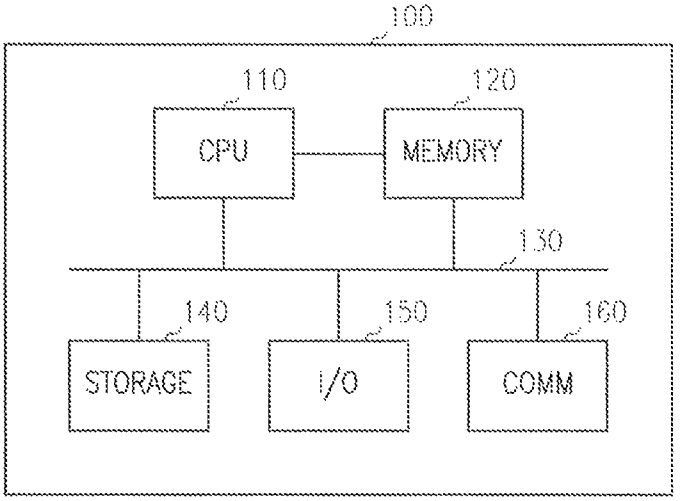


FIG. 1

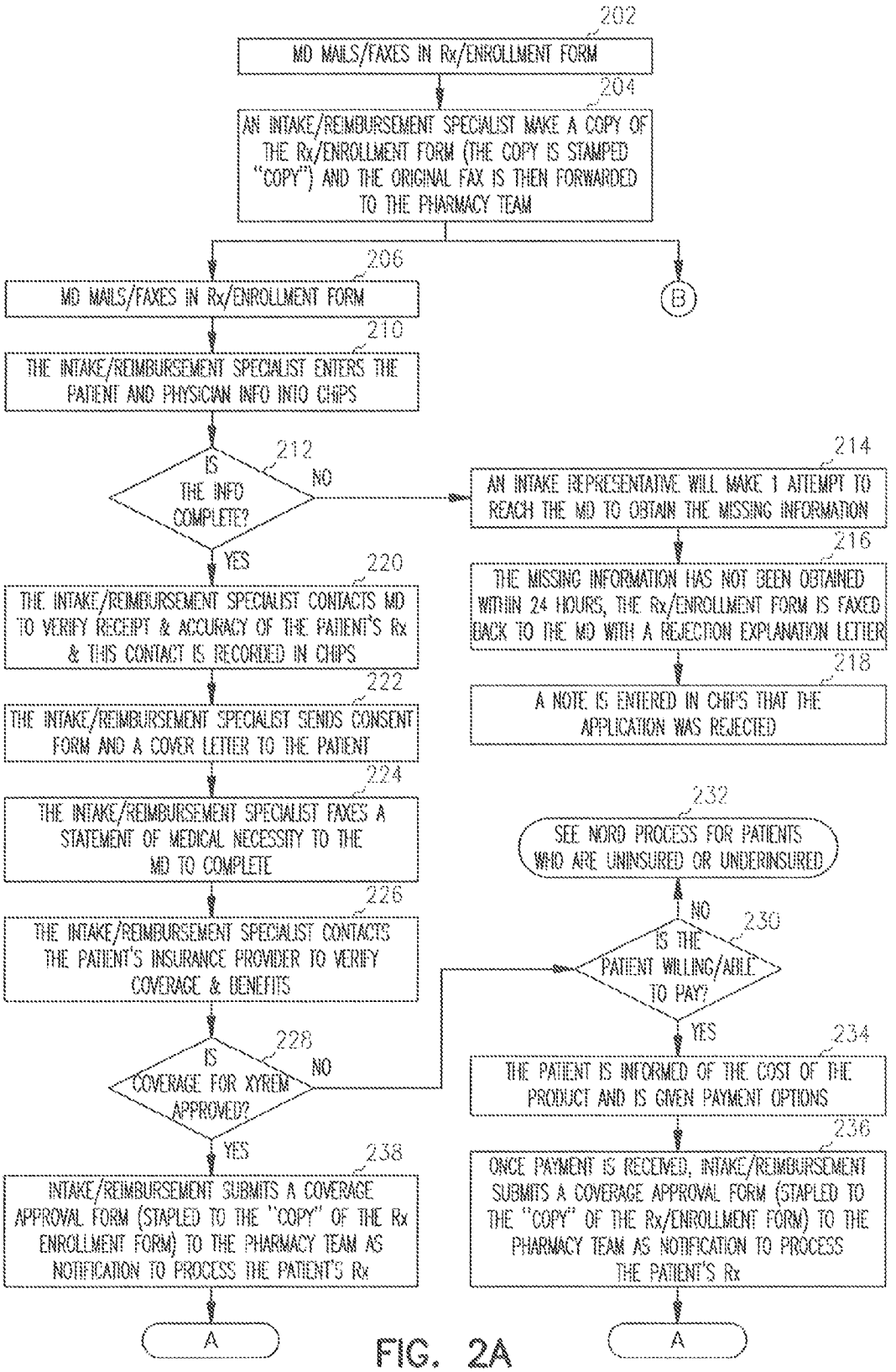

202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE 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
232
SEE NORD PROCESS FOR PATIENTS WHO ARE UNINSURED OR UNDERINSURED
NO
230
IS THE PATIENT WILLING/ABLE TO PAY?
YES
234
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
236
ONCE PAYMENT IS RECEIVED, INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx/ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
YES
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
A

FIG. 2A

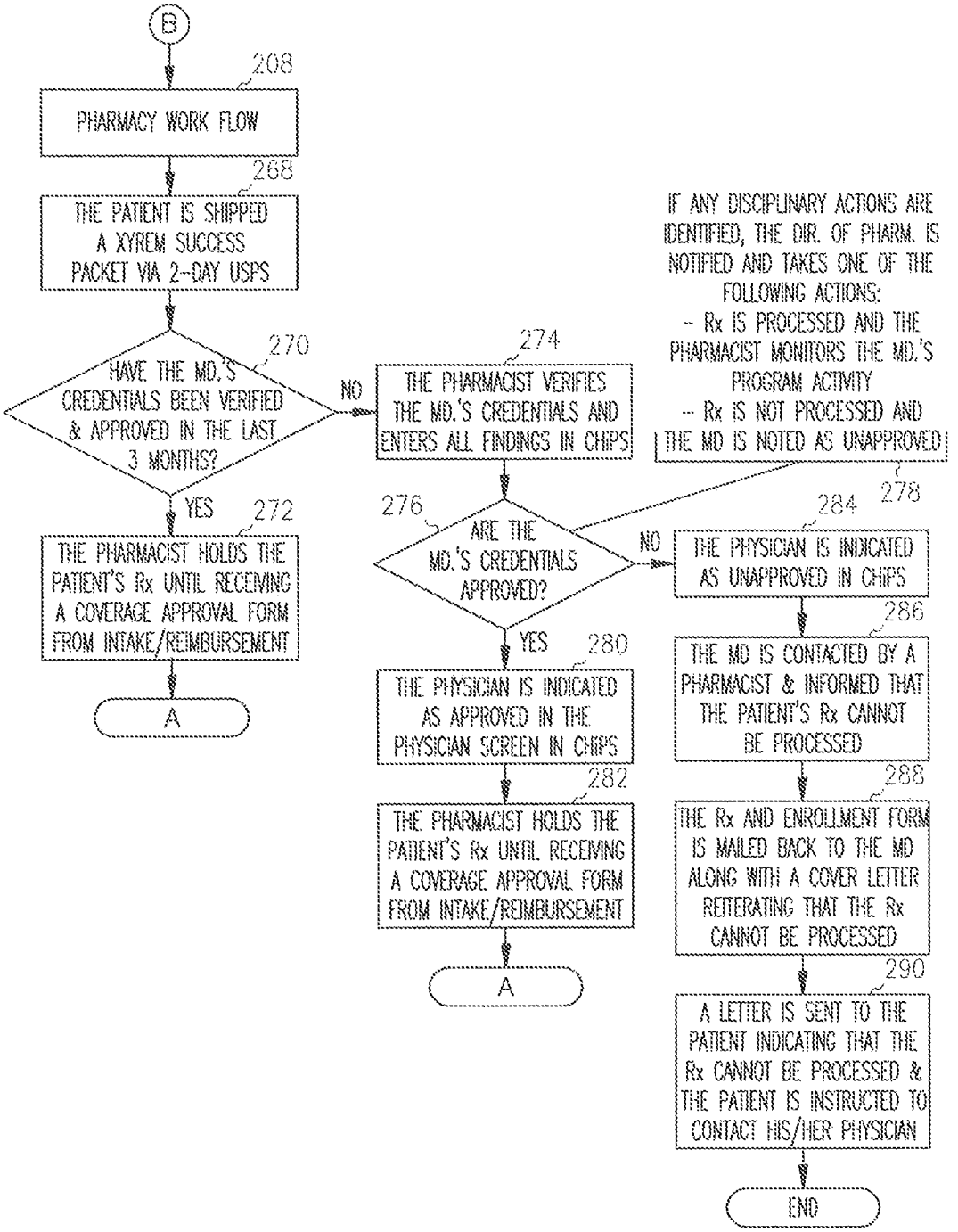

B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHIPS
IF ANY DISCIPLINARY ACTIONS ARE IDENTIFIED, THE 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
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
276
ARE THE MD.'S CREDENTIALS APPROVED?
NO
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
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

FIG. 2B

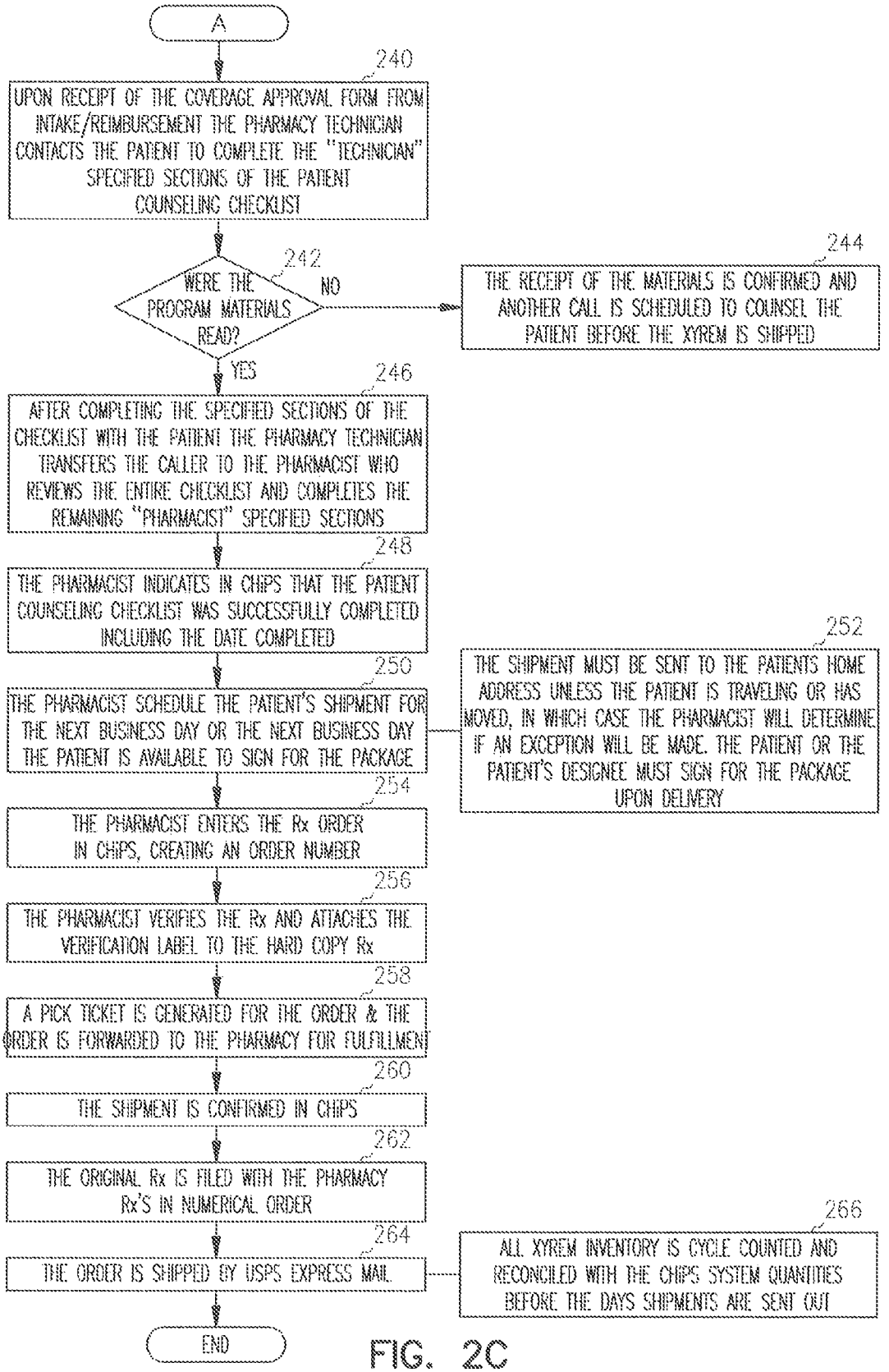

A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER 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

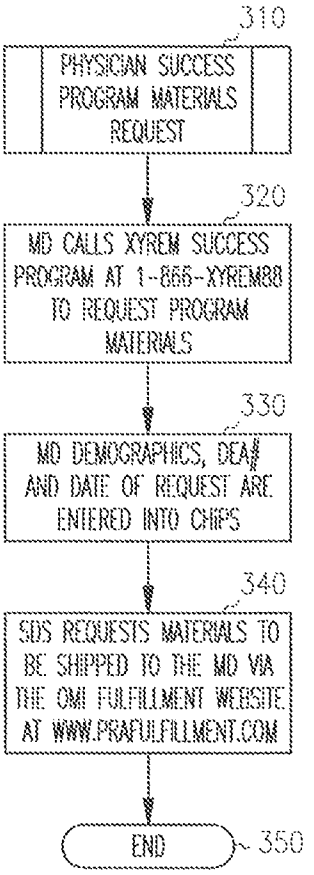

310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHP'S
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM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

FIG. 3

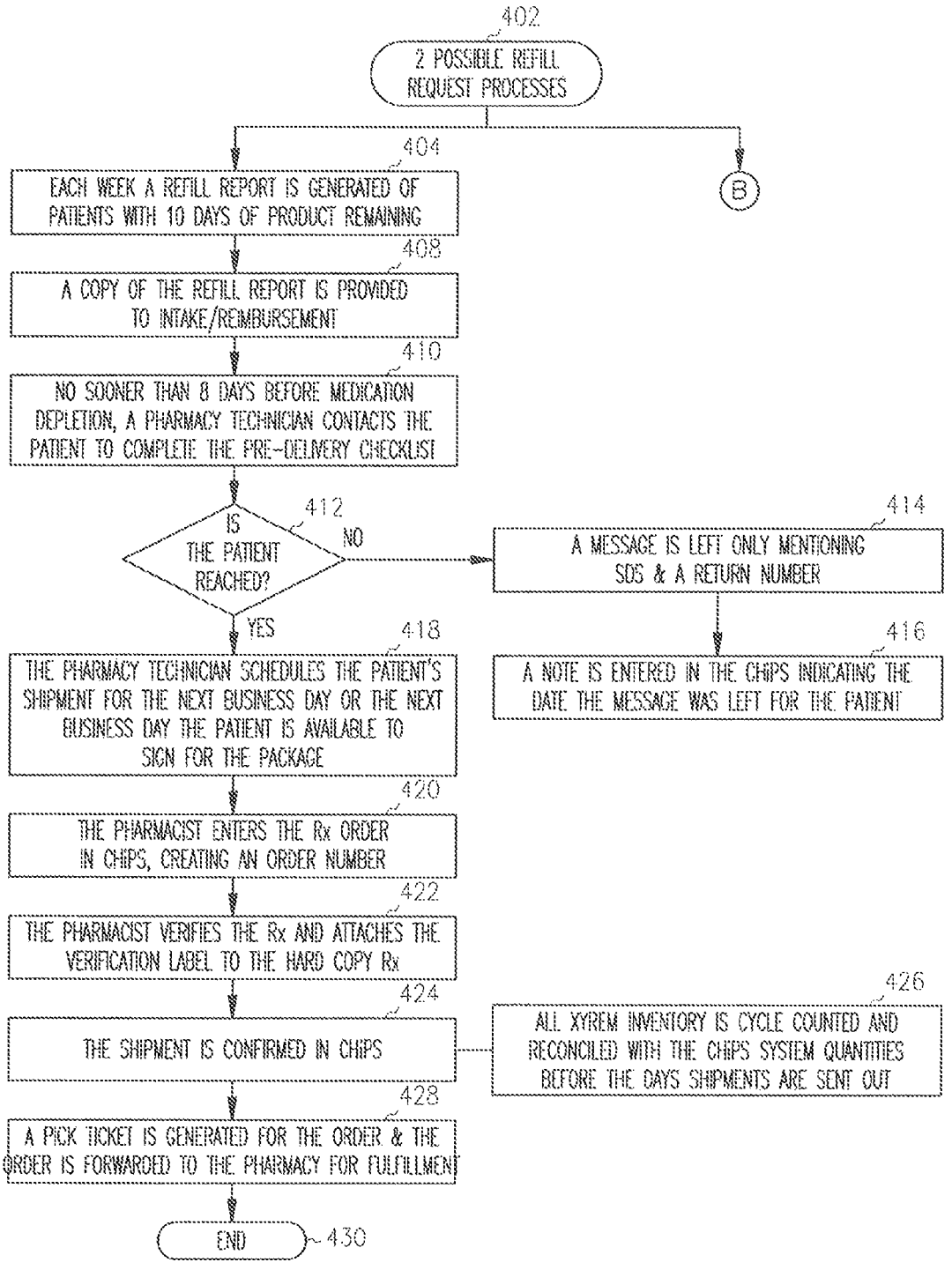

402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE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

FIG. 4A

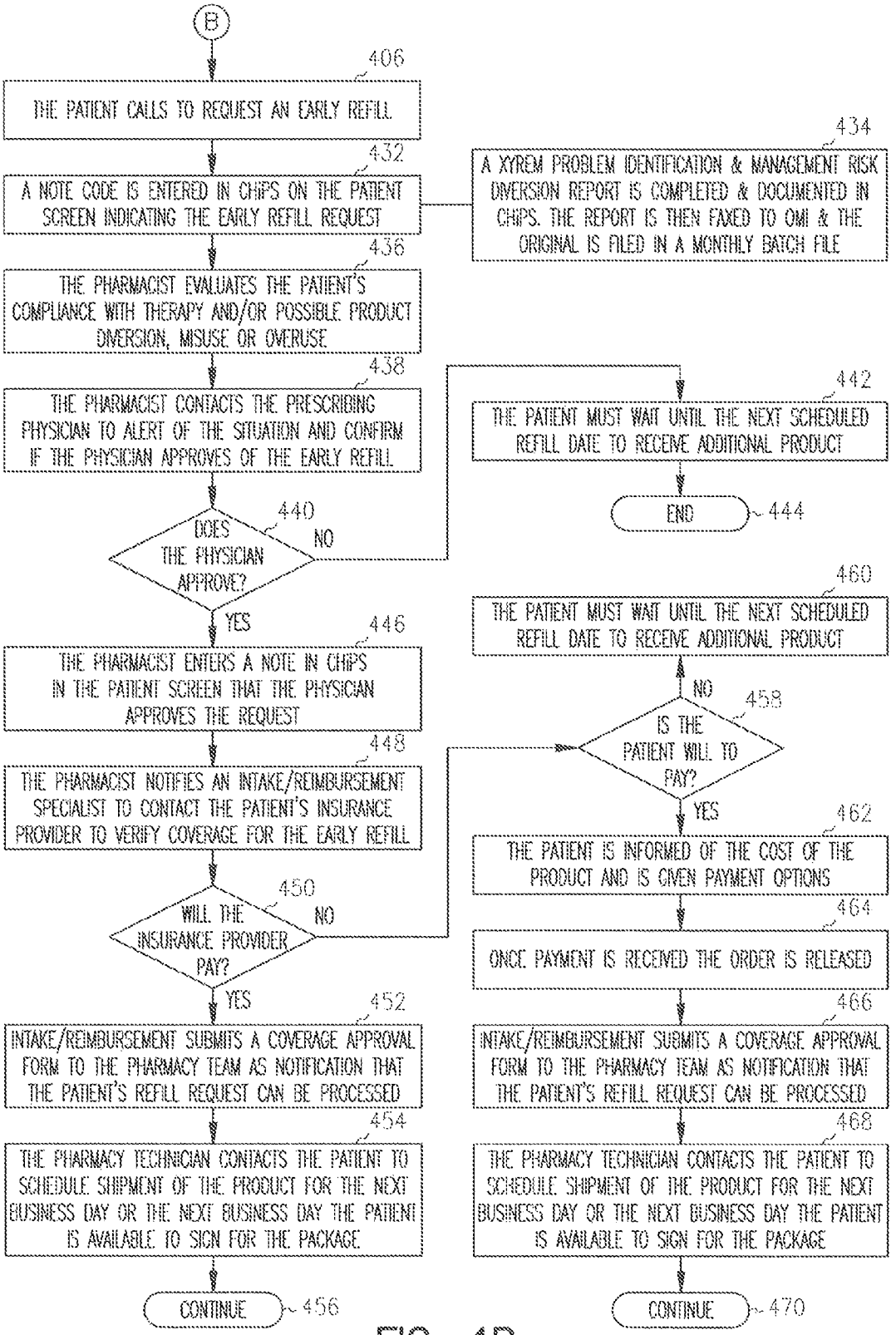

B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYREM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS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

FIG. 4B

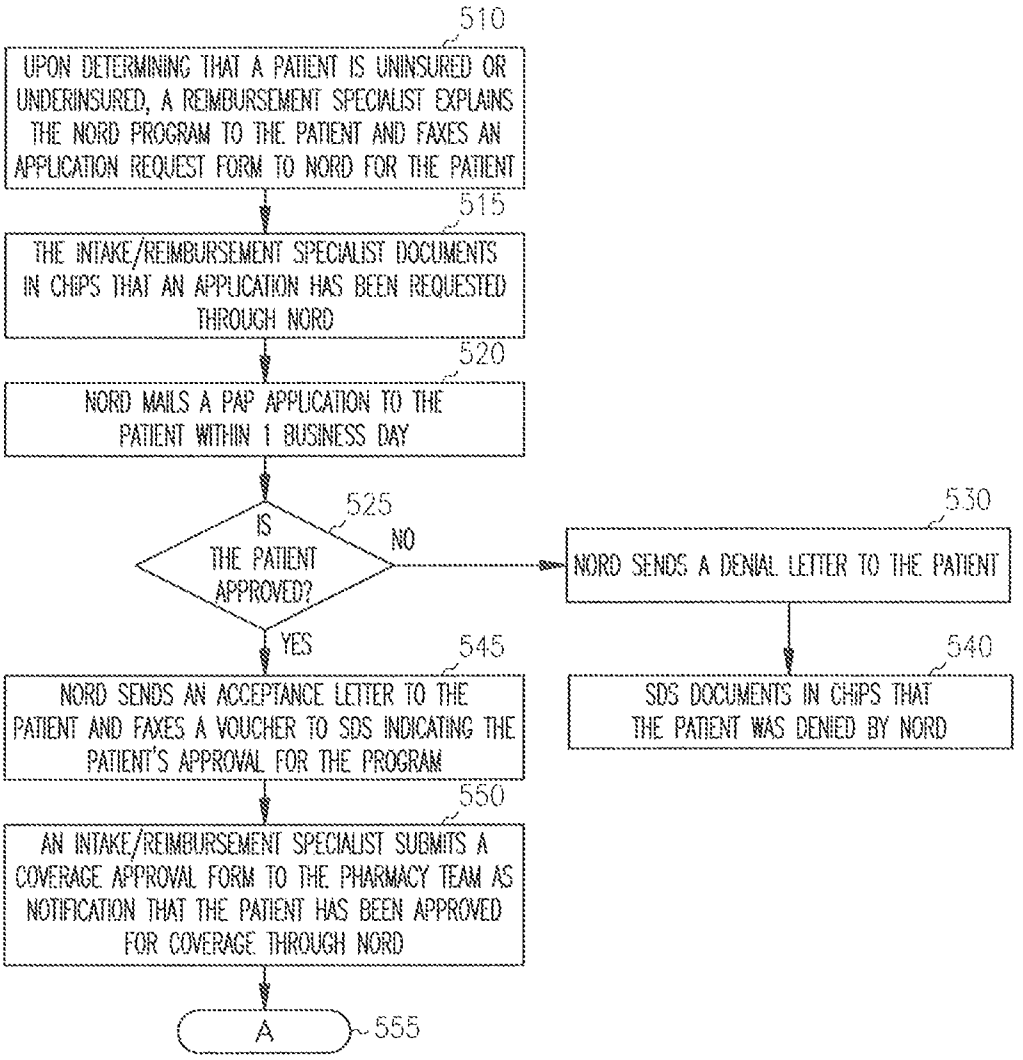

510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHIPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH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

FIG. 5

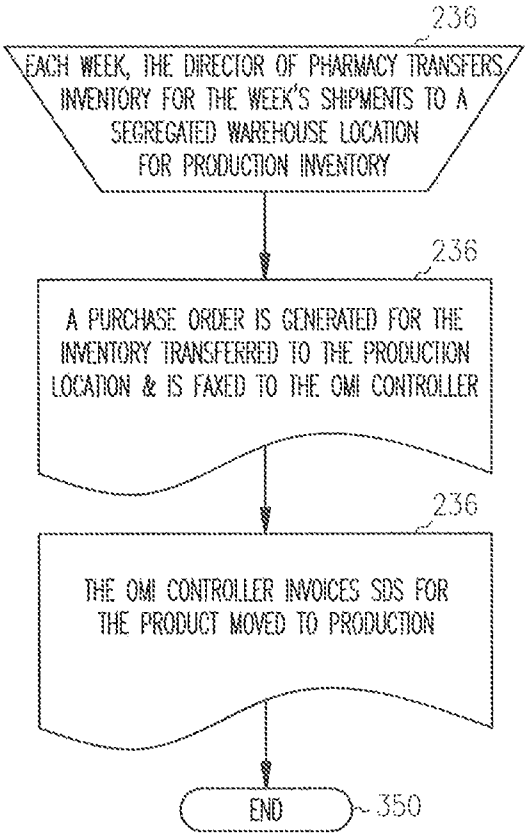


FIG. 6

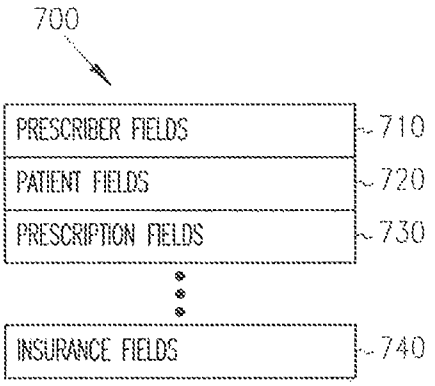


FIG. 7

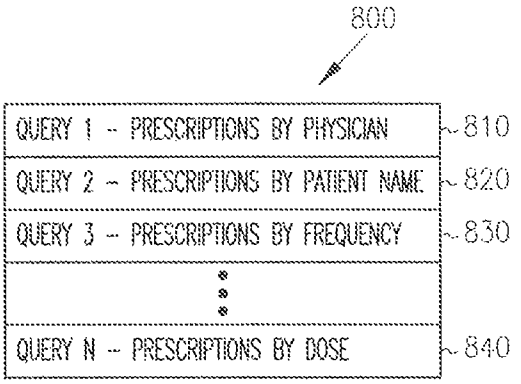


FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

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

PRESCRIPTION FORM

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

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

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

PATIENT INFORMATION

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

PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

FAX COMPLETED FORM TO XYREM SUCCESS PROGRAM (TOLL-FREE) 1-866-470-1744

FOR INFORMATION, CALL THE XYREM TEAM (TOLL FREE) AT 1-866-XYREM88 (1-866-997-3688)

FIG. 9


1000
PATIENT ASSISTANCE APPLICATION REQUEST FORM
DATE:
TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS
FAX #: 203-798-2291
PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:
PATIENT NAME
ADDRESS
TELEPHONE: ( )
PATIENT DOSAGE: (GRAMS) TWICE NIGHTLY FOR A TOTAL DOSAGE OF (GRAMS)
BOTTLES (THREE MONTHS SUPPLY)
BACKGROUND INFORMATION:

FIG. 10

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
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

CASE CODE: ********

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

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml bll	1

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

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

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

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

CASE CODE: ********

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

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREM 180ml bll	1

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

APPROVED _____

PHARMACY USE

FIG. 11

1200

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE
OF MEDICAL NEED

PATIENT INFORMATION

DATE: .....

NAME: .....
LAST FIRST M

DATE OF BIRTH: .....

DRUG BEING PRESCRIBED: XYREM

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

ICD-9: .....

PHYSICIAN INFORMATION

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

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

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

FIG. 12

ACTIVITY REPORTS

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

FIG. 13A

ACTIVITY REPORTS

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

FIG. 13B

ACTIVITY REPORTS

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

FIG. 13C

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 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 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.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,457,988 B1
APPLICATION NO. : 13/595757
DATED : June 4, 2013
INVENTOR(S) : Reardan et al.

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

On the Title page, in column 2, under "(57) Abstract", line 4, after "physicians", insert --who are--, therefor

Title page 3, in column 1, under "Other Publications", line 42, delete "Noninfringement" and insert --Non-Infringement--, therefor

Title page 3, in column 2, under "Other Publications", line 9, after "Jersey", insert --)--, therefor

Title page 3, in column 2, under "Other Publications", line 13, after "Jersey", insert --)--, therefor

Title page 3, in column 2, under "Other Publications", line 32, delete "Inital" and insert --Initial--, therefor

Title page 3, in column 2, under "Other Publications", line 36, delete "Sodiium" and insert --Sodium--, therefor

Title page 3, in column 2, under "Other Publications", line 39, delete "Sodiium" and insert --Sodium--, therefor

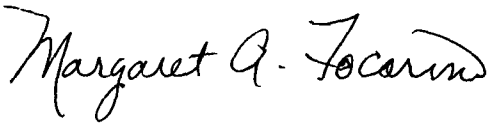
In the Drawings

On Sheet 2 of 16, Fig. 2A, reference numeral 204, line 1, delete "MAKE" and insert --MAKES--, therefor

On sheet 2 of 16, Fig. 2A, reference numeral 210, line 2, delete "INIO" and insert --INTO--, therefor

On sheet 2 of 16, Fig. 2A, reference numeral 216, line 3, delete "LETIER" and insert --LETTER--, therefor

Signed and Sealed this
Twenty-sixth Day of November, 2013



Margaret A. Focarino
Commissioner for Patents of the United States Patent and Trademark Office

On sheet 4 of 16, Fig. 2C, reference numeral 250, line 1, delete "SCHEDULE" and insert --SCHEDULES--, therefor

On sheet 4 of 16, Fig. 2C, reference numeral 252, line 1, delete "PATIENTS" and insert --PATIENT'S--, therefor

On sheet 4 of 16, Fig. 2C, reference numeral 266, line 3, delete "DAYS" and insert --DAY'S--, therefor

On sheet 7 of 16, Fig. 4B, reference numeral 458, line 2, delete "WILL" and insert --WILLING--, therefor

On sheet 9 of 16, Fig. 6, reference numeral 236, line 1, delete "236" and insert --610--, therefor

On sheet 9 of 16, Fig. 6, reference numeral 236, line 6, delete "236" and insert --620--, therefor

On sheet 9 of 16, Fig. 6, reference numeral 236, line 11, delete "236" and insert --630--, therefor

On sheet 9 of 16, Fig. 6, reference numeral 350, line 14, delete "350" and insert --640--, therefor

On sheet 10 of 16, Fig. 9, line 6, delete "SPECIALTY" and insert --SPECIALITY--, therefor

On sheet 12 of 16, Fig. 11, line 12, delete "XYREEM" and insert --XYREM--, therefor

On sheet 14 of 16, Fig. 13A, line 2, delete "Rx/ENROLLEMENT" and insert --Rx/ENROLLMENT--, therefor

In the Specification

In column 3, line 35, delete "subject" and insert --subjected--, therefor

In column 3, line 61, after "speed", insert --the--, therefor

In column 4, line 21, delete "RX/enrollment" and insert --Rx/enrollment--, therefor

In column 4, line 37, delete "206" and insert --210--, therefor

In column 4, line 39, delete "206" and insert --210--, therefor

In column 5, line 10, before “the proper”, delete “of”, therefor

In column 5, line 24, after “held”, insert --for--, therefor

In column 6, line 12, delete “data or” and insert --date of--, therefor

In column 6, line 16, delete “302” and insert --402--, therefor

In column 8, line 1, delete “subject” and insert --subjected--, therefor

EXHIBIT J

Paper No.__
Filed: June 3, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS LLC and PAR PHARMACEUTICAL, INC.

Petitioner,

v.

JAZZ PHARMACEUTICALS, INC.

Patent Owner

Case IPR2015-01903
Patent 8,731,963

PATENT OWNER RESPONSE
PURSUANT TO 37 C.F.R. § 42.120

Paper No.__
Filed: June 3, 2016

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I. INTRODUCTION

Amneal Pharmaceuticals LLC and Par Pharmaceutical, Inc. ("Petitioners") filed an IPR petition ("Petition" or "Pet.") seeking cancelation of claims 1-28 of U.S. Patent No. 8,731,963 (the "'963 patent"). Petitioners presented two grounds of unpatentability: Ground 1 – claims 1-7 and 9-23 as allegedly obvious over the Advisory Committee Art (Exs. 1003-1006) (the "ACA"); and Ground 2 – claims 8 and 24-28 as allegedly obvious over ACA in view of Korfhage (Ex. 1037). *See* Pet. 9. The Board rejected Ground 1 in its entirety, and partially instituted review on Ground 2 as it relates to claims 24, 26, and 27. *See* Paper 10. As explained below, claims 24, 26, and 27 would not have been obvious.

First, Petitioners have failed to meet their burden of proving that the ACA is prior art to the '963 patent.

Second, even assuming that the ACA is prior art—it is not—Petitioners have failed to meet their burden of showing that the ACA in view of Korfhage would have rendered the challenged claims obvious.

Accordingly, Jazz respectfully requests that the Board confirm the patentability of claims 24, 26, and 27 of the '963 patent.

II. BACKGROUND

Petitioners are defendants in a Hatch-Waxman lawsuit involving the '963 patent; Petitioners are seeking to make generic versions of Xyrem® which are covered by the '963 patent. Xyrem is the only FDA-approved treatment for cataplexy and excessive daytime sleepiness, both debilitating symptoms of narcolepsy. Ex. 2001 at 1; Ex. 2002 at 1. Xyrem's active ingredient is a sodium salt of gammahydroxybutyric acid ("GHB"), a substance which has been legislatively defined as a "date rape" drug. Ex. 2003 at 1; Ex. 2004 at 3.

FDA would not have approved Xyrem without a method of restricting access to the drug that could ensure that its benefits would outweigh the risks to patients and third parties. In fact, FDA approved Xyrem under 21 CFR § 314.520 ("Subpart H"), which allows FDA to approve drugs that are effective, but can only be used safely under restricted conditions. Ex. 2001 at 1; Ex. 2002 at 1.

Claims 24, 26, and 27 of the '963 patent claim computer-implemented systems for treating a narcoleptic patient with a prescription drug that has a potential for misuse, abuse, or diversion, while preventing that misuse, abuse, and diversion by means of various controls. *See* 1001 at 11:7-12:10, 12:23-33; *see also id.* at Abstract, 1:41-45. Each of these claims requires a central computer database to be distributed over multiple computers, and a query that operates over the distributed databases. *See id.* at 11:7-12:10, 12:23-33. Claim 27 additionally

requires using periodic reports, generated from the single computer database, to identify a current pattern or an anticipated pattern of abuse of the prescription drug. *See id.* at 12:23-33.

III. ARGUMENT

A. Petitioners have failed to show, by a preponderance of the evidence, that the ACA (Exs. 1003-1006) is prior art

The parties have briefed and argued Petitioners' failure to show that the ACA qualifies as prior art in related IPRs 2015-00545, -546, -547, -548, -551, and -554. Jazz submits that the Board should apply the decision it reaches in those IPRs here.

B. Claim Construction

In an IPR, claims are to be given their broadest reasonable interpretation in light of the specification in which they appear. *See* 37 C.F.R. § 42.100(b). Claim terms are also to be given their ordinary and customary meaning as would be understood by a POSA, in the context of the entire patent's disclosure, at the time of the invention. *In re Translogic Tech.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

In the Institution Decision, the Board "determine[d] that no claim terms require express construction for purposes of this Decision." Paper 10 at 8. Jazz respectfully submits, however, that the phrase "wherein the current pattern or the anticipated pattern [of abuse] are identified using periodic reports generated from the single computer database" in dependent claim 27 requires construction.

Specifically, the phrase requires that the reports are generated: (1) from the single computer database; and (2) on a periodic basis, i.e., at regular frequencies or intervals, as opposed to intermittently or upon request.

Accordingly, Jazz submits that the phrase "wherein the current pattern or the anticipated pattern [of abuse] are identified using periodic reports generated from the single computer database" in claim 27 should be construed to mean: querying the single computer database to generate, ***at regular frequencies or intervals, as opposed to intermittently or upon request***, reports containing prescriber, patient, and/or prescription related information to identify a current pattern or an anticipated pattern of abuse of the prescription drug. *See* Ex. 2005 ¶¶ 26-33; Ex. 2006 ¶¶ 25-31. Jazz's construction gives meaning to the word "periodic" and is supported by the '963 patent's specification, a POSA's understanding of the term, and the plain and ordinary meaning of the word periodic.

First, the specification supports Jazz's construction. *See* Ex. 2005 ¶¶ 27, 29-31; Ex. 2006 ¶¶ 26, 28-29. Specifically, the specification explains that Figures 13A-C are "reports obtained by querying a central database having the fields represented in Fig. 7."[1] Ex. 1001 at 8:23-25; *see also id.* at 8:29-30 ("The reports are obtained by running queries against the database. . . ."). The specification

[1] The fields in Fig. 7 contain prescriber, patient, and/or prescription related information. *See* Ex. 1001 at Fig. 7.

further explains: ***"Each report has an associated frequency or frequencies."*** *Id.* at 8:28-29 (emphasis added). Figures 13A-C of the '963 patent also show that reports regarding prescriber, patient, and/or prescription related information—that allow for identification of a current pattern or an anticipated pattern of abuse of the prescription drug—are run at regular frequencies or intervals, as opposed to intermittently or upon request. *Id.* at Figs. 13A-C. Thus, the specification supports Jazz's construction. *See* Ex. 2005 ¶ 30; Ex. 2006 ¶ 28; *Enpat, Inc. v. Microsoft Corp.*, 26 F. Supp. 2d 806, 808-09 (E.D. Va. 1998) (construing "periodic" to mean "fixed intervals, rather than intermittently or on request" where the specification disclosed the task being performed on a "pre-determined frequency").

Second, Jazz's construction is also supported by the understanding of a POSA. As Petitioners' expert, Dr. Valuck, testified during deposition, reports to investigate abuse can be generated on either "an ad hoc basis or on a regular basis." Ex. 2007 at 184:8-16.[2] A POSA would understand that ad hoc reports are done for a particular purpose. 2005 ¶ 28; Ex. 2006 ¶ 27. A POSA would not consider "ad hoc" reports to be "periodic." *Id.*; *see also* Ex. 2007 at 184:8-16.

[2] The parties have agreed that the expert depositions from IPRs 2015-00545, -546, -547, -548, -551, and -554 can be used in this proceeding. *See* Ex. 2009.

Third, the plain and ordinary meaning of the word periodic supports Jazz's construction. Merriam-Webster's Collegiate Dictionary defines "periodic" as:

> **pe·ri·od·ic** \ˌpir-ē-ˈä-dik\ *adj* (1642) **1** : occurring or recurring at regular intervals **2 a** : consisting of or containing a series of repeated stages, processes, or digits : CYCLIC ⟨~ decimals⟩ ⟨a ~ vibration⟩ **b** : being a function any value of which recurs at regular intervals **3** : expressed in or characterized by periodic sentences

Ex. 2010 at 3. The dictionary reinforces the concept that "periodic" requires events to occur at regular intervals. *See* Ex. 2005 ¶ 32; Ex. 2006 ¶ 30.

Jazz notes that, in related IPRs, the Board cited Figure 4B as illustrative of "a refill request process that permits a pharmacist to identify an early refill request, generate a 'risk diversion report,' and evaluate 'possible product diversion, misuse or over-use' of a prescription drug." *See, e.g.*, IPR2015-00551, Paper 19 at 22-23. As mentioned above, however, Dr. Valuck explained at his deposition that diversion reports can be generated on either "an ad hoc basis or on a regular basis." Ex. 2007 at 184:8-16. A POSA would understand that the reports generated in Figure 4B are "ad hoc" reports done for the particular purpose of investigating specific early refill requests, and ***not*** "regular" or "periodic" reports as set forth in claim 27. Ex. 2005 ¶ 31; Ex. 2006 ¶ 29.

In reply, Petitioners may argue that the '963 patent's parent application's file history supports a finding that Figure 4B should be considered a periodic report because the '963 applicants cited select portions of Figure 4B as support for a

similar periodic report claim element. That portion of the file history is reproduced below.

> generating periodic reports via the exclusive computer database to evaluate potential diversion patterns. [page 2, lines 24-27; *page 11, lines 10-22; page 9, lines 12-19; FIG. 4 436; FIG. 8, 800, 810, 820, 830, 840]*

Ex. 2011 at 8.

But, as Dr. Bergeron explained at his deposition, the claim element in the parent application's file history has two parts – a generating reports part and an evaluation of potential diversion patterns part. *See* Ex. 2012 at 342:6-343:23. Dr. Bergeron further explained that a POSA would understand that the portions of Figure 4B that the applicants relied upon during prosecution do not say anything about generating reports. *See id.* at 339:8-23, 323:25-347:11. Instead, the portions the applicants cited refer only to the evaluation step. *See id.* Further, the only portion of Figure 4B that discloses any type of report is Box 434, and the applicants chose ***not*** to cite that box during prosecution as support for the periodic report claim element. As Dr. Bergeron explained, a POSA would expect that Box 434 was not cited because Figure 4B did not provide support for the generating periodic report part of the claim term. *See id.* at 347:21-348:20. Thus, the '963 patent's parent application's file history does not support a finding that Figure 4B should be considered a periodic report.

Accordingly, the distinction between running "ad hoc" reports (Ex. 1001 at Fig. 4B) and running set-frequency/periodic reports (Ex. 1001 at Figs. 13A-C) in the '963 patent's specification further supports Jazz's construction. *See* Ex. 2005 ¶¶ 29-31; Ex. 2006 ¶¶ 28-29; *Enpat*, 26 F. Supp. 2d at 808 (holding that the specification distinguishing between periodic and on request tasks supported a construction of periodic that means "fixed intervals, rather than intermittently or on request").[3]

For the reasons set forth above, the Board should adopt Jazz's construction.

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[3] "[R]ead in the context of the specification, the claims of the patent need not encompass all disclosed embodiments." *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1373 (Fed. Cir. 2008). Indeed, "[Federal Circuit] precedent is replete with examples of subject matter that is included in the specification, but is not claimed." *Id.* (holding that "the mere fact that there is an alternative embodiment disclosed in the [patent-in-suit]" does not mean it is encompassed by the claims); *see also Schoenhaus v. Genesco, Inc.*, 440 F.3d 1354, 1359 (Fed. Cir. 2006); *Maxwell v. J. Baker, Inc.*, 86 F.3d 1098, 1108 (Fed. Cir. 1996); *Unique Concepts, Inc. v. Brown*, 939 F.2d 1558, 1562-63 (Fed. Cir. 1991). The diversion reports in Figure 4B are an unclaimed embodiment.

C. Petitioners have failed to prove, by a preponderance of the evidence, that the ACA in view of Korfhage would have rendered claims 24, 26, and 27 of the '963 patent obvious

Petitioners have failed to meet their burden of showing that the ACA qualifies as prior art. Even assuming, however, that the ACA is prior art, Petitioners have not met their burden of proving that the ACA in view of Korfhage would have rendered claims 24, 26, and 27 obvious. Specifically, Petitioners have failed to meet their burden of showing that: (1) a POSA would have been motivated to combine the ACA with Korfhage to arrive at the "central computer database being distributed over multiple computers" required for claims 24, 26, and 27 and (2) the ACA would have disclosed, taught, or suggested the periodic reports in dependent claim 27.

1. A POSA would not have been motivated to combine the ACA and Korfhage to arrive at the claimed "central computer database being distributed over multiple computers"

Claims 24, 26, and 27 each require that the central computer database is distributed over multiple computers. Ex. 1001 at claims 24, 26, 27. Petitioners do not identify anything in the ACA that would have disclosed, taught, or suggested a central computer database being distributed over multiple computers. *See generally* Pet; Ex. 1007; Ex. 2006 ¶ 43. To the contrary, Petitioners and Dr. Valuck admit that this limitation does not appear in the ACA. *See* Pet. 52;

Ex. 1007 ¶ 144. Thus, Petitioners argue that a POSA would have combined the ACA with Korfhage. *See* Pet. 52. Petitioners are wrong.

Without the benefit of hindsight and the claimed inventions in hand, a POSA would not have been motivated to look to Korfhage, much less single out the one page discussing a distributed computer architecture. Ex. 2006 ¶ 44. Korfhage is a treatise on Information Storage and Retrieval within computer systems. *See generally* Ex. 1037. Nothing in Korfhage relates to drug distribution or pharmacy practice generally, and nothing relates to drug abuse, misuse, or diversion. *See generally* Ex. 1037; Ex. 2006 ¶ 45. The general concepts simply never appear. *See generally* Ex. 1037.[4] Petitioners cherry-pick two passages from page 276 of the 349 page treatise that relate to "Distributed Document Systems," but their only explanation for doing so is to "increase the efficiency of the distribution of Xyrem." Pet. 52. Elsewhere in the Petition, however, Petitioners argue that large numbers of Xyrem prescriptions can be handled in an "acelerate[d]" manner using a "***conventional*** computer," and that the ACA discloses the use of such a conventional computer. Pet. 22, 29 (emphasis added). Indeed, a POSA would have understood that any computer database would sufficiently accommodate drug distribution by the central pharmacy. Ex. 2006 ¶¶ 46-47.

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[4] Thus, Dr. Valuck's testimony that Korfhage "appl[ies] to pharmacy practice" is entirely unsupported. *See* Ex. 2007 at 206:10-207:3.

In short, Petitioners have not identified any problem with the centralized (i.e., non-distributed) database disclosed in the ACA. *See generally* Pet; Ex. 1007; Ex. 2006 ¶ 47. Thus, a POSA would not have been motivated to look for any substitution, let alone the specific distributed-database architecture in Korfhage. *See Leo Pharm. Prods. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) ("Only after recognizing the existence of the problem would an artisan *then* turn to the prior art. . . .") (emphasis in original).

Further, even if there was a known problem in the prior art, Korfhage discloses too many options for database architectures to a POSA and provides no guidance on which option to choose. *See* Ex. 2006 ¶ 48. Indeed, Petitioners' declarant admitted that Korfhage "would suggest a lot of possibilities." Ex. 2008 at 286:11-17; *see also id.* at 316:23-317:8 (Dr. Valuck admitting that distributed database document systems are not the only database architecture for handling documents for pharmacies), 317:12-14 (Dr. Valuck admitting that Korfhage "covers a host of possibilities for systems"), 318:3-15 (Dr. Valuck testifying that there are "various forms and different architectures for accomplishing the same tasks in different ways"). Dr. Valuck further admitted that "all these different forms were . . . existing in the art and existing in practice for many years in various systems and various permutations and forms." *Id.* at 317:16-23; *see also id.* at 320:3-4 ("[T]here are different architectures and [] a POSA would know that.").

Thus, rather than showing a "finite number of identified, predictable solutions" (*KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 421(2007)), Dr. Valuck admitted that the prior art was replete with a host of possible database architectures.

Notably, Dr. Valuck admitted that he did not consider these other systems because he "was not asked to opine on . . . all of the different possibilities." Ex. 2008 at 316:15-22. Instead, Dr. Valuck admitted that his "whole obviousness opinion" was based on impermissible hindsight:

> A. Again, I looked for where the claim elements were disclosed in the prior art.
>
> . . .
>
> Q. Right. So you used the patent as a guide to pick the elements out of the prior art.
>
> A. Well, again, my – ***my whole obviousness opinion is based on starting with the elements*** and referring to prior art and all available prior art through the eyes of a person of ordinary skill. That was the process I used.

Ex. 2007 at 198:6-22 (emphasis added). It is improper, however, to pick and choose in hindsight from the prior art. *See Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986) (reversing obviousness holding and explaining that the prior art must be considered as a whole); *KSR*, 550 U.S. at 421 (noting that fact finders must guard against "the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning");

In re Fine, 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."). Thus, Petitioners' obviousness analysis fails because it provides no reason to arrive at the specific distributed database architecture in Korfhage. *See* Ex. 2006 ¶ 49.

Further, Petitioners and Dr. Valuck ignore that Korfhage teaches away from using distributed databases and, therefore, teaches away from combining Korfhage with the ACA, because it discloses to a POSA that "three ***major problems*** arise" when a user attempts to have a single query operate over multiple physical databases. *See* Ex. 1037 at 276-277 (describing problems); *see also* Ex. 2006 ¶¶ 50-53. While Dr. Valuck testified that he "wasn't asked to provide an opinion on problems associated with distributed database systems for . . . [his] declarations" (Ex. 2008 at 320:24-321:5), he eventually conceded that Korfhage expressly discloses such problems. *See id.* at 323:15-324:15; *see also id.* at 321:21-322:8 (Dr. Valuck testifying that the "problems arise from the situation described where the user . . . is interested in locating and obtaining a document regardless of where it resides, either physically or within a computer system").

A POSA would have understood that the second "major problem" in Korfhage would have been particularly relevant to the distribution system disclosed in the ACA. Ex. 2006 ¶¶ 51-52. Specifically, Korfhage explains that

"[t]he second problem is that of data redundancy. Different databases may include copies of the same or equivalent document." Ex. 1037 at 276. Korfhage suggests that "eliminating the duplication requires relatively little work," but "in some instances the documents may be sufficiently different to cause problems." *Id.* As Petitioners admit, the ACA explains that the "central data repository 'allows for the identification of duplicate prescriptions.'" Pet. 31. The return of redundant data in the distributed databases might create a false indication of duplicate prescriptions that could prevent a patient from receiving her prescription drug. Ex. 2006 ¶ 52. On the other hand, if the duplicate prescription data is "eliminat[ed]" because a pharmacist believes it was caused by data redundancy, then a potential abuse situation would be overlooked. *Id.*

The "major problems" disclosed in Korfhage would have expressly taught a POSA away from combining it with the ACA and modifying the distribution system disclosed in the ACA. *Id.* ¶ 53. "[R]eferences that teach away cannot serve to create a prima facie case of obviousness." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354 (Fed. Cir. 2001).

Accordingly, Petitioners have failed to meet their burden of proving that claims 24, 26, and 27 would have been obvious.

2. The ACA would not have disclosed, taught, or suggested the claimed periodic reports

Petitioners' challenge also fails for claim 27 because they failed to meet their burden of showing that the ACA would have disclosed, taught, or suggested the additional limitation of claim 27: "wherein the current pattern or the anticipated pattern [of abuse] are identified using periodic reports generated from the single computer database." Petitioners rely on the ACA alone for alleged disclosure of this claim limitation. *See* Pet. 53-54, *see also id.* at 41-43 (citing only the ACA and not Korfhage).

As discussed above, "wherein the current pattern or the anticipated pattern [of abuse] are identified using periodic reports generated from the single computer database" should be construed to mean: querying the single computer database to generate, at regular frequencies or intervals, as opposed to intermittently or upon request, reports containing prescriber, patient, and/or prescription related information to identify a current pattern or an anticipated pattern of abuse of the prescription drug. *See supra* at pp. 3-8. The ACA does not teach this limitation because it does not teach reports to identify current or anticipated patterns of abuse that are generated: (1) periodically, i.e., at regular frequencies or intervals, as opposed to intermittently or upon request; and (2) by querying the single computer database. *See* Ex. 2005 ¶¶ 34-36, 38-42; Ex. 2006 ¶¶ 32-41.

First, Petitioners argue that the "ACA discloses using the central data repository to identify patterns of abuse and diversion." Pet. 42 (citing Ex. 1003 at 184:24-185:7, Slides at 158; Ex. 1005 at 304, 310-11); *see also* Ex. 1007 ¶ 121 (citing same). While these disclosures specify the information available in the "central data repository," none disclose, teach, or suggest running queries on that data to generate any types of reports, much less periodic reports. *See* Ex. 1003 at 184:24-185:7, Slides at 158; Ex. 1005 at 304, 310-11; Ex. 2006 ¶ 34.

Second, Petitioners argue that "the ACA describes preventing diversion and illicit use, as well as providing assistance to 'law enforcement for investigation and prosecution efforts,' as a goal of the system." Pet. 42 (citing Ex. 1003 at 15:6-8; Ex. 1004 at 110; Ex. 1005 at 298, 301, 306-308); *see also* Ex. 1007 ¶ 121 (citing same). Petitioners also argue that the central pharmacy "employs numerous mechanisms, controls, and verification procedures to ensure that Xyrem is not obtained fraudulently or abused or diverted by the patient or prescriber." Pet. 41 (citing Ex. 1003 at 184:24-185:7, Slides at 158; Ex. 1004 at 110; Ex. 1005 at 304, 310, 311; Ex. 1006 at 4 n.14, 8 nn. 29, 33 and 9 n.38); *see also* Ex. 1007 ¶ 120 (citing same). Petitioners further argue that "[i]t would have been obvious to a POSA that, for the database to determine such abuse or patterns of abuse . . . it must be queried periodically to generate reports" and that a POSA "would have understood that such data generation obtained through querying via the central data

repository is synonymous with generating periodic reports via the computer database to evaluate potential diversion patterns." Pet. 41-43 (citing Ex. 1003 at 24:21-24; Ex. 1004 at 110, 115; Ex. 1005 at cover letter, 304, 310, 311; Ex. 1006 at 4 n.14, 7 n.25, 8 nn.29, 33, 9 n.38, 10 nn.41-42; V5 00:10-00:27, V13 00:17-00:31; Ex. 1003 at 24:21-24); *see also* Ex. 1007 ¶¶ 120, 122 (citing same).

Petitioners are wrong. The cited evidence would not have disclosed, taught, or suggested generating periodic reports. *See* Ex. 1003 at 15:6-8, 24:21-24, 184:24-185:7, Slides at 158; Ex. 1004 at 110, 115; Ex. 1005 at cover letter, 298, 301, 304, 306-308, 310, 311; Ex. 1006 at 4 n.14, 7 n.25, 8 nn.29, 33, 9 n.38, 10 nn.41-42; V5 00:10-00:27, V13 00:17-00:31; Ex. 1003 at 24:21-24; Ex. 2006 ¶¶ 35-36. Instead, the evidence cited discloses that "[t]he database will be made available for review by the DEA as well as other federal and state agencies ***upon request***." Ex. 1004 at 110 (emphasis added); *see also* Ex. 2006 ¶ 36. A POSA would understand reports generated "upon request" are "ad hoc" reports, ***not*** "periodic" reports. Ex. 2006 ¶ 36; *see also id.* ¶ 27; Ex. 2005 ¶ 28. Further, as discussed in detail below, the ACA discloses that the proposed system "preserves [the] important feature" of ***not*** having the central pharmacy police medicine. Instead, the ACA contemplated having the central pharmacy become involved in an investigation of abuse only on an ad hoc basis, after authorities asked for its

assistance. *See infra* at pp. 19-20. In other words, the ACA only taught the generation of ad hoc reports.

Third, Petitioners argue that "the ACA discloses generating data by 'recording prescribers, patients, and dosing that could provide information for any possible investigations and prosecutions for state and federal authorities' using a computer." Pet. 32 (citing Ex. 1006 at 4 nn.13-14; V5 00:10-00:27); *see also* Ex. 1007 ¶ 122 (citing same). Petitioners also argue that the ACA discloses that "[a]ll data collected will be available to state and federal authorities, on whatever timeframe they determine appropriate," and imply that "timeframe" refers to periodic reporting. Pet. 42 (citing Ex. 1005 at 307); Ex. 1007 ¶ 122.

But Petitioners ignore that "[g]enerating data . . . for any possible investigations and prosecutions" is not the same as generating periodic reports. *See* Ex. 2005 ¶¶ 38-41; Ex. 2006 ¶¶ 37-40. The ACA's full disclosure teaches a POSA that any reports generated for state or federal agencies are done so "upon request" to assist the authorities with cases of abuse, which the ACA indicates will be rare. Ex. 2005 ¶ 39; Ex. 2006 ¶ 38; Ex. 1004 at 110; Ex. 1005 at 306 ("Available data … 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***.") (emphasis added).) Thus, the ACA only discloses generating retrospective reports to aid in investigations of

abuse. The ACA would not have disclosed, taught, or suggested the claimed prospective reports to identify current or anticipated patterns of abuse. Ex. 2005 ¶ 39; Ex. 2006 ¶ 38

Indeed, the ACA discloses to a POSA that the pharmacy can only assist with an investigation once it becomes necessary and has begun. Ex. 2005 ¶ 40. Specifically, the ACA discloses that "[t]he practicalities of how prescriptions are filled in the U.S. do not allow for a specialty pharmacy to 'police' the practice of medicine." Ex. 1005 at 307. Instead, "the current system used in the U.S. for managing the risks associated with controlled substances allows for appropriate stakeholders to police individual physician and patient behavior. The Xyrem system preserves this important feature." *Id.*; *see also id.* (noting the pharmacy will cooperate with the appropriate stakeholders—"state and federal authorities, including State Medical Boards, DEA and FDA, in any investigation dealing with physician or patient behavior").

Based on the ACA's disclosures, a POSA would have understood that the "timeframe" statement cited by Petitioners is similar to the statement in Ex. 1005 that the centralized data "allow[s] for rapid identification in the rare case of diversion." Ex. 1005 at 306. Specifically, a POSA would have understood that the statement boasts the benefit of centralized data being available in real-time, which is that potential investigations will be able to proceed without delay from the

pharmacy. Ex. 2005 ¶ 41; Ex. 2006 ¶¶ 39-40. The timeframe is contingent on particular events. It is not an implication of periodic reporting. *Id.*

Accordingly, Petitioners have failed to meet their burden of proving that claim 27 would have been obvious for this additional reason.

IV. CONCLUSION

For the foregoing reasons, Petitioners have failed to prove, by a preponderance of the evidence, that claims 24, 26, and 27 of the '963 patent would have been obvious.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS LLC and PAR PHARMACEUTICAL, INC.,

Petitioners,

v.

JAZZ PHARMACEUTICALS, INC.

Patent Owner

Case IPR2015-01903
Patent 8,731,963

CERTIFICATE OF SERVICE

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), the undersigned hereby certifies that PATENT OWNER RESPONSE PURSUANT TO 37 C.F.R. § 42.120 and Exhibits (2001-2013) were served on June 3, 2016 by filing these documents through the Patent Review Processing System, as well as e-mailing copies to bradford.frese@arentfox.com, janine.carlan@arentfox.com, richard.berman@arentfox.com, and XYREM@arentfox.com.

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CERTIFICATE OF COMPLIANCE PURSUANT TO 37 C.F.R. § 42.24

This paper complies with the type-volume limitation of 37 C.F.R. § 42.24. The paper contains 4,439 words, excluding the parts of the paper exempted by § 42.24(a).

This paper also complies with the typeface requirements of 37 C.F.R. § 42.6(a)(ii) and the type style requirements of § 42.6(a)(iii)-(iv).

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EXHIBIT K

US008771735B2

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

(10) **Patent No.: US 8,771,735 B2**
(45) **Date of Patent: *Jul. 8, 2014**

(54) **IMMEDIATE RELEASE DOSAGE FORMS OF SODIUM OXYBATE**

(75) Inventors: **Andrea Rourke**, San Mateo, CA (US); **Clark Allphin**, Los Altos, CA (US); **Maura Murphy**, Baltimore, MD (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 501 days.

This patent is subject to a terminal disclaimer.

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(22) Filed: **Nov. 4, 2008**

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USPC **424/479**

(58) **Field of Classification Search**
USPC 424/479
See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides a pharmaceutical composition, presented as a solid unit dosage form adapted for oral administration of sodium oxybate. The preferred unit dosage form is a tablet comprising a relatively high weight-percentage of sodium oxybate, in combination with a relatively small weight-percentage of total excipients. This permits the tablets to contain/deliver a pharmaceutically effective amount, e.g., about 0.5-1.5 g of sodium oxybate in each tablet with a delivery profile similar to that of the liquid form. The tablets are bioequivalent to the liquid form.

19 Claims, 2 Drawing Sheets

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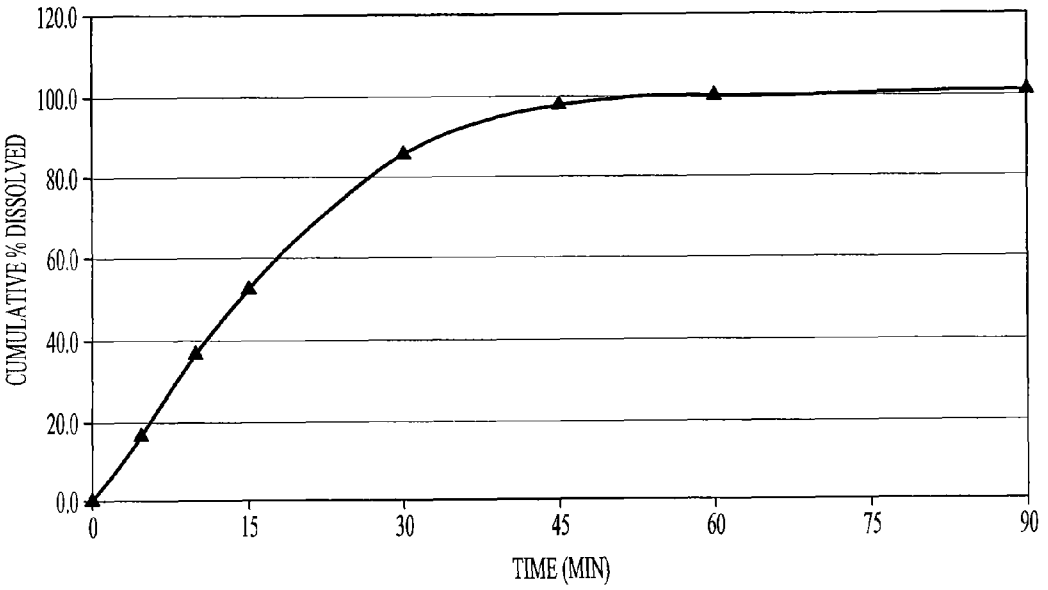
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100.0
80.0
60.0
40.0
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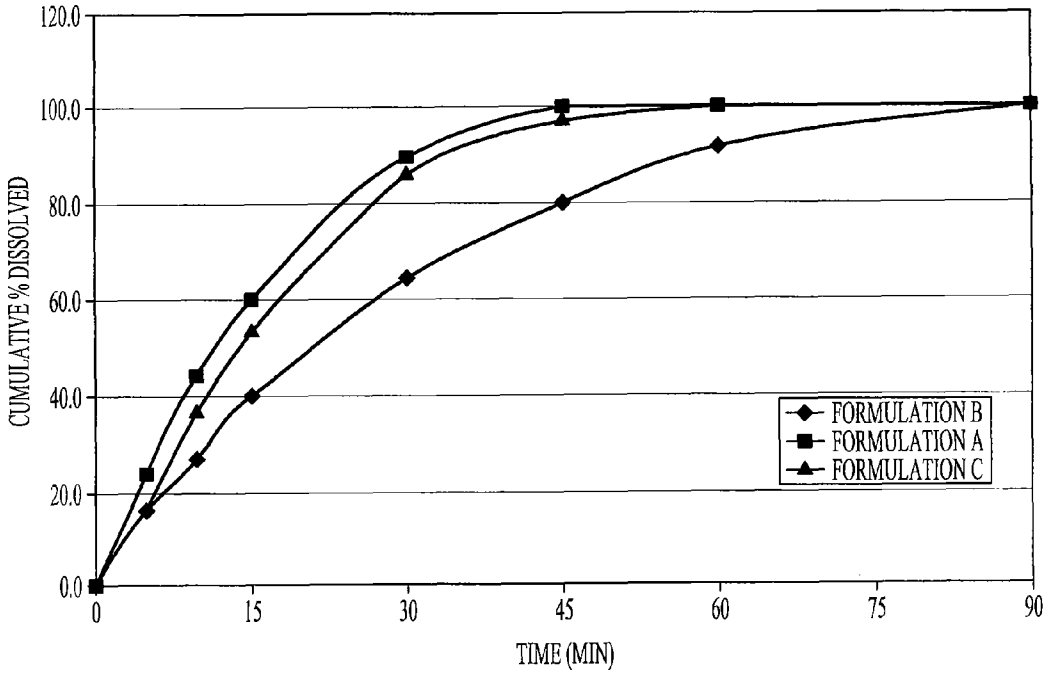
0.0
CUMULATIVE % DISSOLVED
0
15
30
45
60
75
90
TIME (MIN)

FIG. 1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20.0
0.0
CUMULATIVE % DISSOLVED
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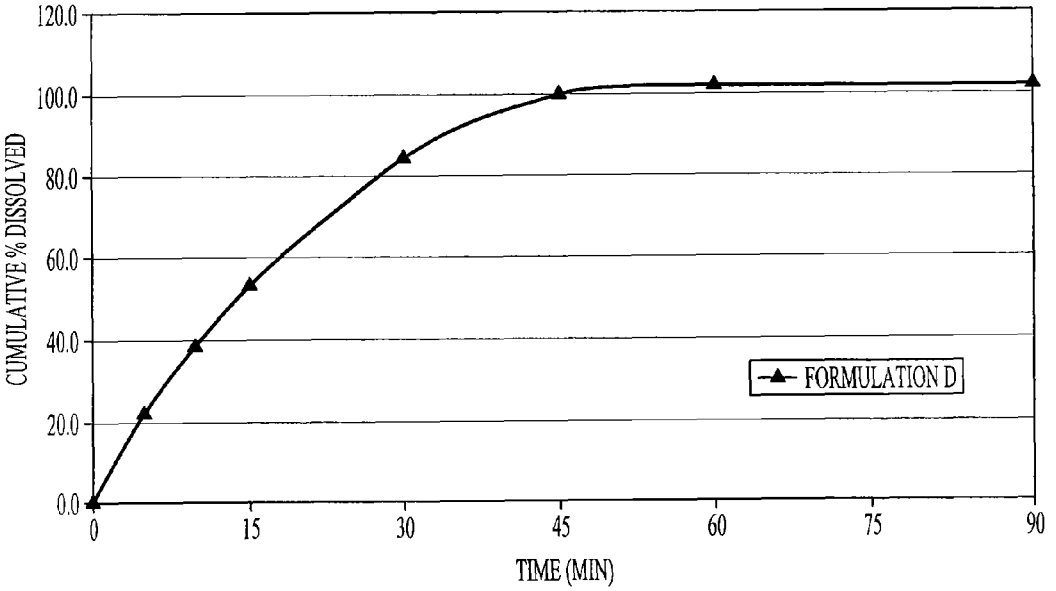
15
30
45
60
75
90
TIME (MIN)
FORMULATION B
FORMULATION A
FORMULATION C

FIG. 2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80.0
60.0
40.0
20.0
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CUMULATIVE % DISSOLVED
0
15
30
45
60
75
90
TIME (MIN)
FORMULATION D

FIG. 3

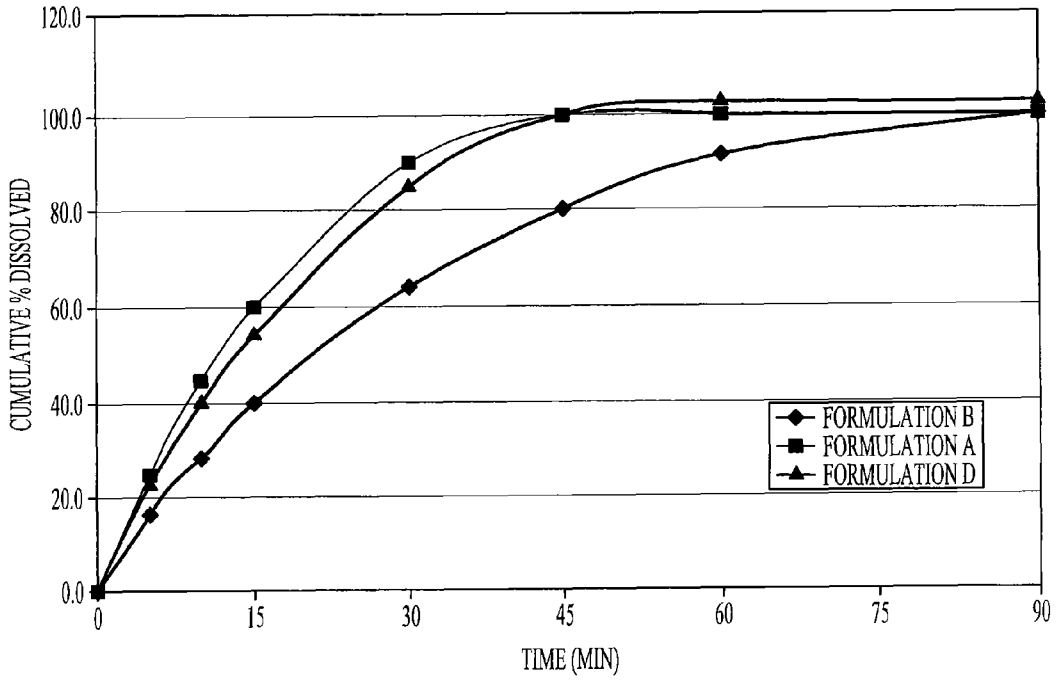

120.0
100.0
80.0
60.0
40.0
20.0
0.0
CUMULATIVE % DISSOLVED
0
15
30
45
60
75
90
TIME (MIN)
FORMULATION B
FORMULATION A
FORMULATION D

FIG. 4

IMMEDIATE RELEASE DOSAGE FORMS OF SODIUM OXYBATE

BACKGROUND OF THE INVENTION

Initial interest in the use of sodium oxybate as a potential treatment for narcolepsy arose from observations made during the use of sodium oxybate (known as gamma-hydroxybutyrate in older literature) for anesthesia. Unlike traditional hypnotics, sodium oxybate induces sleep that closely resembles normal, physiologic sleep (Mamelak et al., Biol Psych 1977:12:273-288). Therefore, early investigators administered gamma-hydroxybutyrate (GHB) to patients suffering from disorders of disturbed sleep, including narcolepsy (Broughton et al. in Narcolepsy, NY, N.Y.: Spectrum Publications, Inc. 1976:659-668), where it was found to increase total nocturnal sleep time, decrease nocturnal awakenings and increase Stage 3-4 (slow wave) sleep. Three open-label and two placebo-controlled studies provided a body of evidence demonstrating that improvements in nocturnal sleep were associated with a reduction in cataplexy and improvements in excessive daytime sleepiness (Broughton et al., Can J. Neurol Sci 1979; 6:1-6, and Broughton et al., Can J. Neurol Sci 1980; 7:23-30)

Scharf et al. conducted an open-label study to evaluate the effects of GHB on the sleep patterns and symptoms of non-narcoleptic patients with fibromyalgia (Scharf et al., J Rheumatol 1998; 25: 1986-1990). Eleven patients with previously confirmed diagnosis of fibromyalgia who reported at least a 3-month history of widespread musculoskeletal pain in all body quadrants and tenderness in a least 5 specific trigger point sites participated in the study. Results showed that patients reported significant improvements in the subjective assessments of their levels of pain and fatigue over all 4 weeks of GHB treatment as compared to baseline, as well as a significant improvement in their estimates of overall wellness before and after GHB treatment.

WO 2006/053186 to Frucht describes an open label study of 5 patients with hyperkinetic movement disorders including ethanol responsive myoclonus and essential tremor. Sodium oxybate was reported to produce dose-dependent improvements in blinded ratings of ethanol responsive myoclonus and tremor and was said to be tolerated at doses that provided clinical benefit.

Xyrem® sodium oxybate oral solution, the FDA approved treatment for cataplexy and excessive daytime sleepiness associated with narcolepsy, contains 500 mg sodium oxybate/ml water, adjusted to pH=7.5 with malic acid. In man, the plasma half-life of sodium oxybate given orally is about 45 minutes and doses of 2.25 grams to 4.5 grams induce about 2 to 3 hours of sleep (See, L. Borgen et al., *J. Clin. Pharmacol.*, 40, 1053 (2000)). For optimal clinical effectiveness in narcolepsy, sodium oxybate must be given twice during the night, and is administered as an aqueous solution. For each dose, a measured amount of the oral solution must be removed from the primary container and transferred to a separate container where it is diluted with water before administration. The second dose is prepared at bedtime and stored for administration in the middle of the night. This regimen is cumbersome and prone to errors in the preparation of the individual doses. For this reason, a more convenient unit dosage form of the drug would be clinically advantageous. Sodium oxybate is highly water-soluble, hygroscopic and strongly alkaline. Paradoxically, despite its high water solubility, it forms a gel when dissolved in water. These properties, along with the large amount of the drug that is required to achieve the clinical effect, present challenges in preparing solid unit dosage forms that are designed for immediate release of the sodium oxybate into the gastrointestinal tract of the user.

L. Liang et al. (published U.S. patent application US 2006/0210630 A1) discloses administration of gamma-hydroxybutyric acid using an immediate release component and a delayed/controlled release component. The immediate release component is disclosed to be an aqueous solution, or a "solid pellet, bead or mini tablet." While the pellets disclosed in Example 1 comprise as much as 80-90 wt-% sodium gamma-hydroxybutyrate, they are the immediate release portion of the controlled release dosage form and are not formed into a compressed tablet. They are added to other forms of sodium oxybate to prepare controlled release dosage forms.

A continuing need exists for solid immediate release dosage forms of sodium oxybate that can deliver therapeutically effective amounts of sodium oxybate following in vivo administration and which have pharmacokinetic profiles similar to that of the oral solution.

SUMMARY OF THE INVENTION

The present invention provides a pharmaceutical composition, presented as a solid unit dosage form adapted for oral administration of a therapeutic dose of sodium oxybate. The preferred unit dosage form is a tablet comprising a relatively high weight-percentage of sodium oxybate, in combination with a relatively small weight-percentage of total excipients. This permits the tablets to contain/deliver a pharmaceutically effective amount, e.g., about 0.5-1.5 g of sodium oxybate in each tablet with a delivery profile similar to that of the liquid form. The tablets are bioequivalent to the liquid form.

In one aspect the invention is a compressed tablet of sodium oxybate for oral delivery of 0.5-1.25 g of sodium oxybate comprising at least 50 wt % sodium oxybate; 1-10 wt % compression aid; and 1-50% binder; wherein the tablet is bioequivalent to sodium oxybate oral solution.

According to one embodiment, the tablet may be coated to 1-10 wt % gain with a film coating. The tablet may comprise 70-90 wt % sodium oxybate, or 80-90 wt % sodium oxybate. The tablet need not contain a super-disintegrant. The tablet may further comprise 0.1-10 wt % of a surfactant.

In another aspect, the invention is directed to an immediate release unit dosage form comprising an about 0.5-1.5 g tablet comprising about 50-95 wt-% sodium oxybate; about 2.5-7.5 wt-% microcrystalline cellulose and about 0.25-2.5 wt-% surfactant, wherein at least 90% of the sodium oxybate is released from the tablet within one hour from exposure of the tablet to an aqueous medium.

In a particular embodiment, the unit dosage form is coated with a water resistant coating. Further, the surfactant may be an ionic or nonionic surfactant. The dosage form may further comprise a minor but effective amount of at least one of a second binder, a disintegrant, a glidant and a lubricant and also may comprise 0.5-5 wt-% polyvinylpyrrolidone, 2.5-7.5 wt-% pregelatinized starch, 0.1-2.0 wt-% silicon dioxide and/or magnesium stearate.

In still another aspect, the invention is directed to a therapeutic method for treating a human afflicted with a condition treatable with sodium oxybate by orally administering to said human an effective amount of one or more of the unit dosage forms or tablets described above. The conditions may include narcolepsy, a movement disorder (such as restless leg syndrome or essential tremor), fibromyalgia or chronic fatigue syndrome.

Another aspect of the invention is a method for preparing the tablets and dosage forms described above by granulating a water-free composition comprising the sodium oxybate, the

compression and the binder; and compressing the granulated composition to yield said tablet. The tablet may be coated with a water resistant coating that may comprise PVA and lecithin.

In a further aspect the invention is a compressed tablet of an oxybate salt for oral delivery of 0.5-1.25 g of oxybate salt comprising at least 50 wt % oxybate salt; 5-10 wt % compression aid; and 1-50% binder; wherein the tablet is bioequivalent to sodium oxybate oral solution. The oxybate salt may be selected from the group consisting of potassium oxybate, calcium oxybate, lithium oxybate and magnesium oxybate.

BRIEF DESCRIPTIONS OF THE FIGURES

FIG. **1** is a graph depicting the dissolution curve of an immediate release sodium oxybate tablet of the invention.

FIG. **2** is a graph depicting the dissolution curves of three immediate release sodium oxybate tablets according to the invention.

FIG. **3** is a graph depicting the dissolution curve of a further immediate release sodium oxybate tablet according to the invention.

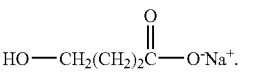
FIG. **4** is a graph depicting the dissolution curves of three immediate release sodium oxybate tablets according to the invention.

DETAILED DESCRIPTION OF THE INVENTION

Administration of sodium oxybate in solid form presents several challenges. The amount of drug taken by the patient for each dose is high, generally at least 1.5 grams and as high as 4.5 grams. Patients treated with sodium oxybate may have difficulty taking solid medications by mouth either because they have disease states that make handling and swallowing difficult or because they must take the medication upon being awakened in the middle of the night. The situation is exacerbated by the large quantity of drug that is administered in each dose. Accordingly, it is desirable to keep the size of the tablet as small as possible while incorporating the largest amount of active ingredient. In addition, the tablet must dissolve quickly in order to be bioequivalent to the existing Xyrem oral solution, without high levels of excipients to speed dissolution.

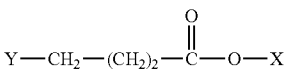
Therefore, according to the invention, the immediate release sodium oxybate composition will comprise a therapeutically effective amount of sodium oxybate or an alternative salt thereof. The structure of sodium oxybate is given below as formula (Ia):

(Ia)



Alternative salts useful in the present invention include compounds of formula (I):

(I)



wherein X is a pharmaceutically-acceptable cation and may be selected from the group consisting of potassium, calcium, lithium and magnesium and Y is OH. Sodium gamma-hydroxybutyrate (GHB) is currently available from Jazz Pharmaceuticals, Inc. as Xyrem® oral solution.

A "delivery rate" refers to the quantity of sodium oxybate released in vivo from a composition (tablet or dosage form) according to the invention per unit time, e.g., milligrams of sodium oxybate released per unit time.

By "immediate release" is intended a composition that releases sodium oxybate substantially completely into the gastrointestinal tract of the user within a period of less than an hour, usually between about 0.1 and about 1 hour and less than about 0.75 hours from ingestion. Such a delivery rate allows the drug to be absorbed by the gastrointestinal tract in a manner that is bioequivalent to the oral solution. The rapid release of sodium oxybate from the tablet is especially important because following delivery of the oral solution, peak plasma concentration of sodium oxybate occurs within an hour. Such rapid absorption could only occur if the tablet dissolves in the upper portion the gastrointestinal tract.

A "dissolution rate" refers to the quantity of drug released in vitro from a dosage form per unit time into a release medium. In vitro dissolution rates in the studies described herein were performed on dosage forms placed in a USP Type II bath containing water which is stirred while maintained at a constant temperature of 37° C. Aliquots of the dissolution media were injected into a chromatographic system to quantify the amounts of drug dissolved during each testing interval.

By "bioavailability" as used herein is intended the estimated area under the curve, or AUC of the active drug in systemic circulation after oral administration with a dosage form according to the invention compared with the AUC of the active drug in systemic circulation after oral administration of Xyrem, sodium oxybate oral solution. The AUC is affected by the extent to which the drug is absorbed in the GI tract. In the case of sodium oxybate, absorption is greatest in the upper GI tract, so that a solid dosage form must dissolve quickly in order to be bioequivalent to the oral solution.

Products are considered to be "bioequivalent" if the relative mean C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of the test product to reference product is within 80% to 125%.

A "compressed" tablet is one in which the drug and the excipients are bonded together sufficiently that they exhibit minimum friability (less than 1%) when tumbled in a testing apparatus designed for that purpose.

By "sodium oxybate oral solution" is intended the product currently known as Xyrem, a solution that contains 500 mg sodium oxybate/ml water, adjusted to pH=7.5 with malic acid.

The term "AUC_{0-t}" means the area under the plasma concentration curve from time 0 to time t.

The term "$AUC_{0-\infty}$" or "AUC_{0-inf}" means the area under the plasma concentration time curve from time 0 to infinity.

By "C_{max}" is intended the maximum plasma concentration of sodium oxybate. The C_{max} of a 3 gram dose of immediate release tablets is between 10 and 200 μg/mL, often between 20 and 120 μg/mL. Such profiles are especially desirable for diseases such as narcolepsy, cataplexy, movement disorders such as essential tremor and restless leg syndrome, fibromyalgia and chronic fatigue syndrome.

By "t_{max}" is intended the time to maximum plasma concentration and for sodium oxybate is between 0.5 and 2.5 hours, often between 0.5 and 1.5 hours and "$t_{1/2}$" is intended the time to 50% plasma concentration and for sodium oxybate is between 0.4 and 0.9 hours, often between 0.5 and 0.7 hours.

The apparent elimination rate constant is "λ_z" and may be between 0.5 and 2.5 hours^{-1}.

By "oxybate salt" is intended a compound of formula I wherein X is a pharmaceutically-acceptable cation and may be selected from the group consisting of sodium, potassium, calcium, lithium and magnesium and Y is OH.

By "sodium oxybate" is intended a compound of formula Ia.

The pharmaceutical immediate release compositions suitable for oral administration comprise solid unit dosage forms or "tablets" which can deliver a therapeutically effective dose of sodium oxybate upon ingestion thereof by the patient of one or more of said tablets, each of which can provide a dosage of about 0.5-1.5 g of sodium oxybate (or equivalent thereof). Additionally, the tablets could be shaped and scored to make them easier to swallow.

Examples of fillers/compression aids useful in said tablets include: lactose, calcium carbonate, calcium sulfate, compressible sugars, dextrates, dextrin, dextrose, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, powdered cellulose, and/or sucrose.

Examples of binders useful in said tablets include povidone and pregelatinized starch. Other examples of binders include dextrin, gelatin, hydroxypropyl methylcellulose, maltodextrin, starch, and zein. Further examples of binders include but are not limited to: acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, carboxymethylcellulose sodium, ethylcellulose, guar gum, hydrogenated vegetable oil (type 1), hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, magnesium aluminum silicate, and/or sodium alginate.

Surfactant/wetting agent concentrations can be varied between 0.1 and 10 wt-% to complement the drug amount in said tablets. Examples of surfactants/wetting agents comprise ionic and nonionic surfactants. Examples of non-ionic surfactants include polyoxyethyelene alkyl ethers, polyoxyethylene stearates, and/or poloxamers. Examples of ionic surfactants include but are not limited to sodium lauryl sulfate, docusate sodium (dioctyl sulfosuccinate sodium salt), benzalkonium chloride, benzethonium chloride, and cetrimide (alkyltrimethylammonium bromide, predominantly C_{14}-alkyl). Further examples of non-ionic surfactants include but are not limited to polysorbate, sorbitan esters, and glyceryl monooleate.

Glidant agent concentrations in said tablets can be varied between 0.1 and 5 wt-% to complement the drug amount. Examples of glidant agents are calcium phosphate dibasic, calcium silicate, colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, silicon dioxide, starch, talc or combinations thereof.

Lubricant concentrations in said tablets can be varied from 0.1 to 5 wt-%. Examples of useful lubricants include: calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, stearic acid, and zinc stearate.

Protection of the sodium oxybate composition from water during storage may also be provided or enhanced by coating the tablet with a continuous coating of a substantially water soluble or insoluble polymer. Useful water-insoluble or water-resistant coating polymers include ethyl cellulose and polyvinyl acetates. Further water-insoluble or water resistant coating polymers include polyacrylates, polymethacrylates or the like. Suitable water-soluble polymers include polyvinyl alcohol and HPMC. Further suitable water-soluble polymers include PVP, HPC, HPEC, PEG, HEC and the like.

For example, the present tablet is a solid body of about 750 mg-1.5 g of a composition comprising about 50-95 wt-%, preferably about 70-92.5 wt-% sodium oxybate, preferably about 75-90 wt-% sodium oxybate. The present tablets also comprise about 2.5-7.5 wt-% of one or more microcrystalline cellulose(s). These materials, which can include Avicel® PH 101 and SMCC 50, function as direct compression binders.

The present tablets also preferably comprise about 0.25-2.5 wt-% surfactant, preferably an anionic surfactant such as sodium lauryl sulfate or docusate sodium. Nonionic surfactants such as a poloxamer, a polysorbate, glyceryl mono-fatty acid esters, polyoxyethylene fatty acid esters and/or polyoxyethylene ethers of fatty alcohols; and cationic surfactants such as benzalkonium chlorides, benzethonium chlorides and cetrimide, can also be used. Normally, surfactants are added to formulations of drugs that are poorly water soluble in order to wet the surface of the drug particles. They generally have little or no effect on the dissolution of water soluble drugs like sodium oxybate. However, it was surprising that the addition of small amounts of surfactant to the tablets produced substantially faster dissolution, although addition of surfactant to the dissolution media, in equivalent or higher amounts did not produce the same effect.

The present tablets can also contain minor but effective amounts of other compression aids, fillers, binders, disintegrants, glidants and/or lubricants. For example, the present tablets can preferably contain about 2.5-15 wt-%, e.g., about 3-10 wt-% of other binder(s), disintegrant(s), glidant(s), or a combination thereof, including polyvinylpyrrolidone, pregelatinized starch, lactose, dibasic calcium phosphate and a compressible sugar such as sorbitol.

Preferably, the secondary binders comprise a mixture of about 0.5-5 wt-% polyvinylpyrrolidone (povidone) and about 2.5-7.5 wt-% pregelatinized starch. The glidant/disintegrant is preferably 0.1-0.75 wt-% silicon dioxide (e.g., Cab-O-Sil® MPS) and the lubricant is a fatty acid salt such as magnesium stearate or stearic acid. The present weight percentages are weight percentages of the ingredients in an uncoated capsule.

Because sodium oxybate is hygroscopic, it is preferred to coat the present tablet of the invention with a moisture-resistant coating such as a polyvinyl alcohol/lecithin-based coating (Opadry® AMB) or a hypromellose, microcrystalline cellulose, stearic acid coating (Sepifilm® LP 014). The coating can make up about 1-5 wt-% of the weight of the coated capsule, e.g., about 1.25-5.5 wt-% of the uncoated capsule.

Unexpectedly, the present tablets do not require the use of a high-performance disintegrant, such as a modified cellulosic disintegrant, e.g., croscarmellose sodium, (a cross-linked carboxymethyl cellulose) to achieve in vivo bioavailability equivalent to that achieved by the Xyrem® sodium oxybate oral solution. Typically, such high performance disintegrants are added at about 5-10 wt-% of immediate release compositions. In this case, the drug forms a gel upon exposure to water, so despite the high solubility of sodium oxybate, unique issues arise when attempting to produce a solid oral dosage form that will rapidly disintegrate. A "superdisintegrant' is usually added, but with this gel forming drug, such an additive would not aid in disintegration. Instead, a surfactant was added to the mixture prior to roller compaction so that it is intra-granularly incorporated. Such intra-granular incorporation speeds up dispersion of the gelled drug so that the tablet dissolves faster. Further, it allows water to enter the dosage form and aid in its disintegration, a phenomenon that would be expected with a hydrophilic drug, rather than a hydrophobic one such as sodium oxybate.

Controlled release formulations of gamma-hydroxybutyrate comprising a delayed or controlled release component and an immediate release component are described in U.S. 2006/0210630 A1. Pellets are formed from compositions that

typically comprise 10-50 wt-% of one or more microcrystalline celluloses, in combination with 40-90 wt-% sodium oxybate. The pellets are formed by adding 10-20 wt-% water during the granulation and extrusion process of the composition that yields the GHB pellets. The pellets are then dispersed in a solution of GHB.

The present immediate release dosage form is adapted for oral administration, so as to attain and maintain a therapeutic level of sodium oxybate over a preselected interval. The tablet contains a relatively large percentage and absolute amount of sodium oxybate and so is expected to improve patient compliance and convenience, by replacing the need to ingest large amounts of liquids or liquid/solid suspensions. One or more immediate release tablets can be administered, by oral ingestion, e.g., closely spaced, in order to provide a therapeutically effective dose of sodium oxybate to the subject in a relatively short period of time. For example, disintegration of a 500 mg-1.0 g tablet can provide about 95-100% of the oxybate to the subject in about 30-60 minutes.

The present invention also provides therapeutic methods to treat conditions amenable to treatment by sodium oxybate, such as those discussed hereinabove, by administering an effective amount of one or more dosage forms of the invention.

The present dosage forms can be administered to treat a human afflicted with narcolepsy to reduce cataplexy and/or daytime sleepiness.

The present dosage forms can be administered to humans, particularly in the elderly (>50 years old), to improve the quality of sleep, or in conditions in which an increase in growth hormone levels in vivo is desired.

The present dosage forms can also be used to treat fibromyalgia or chronic fatigue syndrome, e.g., to alleviate at least one symptom of fibromyalgia or chronic fatigue syndrome. See, U.S. Pat. No. 5,990,162.

The dosage forms of the present invention can also be provided as a kit comprising, separately packaged, a container comprising a plurality of the immediate release tablets of the invention, which tablets can be individually packaged, as in foil envelopes or in a blister pack. The tablets can be packaged in many conformations with or without dessicants or other materials to prevent ingress of water. Instruction materials or means, such as printed labeling, can also be included for their administration, e.g., sequentially over a preselected time period and/or at preselected intervals, to yield the desired levels of sodium oxybate in vivo for preselected periods of time, to treat a preselected condition.

The present invention also provides a particulate composition, such as granules, that can be tabletted by compression without the addition of exogeneous water before, during or after the tabletting process. This can assist in preserving the bioactivity of the sodium oxybate during the tablet preparation process.

A daily dose of about 1-1000 mg/kg of sodium oxybate or other oxybate salt such as a compound of formula (I) can be administered to accomplish the therapeutic results disclosed herein. For example, a daily dosage of about 0.5-20 g of the sodium oxybate or of a compound of formula (I) can be administered, preferably about 1-15 g, in single or divided doses. For example, useful dosages and modes of administration are disclosed in U.S. Pat. Nos. 5,990,162 and 6,472,432. Methods to extrapolate from dosages found to be effective in laboratory animals such as mice, to doses effective in humans are known to the art. See U.S. Pat. No. 5,294,430, or 4,939,949.

As noted herein above, the dosage forms of the present invention may be useful in the treatment of a variety of conditions amenable to treatment by sodium oxybate, such as narcolepsy to reduce cataplexy and/or daytime sleepiness, to improve the quality of sleep, or in conditions in which an increase in growth hormone levels in vivo is desired, and to treat fibromyalgia or chronic fatigue syndrome. The present dosage forms may be used to treat a host of other indications including drug and alcohol abuse, anxiety, cerebrovascular diseases, central nervous system disorders, neurological disorders including Parkinson's Disease and Alzheimer Disease, Multiple Sclerosis, autism, depression, inflammatory disorders, including those of the bowel, such as irritable bowel disorder, regional illitis and ulcerative colitis, autoimmune inflammatory disorders, certain endocrine disturbances and diabetes.

The present dosage forms may also be administered for the purpose of tissue protection including protection following hypoxia/anoxia such as in stroke, organ transplantation, organ preservation, myocardial infarction or ischemia, reperfusion injury, protection following chemotherapy, radiation, progeria, or an increased level of intracranial pressure, e.g. due to head trauma. The present dosage forms can also be used to treat other pathologies believed to be caused or exacerbated by lipid peroxidation and/or free radicals, such as pathologies associated with oxidative stress, including normal aging. See Patent Publication US 2004/0092455 A1. The present dosage forms may also be used to treat movement disorders including restless leg syndrome, myoclonus, dystonia and/or essential tremor. See Frucht et al, *Movement Disorders,* 20(10), 1330 (2005).

The invention will be further described by reference to the following detailed examples.

Example 1

Immediate Release Sodium Oxybate Tablets

This example provides 3 formulations of compressed tablets of sodium oxybate which have greater than 70% drug loading. The tablets were prepared using roller compaction as the manufacturing method for the granulation. The composition of the tablets is summarized on Table 1, below:

TABLE 1

Ingredient(s)	% (w/w)	Qty/Unit (mg)
Formulation A		
Sodium Oxybate	71.4	750.0
Microcrystalline Cellulose (Avicel PH 101)	12.1	126.7
Povidone (PVP K-17)	2.00	21.0
Croscarmellose Sodium NF/EP (Ac-Di-Sol SD-711)	12.0	126.0
Colloidal Silicon Dioxide (Cab-O-Sil MP5)	0.50	5.3
Sodium Lauryl Sulfate	1.00	10.5
Magnesium Stearate, NF (vegetable grade) (0.7% intragranular, 0.5% extragranular)	1.0	10.5
Formulation B		
Sodium Oxybate	78.9	750.0
Microcrystalline Cellulose (Avicel PH 101)	5.9	55.6
Povidone (PVP K-17)	2.0	19.0
Pregelatinized Starch (Starch 1500)	5.0	47.5
Colloidal Silicon Dioxide (Cab-O-Sil MP5)	0.5	4.8
Magnesium Stearate, NF (vegetable grade) (0.7% intragranular, 0.5% extragranular)	1.2	11.4
Croscarmellose Sodium, NF/EP (Ac-Di-Sol SD-711)	6.5	61.8

TABLE 1-continued

Ingredient(s)	% (w/w)	Qty/Unit (mg)
Formulation C		
Sodium Oxybate	84.46	750.0
Microcrystalline Cellulose (Avicel PH 101)	5.84	51.9
Povidone (PVP K-17)	2.00	17.8
Pregelatinized Starch (Starch 1500)	5.00	44.4
Colloidal Silicon Dioxide (Cab-O-Sil MP5)	0.50	4.4
Sodium Lauryl Sulfate	1.00	8.9
Magnesium Stearate, NF (vegetable grade) (0.7% intragranular, 0.5% extragranular)	1.20	10.7

To prepare a one kilogram batch of the tablets in Table 1, all the ingredients were hand-screened through a 20 mesh screen. All of the ingredients except the magnesium stearate, were transferred to a blender, and mixed for five minutes. A intragranular portion of the magnesium stearate (6.2 g) was added to the blender and mixing continued for 3 minutes. The material was passed through a roller compactor to make ribbons with thickness of 1.4±0.5 mm, without added water. The ribbons were milled and then granulated with a 16-mesh screen. The granulate was added to the blender and mixed for 5 minutes. The remaining magnesium stearate (4.5 g) was added to the blend, and mixed for 3 minutes. The blend was compressed into tablets on a standard tablet press to the following specifications: (a) Weight 888 mg; (b) Hardness: 15 kP hardness; (c) Disintegration time: NMT 15 min.; and (d) Friability: NMT 1.0% after 100 drops (n=10).

To coat the tablets of Formulation C, a 10% Opadry® AMB dispersion was prepared in ethanol/water. The ethanol and water was charged into a stainless steel pot and mixed for 3 minutes using an overhead mixer. Opadry® AMB Blue was slowly added into the vortex of the stirred liquid. The stirring speed was reduced and stirring continued for ≥30 minutes. The tablets were placed in the coating pan and preheated to 45° C. The tablets were coated to a 4% weight gain (35.5 mg/unit).

Example 2

Bioavailability and Bioequivalence of Sodium Oxybate Tablets

A Phase I, three-way, open-label, randomized single-dose crossover study of Formulation A (4.5 grams of Formulation A given as 6 tablets: Treatment A), Formulation B (4.5 grams of Formulation B given as 6 tablets: Treatment B), and Xyrem (4.5 grams of sodium oxybate oral solution: Treatment C). Following a 1 to 21-day screening period, the study duration for each subject was approximately 7 days, Period 1 comprising Days 1 to 2, Period 2 comprising Days 3 to 4, and Period 3 Days 5 to 6. A 2-day washout period (dosing on the morning of the first day followed by a I day washout) separated the Treatments A, B and C.

Single doses (4.5 g, given as 6×750 mg tablets) of sodium oxybate solid dosage Formulations A and B and Single doses (4.5 g) of sodium oxybate oral solution (Xyrem) were administered orally in the morning following a 10-hour fast, with subjects remaining fasted for a further 4 hours after dosing. The PK profile for sodium oxybate was evaluated over an 8-hour period, based on blood samples (5 mL) collected pre-dose; at 10, 20, 30, 45, 60 and 75 minutes post-dose; and at 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7 and 8 hours post-dose following each treatment. The PK parameters calculated for plasma sodium oxybate concentrations included: the area under the plasma concentration time curve from time 0 to time t of the last quantifiable concentration [AUC_{0-t}], and area under the plasma concentration time curve from time 0 to infinity[$AUC_{0-\infty}$], maximum plasma concentration of sodium oxybate (C_{max}), time to maximum plasma concentration (t_{max}), the apparent elimination rate constant (λ_z) and half-life ($t_{1/2}$) and the relative bioavailability for solid dosage Formulations A and B versus Xyrem.

The relative bioavailability of Treatments A and B versus Treatment C (Xyrem) based on AUC values were 98% and 100%, respectively. All treatments were found to be bioequivalent with regard to C_{max} and total exposure AUC after oral administration of sodium oxybate.

TABLE 2

Summary of Mean (SD) Sodium Oxybate Pharmacokinetic Parameters

PK Parameter	Units		Treatment A (Test)	Treatment B (Test)	Treatment C (Reference)
C_{max}	(µg/mL)	Mean	129	135	143
		SD	37.6	37.2	29.2
		Geometric Mean	123	131	140
		Geometric SD	1.39	1.32	1.23
t_{max}	(hr)	Median	1.00	1.00	0.750
		Min, Max	0.750, 2.50	0.500, 2.50	0.500, 1.50
AUC_{0-t}	(µg * hr/mL)	Mean	297	303	298
		SD	104	112	96.3
		Geometric Mean	275	280	281
		Geometric SD	1.53	1.53	1.45
AUC_{0-inf}	(µg * hr/mL)	Mean	298	304	300
		SD	104	112	96.6
		Geometric Mean	277	282	283
		Geometric SD	1.53	1.53	1.45
$t_{1/2}$	(hr)	Mean	0.584	0.561	0.646
		SD	0.196	0.139	0.245
λ_z	(hr^{-1})	Mean	1.30	1.32	1.19
		SD	0.414	0.398	0.345

Example 3

Dissolution Profiles of Sodium Oxybate Tablets

FIG. **1** shows the dissolution profile of one embodiment of the invention. The dosage form described in Example 1 as Formulation C has an immediate release profile. The immediate release tablets release sodium oxybate in less than 1 hour. This release profile was intermediate between the two dissolution curves of immediate release compositions described in Example 1 (Formulations A and B—see FIG. **2**) which was shown to be bioequivalent to Xyrem® solution (see Example 2), thus demonstrating that this composition is also bioequivalent to Xyrem® solution.

Example 4

Dissolution Profiles of Sodium Oxybate Tablets

Formulation D

Ingredient(s)	% (w/w)	Qty/Unit (mg)
Sodium Oxybate	78.95	750.0
Microcrystalline Cellulose (Avicel PH 101)	4.85	46.1
Povidone (PVP K-17)	2.00	19.0
Pregelatinized Starch (Starch 1500)	5.00	47.5
Croscarmellose Sodium NF/EP (Ac-Di-Sol SD-711)	6.50	61.8
Poloxamer 188	1.00	9.5
Colloidal Silicon Dioxide (Cab-O-Sil MP5)	0.50	4.8
Magnesium Stearate, NF (vegetable grade)	1.20	11.4

A one kilogram batch of tablets of Formulation D were prepared as described in Example 1 except using poloxamer as a surfactant rather than sodium lauryl sulfate. FIG. **3** shows the dissolution profile of Formulation D. The tablets have an immediate release profile and deliver sodium oxybate in less than 1 hour. This release profile was intermediate between the two dissolution curves of immediate release compositions described in Example 1 (Formulations A and B—see FIG. **4**) which were shown to be bioequivalent to Xyrem® solution (see Example 2), thus demonstrating that this composition is also bioequivalent to Xyrem® solution.

All publications, patents, and patent applications are incorporated herein by reference. While in the foregoing specification this invention has been described in relation to certain preferred embodiments thereof, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that certain of the details described herein may be varied considerably without departing from the basic principles of the invention.

What is claimed is:

1. A compressed tablet of sodium oxybate for oral delivery of 0.5-1.25 g of sodium oxybate comprising 80-95 wt % sodium oxybate; 5-10 wt % compression aid; and 1-50% binder; wherein the tablet is bioequivalent to sodium oxybate oral solution.

2. The compressed tablet of claim **1**, wherein the tablet is coated to 1-10 wt % gain with a film coating.

3. The compressed tablet of claim **1**, wherein the tablet comprises 80-90 wt % sodium oxybate.

4. The compressed tablet of claim **1**, wherein the tablet does not contain a super-disintegrant.

5. The compressed tablet of claim **1**, wherein the tablet further comprises 0.1-10 wt % of a surfactant.

6. An immediate release unit dosage form comprising an about 0.5-1.5 g compressed tablet comprising 80-95 wt-% sodium oxybate; about 2.5-7.5 wt-% microcrystalline cellulose and about 0.25-2.5 wt-% surfactant, wherein at least 90% of the sodium oxybate is released from the tablet within one hour from exposure of the tablet to an aqueous medium.

7. The unit dosage form of claim **6**, wherein the tablet is coated with a water resistant coating.

8. The unit dosage form of claim **6**, wherein the surfactant is an ionic surfactant.

9. The unit dosage form of claim **6**, further comprising a minor but effective amount of at least one of a second binder, a disintegrant, a glidant and a lubricant.

10. The unit dosage form of claim **9**, further comprising about 0.5-5 wt-% polyvinylpyrrolidone.

11. The unit dosage form of claim **9**, further comprising about 2.5-7.5 wt-% pregelatinized starch.

12. The unit dosage form of claim **9**, further comprising about 0.1-0.75 wt-% silicon dioxide.

13. The unit dosage form of claim **9**, further comprising magnesium stearate.

14. A therapeutic method for treating a human afflicted with narcolepsy, restless leg syndrome, essential tremor, fibromyalgia, or chronic fatigue syndrome by orally administering to said human an effective amount of a unit dosage form of claim **6**.

15. A method for preparing the tablet of claim **1** by granulating a water-free composition comprising the sodium oxybate, the compression and the binder; and compressing the granulated composition to yield said tablet.

16. The method of claim **15** further comprising coating said tablet with a water resistant coating.

17. The method of claim **16** wherein the coating comprises PVA and lecithin.

18. A compressed tablet of an oxybate salt for oral delivery of 0.5-1.25 g of oxybate salt comprising 80-95 wt % oxybate salt; 5-10 wt % compression aid; and 1-50% binder; wherein the tablet is bioequivalent to sodium oxybate oral solution.

19. The tablet of claim **18** wherein the oxybate salt is selected from the group consisting of potassium oxybate, calcium oxybate, lithium oxybate and magnesium oxybate.

* * * * *

EXHIBIT L

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carving knife *n.* a knife with a long blade, for carving meat.

car wash *n.* **1** an establishment containing equipment for washing vehicles automatically. **2** the equipment itself.

caryatid /karɪ'atɪd/ *n.* (*pl.* **caryatides** /-di:z/ or **caryatids**) *Archit.* a pillar in the form of a draped female figure, supporting an entablature. [French *caryatide* from Italian *cariatide* or their Latin source, from Greek *karuatis -idos* 'priestess at Caryae' (*Karuai*) in Laconia]

caryopsis /karɪ'ɒpsɪs/ *n.* (*pl.* **caryopses** /-si:z/) *Bot.* a dry one-seeded indehiscent fruit, as in wheat and maize. [modern Latin, from Greek *karuon* 'nut' + *opsis* 'appearance']

Casanova /kasə'nəʊvə, -z-/ *n.* a man notorious for seducing women. [G. J. *Casanova* de Seingalt, Italian adventurer d. 1798]

casbah var. of KASBAH.

cascade /kas'keɪd/ *n.* & *v.* ● *n.* **1** a small waterfall, esp. forming one in a series or part of a large broken waterfall. **2** a mass or quantity (of material, hair, etc.) in descending waves. **3** (foll. by *of*) a succession (of notes, ideas, etc.). **4 a** a process consisting of a series of similar stages with a cumulative effect. **b** a succession of devices, events, etc., each of which triggers or initiates the next. ● *v.intr.* fall in or like a cascade. [French from Italian *cascata*, from *cascare* 'to fall', ultimately from Latin *casus*: see CASE¹]

cascara /ka'skɑ:rə/ *n.* (in full **cascara sagrada** /sə'grɑ:də/) the bark of a Californian buckthorn, *Rhamnus purshiana*, used as a purgative. [Spanish, = sacred bark]

case¹ /keɪs/ *n.* **1** an instance of something occurring. **2** a state of affairs, hypothetical or actual. **3 a** an instance of a person receiving professional guidance or treatment, e.g. from a doctor or social worker. **b** this person or the circumstances involved. **4** a matter under official investigation, esp. by the police. **5** *Law* **a** a cause or suit for trial. **b** a statement of the facts in a cause sub judice, drawn up for a higher court's consideration (*judge states a case*). **c** a cause that has been decided and may be cited (*leading case*). **6 a** the sum of the arguments on one side, esp. in a lawsuit (*that is our case*). **b** a set of arguments, esp. in relation to persuasiveness (*have a good case; have a weak case*). **c** a valid set of arguments (*have no case*). **7** *Gram.* **a** the relation of a word to other words in a sentence. **b** a form of a noun, adjective, or pronoun expressing this. **8** *colloq.* a comical person. **9** one's position or circumstances (*in our case*). □ **as the case may be** according to the situation. **in any case** whatever the truth is; whatever may happen; what's more. **in case 1** in the event that; if. **2** lest; in provision against a stated or implied possibility (*take an umbrella in case it rains; took it in case*). **in case of** in the event of. **in the case of** as regards. **in no case** under no circumstances. **in that case** if that is true; should that happen. **is** (or **is not**) **the case** is (or is not) so. [Middle English in the sense 'a thing that befalls': via Old French *cas* from Latin *casus* 'fall', from *cadere cas-* 'to fall']

case² /keɪs/ *n.* & *v.* ● *n.* **1** a container or covering serving to enclose or contain. **2** a container with its contents. **3** the outer protective covering of a watch, book, seed vessel, sausage, etc. **4** *Brit.* an item of luggage, esp. a suitcase. **5** *Printing* a partitioned receptacle for type. **6** a glass box for showing specimens, curiosities, etc. ● *v.tr.* **1** enclose in a case. **2** (foll. by *with*) surround. **3** (esp. in phr. **case the joint**) *slang* reconnoitre (a house etc.), esp. with a view to robbery. [Middle English via Old French *casse*, *chasse* from Latin *capsa*, from *capere* 'hold']

casebook /'keɪsbʊk/ *n.* a book containing a record of legal or medical cases.

case-bound *adj.* (of a book) in a hard cover.

case-harden *v.tr.* **1** harden the surface of, esp. give a steel surface to (iron) by carbonizing. **2** make callous.

case history *n.* information about a person for use in professional treatment, e.g. by a doctor.

casein /'keɪsi:ɪn, -sɪn/ *n.* the main protein in milk, which occurs in coagulated form in cheese, and is used in plastics, adhesives, paint, etc. [Latin *caseus* 'cheese']

case knife *n.* a knife carried in a sheath.

case law *n.* the law as established by the outcome of former cases (cf. COMMON LAW, STATUTE LAW).

caseload /'keɪsləʊd/ *n.* the cases with which a doctor etc. is concerned at one time.

casemate /'keɪsmeɪt/ *n.* **1** a chamber in the thickness of the wall of a fortress, with embrasures. **2** an armoured enclosure for guns on a warship. [French *casemate* & Italian *casamatta* or Spanish *-mata*, from *camata*, perhaps from Greek *khasma -atos* 'gap']

casement /'keɪsm(ə)nt/ *n.* **1** a window or part of a window hinged vertically to open like a door. **2** *poet.* a window. [Middle English from Anglo-Latin *cassimentum*, from *cassa* CASE²]

case of conscience *n.* a matter in which one's conscience has to decide a conflict of principles.

case-shot *n.* **1** bullets in an iron case fired from a cannon. **2** shrapnel.

case study *n.* **1** an attempt to understand a person, institution, etc., from collected information. **2** a record of such an attempt. **3** the use of a particular instance as an exemplar of general principles.

casework /'keɪswɜ:k/ *n.* social work concerned with individuals, esp. involving understanding of the client's family and background. □ **caseworker** *n.*

cash¹ /kaʃ/ *n.* & *v.* ● *n.* **1** money in coins or notes, as distinct from cheques or orders. **2** (also **cash down**) money paid as full payment at the time of purchase, as distinct from credit. **3** *colloq.* wealth. ● *v.tr.* give or obtain cash for (a note, cheque, etc.). □ **cash in 1** obtain cash for. **2** (usu. foll. by *on*) *colloq.* profit (from); take advantage (of). **3** pay into a bank etc. **4** (in full **cash in one's checks**) *colloq.* die. **cash up** *Brit.* count and check cash takings at the end of a day's trading. □ **cashable** *adj.* **cashless** *adj.* [in earlier use = a box for money: obsolete French *casse* 'box' or Italian *cassa*, from Latin *capsa* CASE²]

cash² /kaʃ/ *n.* (*pl.* same) *hist.* any of various small coins of China or the E. Indies. [Portuguese *ca(i)xa* via Tamil *kāsu* from Sanskrit *karsha*, influenced by CASH¹]

cash and carry *n.* **1** a system of wholesaling in which goods are paid for in cash and taken away by the purchaser. **2** a store where this system operates.

cash book *n.* a book in which receipts and payments of cash are recorded.

cash box *n.* a box for keeping cash in.

cash card *n.* *Brit.* a plastic card (see CARD¹ *n.* 9a) which enables the holder to draw money from a cash dispenser.

cash cow *n.* *colloq.* a business, or part of one, that provides a steady cash flow.

cash crop *n.* a crop produced for sale, not for use as food etc.

cash desk *n.* a counter or compartment in a shop where goods are paid for.

cash dispenser *n.* *Brit.* an automatic machine from which customers of a bank etc. may withdraw cash, esp. by using a cash card.

cashew /'kaʃu:, kə'ʃu:/ *n.* **1** (also **cashew tree**) a bushy evergreen tree, *Anacardium occidentale*, native to Central and S. America, bearing kidney-shaped nuts attached to fleshy fruits. **2** (in full **cashew nut**) the edible nut of this tree. [Portuguese from Tupi (*a*)*caju*]

cashew apple *n.* the edible fleshy fruit of the cashew tree.

cash flow *n.* the movement of money into and out of a business, as a measure of profitability, or as affecting liquidity.

cashier¹ /ka'ʃɪə/ *n.* a person dealing with cash transactions in a shop, bank, etc. [Dutch *cassier* or French *caissier* (as CASH¹)]

lower layer of the earth's oceans and continental is, relatively heavy basic ia. [SILICA + MAGNESIA]
ij. 1 of or concerning the pe or monkey (*a simian* key. [Latin *simia* 'ape', Greek *simos* 'flat-nosed']
1 (often foll. by *to*) like, e, or amount; having a *nilar to mine; we have* alike. ●*n.* a person or unterpart. □ **similarity** *dv.* [French *similaire* or Latin *similis* 'like']

ould be followed by *to*, standard: *I have had You've come up with* They can be reworded *imilar to yours; You've o ours.*

speech involving the nother of a different ent (e.g. *as brave as a* son. [Middle English

likeness, guise, or g or person. 2 a of a comparison. 3 le. [Middle English Latin *similitudo* (as

r. & *tr.* be or keep be in a state of ●*n.* a simmering me calm or less dish (now dialect)

ch fruit cake, usu. ion, eaten esp. at h from Old French *simila* or Greek

enuine. [*the real*) *Bold Stroke for a* impersonated by

ng or selling of is or benefices. *n.* **simoniacal** d French *simonie* agus (Acts 8:18)] u:n/) a hot dry ls esp. in the *nma* 'to poison'] breviation]
nial, likeable.

le in a silly or npering. ●*n.* a *dv.* [16th c., of avian *semper*, te']

r, simplest) 1 o difficulty (*a* omplicated or ation. **3** not one element unqualified, *majority*). **5** d (*am not so* pearance or ss. **7** of low e). **8** *Bot.* **a** d from one inally. **2** a

k cat l *leg* m *man* n *no* p *pen* r *red* s *sit* t *top* v *vine*

medicine made from it. □ **simpleness** *n.* [ME English via Old French from Latin *simplus*]
simple eye *n.* an eye of an insect etc. having only lens. Also called OCELLUS; cf. COMPOUND EYE.
simple fracture *n.* a fracture of the bone only, a skin wound.
simple harmonic motion see HARMONIC MOTION.
simple interest *n.* interest payable on a capital only (cf. COMPOUND INTEREST).
simple interval *n. Mus.* an interval of one octave less.
simple machine *n.* any of the basic mechanical devices for applying a force (e.g. an inclined plane, wedge, or lever).
simple-minded *adj.* **1** feeble-minded; foolish. **2** unsophisticated; ingenuous. □ **simple-mindedly** *adv.* **simple-mindedness** *n.*
simple sentence *n.* a sentence with a single subject and predicate.
Simple Simon *n.* a foolish person (from the nursery rhyme character).
simple time *n. Mus.* a tempo with two, three, or four beats in a bar.
simpleton /'sɪmp(ə)lt(ə)n/ *n.* a foolish, gullible, or half-witted person. [SIMPLE, on the pattern of surnames from place names in *-ton*]
simplex /'sɪmplɛks/ *adj.* & *n.* ●*adj.* **1** simple; uncompounded. **2** *Computing* (of a communication system, computer circuit, etc.) allowing transmission of signals in one direction only (opp. DUPLEX *adj.* 3). ●*n.* a simple or uncompounded thing, esp. a word. [Latin, = simplus variant of *simplus* 'simple']
simplicity /sɪm'plɪsɪtɪ/ *n.* the fact or condition of being simple. □ **be simplicity itself** be extremely easy. [ME French *simplicité* or Latin *simplicitas* (as SIMPLEX)]
simplify /'sɪmplɪfʌɪ/ *v.tr.* (**-ies, -ied**) make simpler, easy or easier to do or understand. □ **simplification** /-fɪ'keɪʃ(ə)n/ *n.* [French *simplifier* from medieval Latin *simplificare* (as SIMPLE)]
simplism /'sɪmplɪz(ə)m/ *n.* **1** affected simplicity. **2** the unjustifiable simplification of a problem etc.
simplistic /sɪm'plɪstɪk/ *adj.* **1** excessively or affectedly simple. **2** oversimplified so as to conceal or distort difficulties. □ **simplistically** *adv.*
simply /'sɪmplɪ/ *adv.* **1** in a simple manner. **2** absolutely; without doubt (*simply astonishing*). **3** merely (*was simply trying to please*).
simulacrum /sɪmjʊ'leɪkrəm/ *n.* (*pl.* **simulacra** /-krə/) **1** an image of something. **2 a** a shadowy likeness; a deceptive substitute. **b** mere pretence. [Latin (as SIMULATE)]
simulate /'sɪmjʊleɪt/ *v.tr.* **1 a** pretend to have or feel (an attribute or feeling). **b** pretend to be. **2** imitate or counterfeit. **3 a** imitate the conditions of (a situation etc.), e.g. for training. **b** produce a computer model of (a process). **4** (as **simulated** *adj.*) made to resemble the real thing but not genuinely such (*simulated fur*). **5** (of a word) take or have an altered form suggested by a word wrongly taken to be its source, e.g. *asparagus* for *sparagus*. □ **simulation** /-'leɪʃ(ə)n/ *n.* **simulative** /-lətɪv/ *adj.* [Latin *simulare* from *similis* 'like']
simulator /'sɪmjʊleɪtə/ *n.* **1** a person or thing that simulates. **2** a device designed to simulate the operations of a complex system, used esp. in training (*flight simulator*).
simulcast /'sɪm(ə)lkɑːst/ *n.* simultaneous transmission of the same programme on radio and television. [SIMULTANEOUS + BROADCAST]
simultaneous /sɪm(ə)l'teɪnɪəs/ *adj.* (often foll. by *with*) occurring or operating at the same time. □ **simultaneity** /-tə'neɪtɪ/ *n.* **simultaneously** *adv.* **simultaneousness** *n.* [medieval Latin *simultaneus* from Latin *simul* 'at the same time', probably influenced by *instantaneus* etc.]

…neous equations *n.pl.* equations involving …ance unknowns that are to have the same …each equation.
…rmuːg/ *n.* a monstrous bird of Persian myth, …power of reasoning and speech. [Persian …om Pahlavi *sīn* 'eagle' + *murġ* 'bird']
… & *v.* ●*n.* **1 a** the breaking of divine or …esp. by a conscious act. **b** such an act. **2** an …inst good taste or propriety etc. ●*v.* (**sinned**, …**1** *intr.* commit a sin. **2** *intr.* (foll. by *against*) …*archaic* commit (a sin). □ **as sin** *colloq.* …*(ugly as sin).* **for one's sins** esp. *Brit. joc.* as …nt on one for something or other. **like sin** …ehemently or forcefully. **live in sin** *colloq.* live without being married. □ **sinless** *adj.* …*adv.* **sinlessness** *n.* [Old English *syn(n)*]
… *abbr.* sine.
…aɪnaɪ'ɪtɪk/ *adj.* of or relating to Mount Sinai …Sinai peninsula. [variant of *Sinaic*, from *Sinai*, …rew *sinay*, with *t* added for euphony]
…opus /sɪ'nanθrəpəs/ *n.* a fossil hominid now …ssed as *Homo erectus*. [modern Latin former …ame, as SINO- 'Chinese' (remains having been …ast Beijing) + Greek *anthrōpos* 'man']
… *colloq.* **1** *Ice Hockey* a penalty box. **2** *Brit.* a …aside for offenders of various kinds.
… *prep., conj., & adv.* ●*prep.* throughout, or at …n; the period between (a specified time, event, …the time present or being considered (*must …ceened since yesterday; has been going on since …greatest composer since Beethoven*). ●*conj.* **1** …in the time after (*what have you been doing …me?; has not spoken since the dog died*). **2** for …on that, because; inasmuch as (*since you are …will drive you home*). **3** (*ellipt.*) as being (*a more …ince better designed, too!*). ●*adv.* **1** from that …event until now or the time being considered …seen them since; had been healthy ever since; …been cut down*). **2** ago (*happened many years* [Middle English, reduced form of obsolete … or from dialect *sin* (from *sithen* 'then, …n, afterwards') from Old English *siththon*]
…sɪn'sɪə/ *adj.* (**sincerer**, **sincerest**) **1** free from …or deceit; the same in reality as in appearance. …ine, honest, frank. □ **sincereness** *n.* **sincerity** …*n.* [Latin *sincerus* 'clean, pure']
…rely /sɪn'sɪəlɪ/ *adv.* in a sincere manner. □ **yours …ly** a formula for ending a usu. informal letter.
…cipital /'sɪnsɪpʌl/ *n. Anat.* the front of the skull from …forehead to the crown. □ **sincipital** /-'sɪpɪt(ə)l/ *adj.* …from *semi-* 'half' + *caput* 'head']
… *n. Math.* **1** the trigonometric function that is … the ratio of the side opposite a given angle (in …a right-angled triangle) to the hypotenuse. **2** a function …line drawn from one end of an arc …erpendicularly to the radius through the other. [Latin …*curve*, fold of a toga', used in medieval Latin as …translation of Arabic *jayb* 'bosom, sine']
…cure /'sʌnɪkjʊə, 'sɪn-/ *n.* a position that requires …or no work but usu. yields profit or honour. …**cecurism** *n.* **sinecurist** *n.* [Latin *sine cura* 'without …care']
…e curve *n.* (also **sine wave**) a curve representing …oscillations of constant amplitude as given by …sine function; also called SINUSOID.
…e die /'sʌnɪ 'daɪiː, 'sɪneɪ 'diːeɪ/ *adv.* (of business etc.) …adjourned indefinitely) with no appointed date. [Latin, …without day]
…e qua non /ˌsʌnɪ kweɪ 'nɒn, ˌsɪneɪ kwɑː 'nəʊn/ *n.* an …indispensable condition or qualification. [Latin, = …thing without which not]
…ew /'sɪnjuː/ *n.* & *v.* ●*n.* **1** tough fibrous tissue …connecting muscle to bone; a tendon. **2** (in *pl.*) muscles; …muscular strength; wiriness. **3** (in *pl.*) that which forms …the strength or framework of a plan, city, organization, …etc. ●*v.tr. poet.* serve as the sinews of; sustain; hold …together. □ **sinewless** *adj.* **sinewy** *adj.* [Old English *sin(e)we*, from Germanic]
sinews of war *n.pl.* money.
sinfonia /sɪnfə'nɪːə, sɪn'fəʊnɪə/ *n. Mus.* **1** a symphony. **2** (in baroque music) an orchestral piece used as an introduction to an opera, cantata, or suite. **3** (**Sinfonia**; usu. in names) a small symphony orchestra. [Italian, = SYMPHONY]
sinfonietta /ˌsɪnfəʊnɪ'ɛtə/ *n. Mus.* **1** a short or simple symphony. **2** (**Sinfonietta**; usu. in names) a small symphony orchestra. [Italian, diminutive of SINFONIA]
sinful /'sɪnfʊl, -f(ə)l/ *adj.* **1** (of a person) committing sin, esp. habitually. **2 a** (of an act) involving or characterized by sin. **b** *colloq.* reprehensible. □ **sinfully** *adv.* **sinfulness** *n.* [Old English *synfull* (as SIN[1], -FUL)]
sing /sɪŋ/ *v.* & *n.* ●*v.* (*past* **sang** /saŋ/; *past part.* **sung** /sʌŋ/) **1** *intr.* utter musical sounds with the voice, esp. words with a set tune. **2** *tr.* utter or produce by singing (*sing another song*). **3** *intr.* (of the wind, a kettle, etc.) make melodious, humming, buzzing, or whistling sounds. **4** *intr.* (of the ears) be affected as with a buzzing sound. **5** *tr.* bring to a specified state by singing (*sang the child to sleep*). **6** *tr.* (foll. by *in*, *out*) usher (esp. the new or old year) in or out with singing. **7** *intr. slang* turn informer; confess. **8** *intr. archaic* compose poetry. **9** *tr.* & (foll. by *of*) *intr.* celebrate in verse. ●*n.* **1** an act or spell of singing. **2** *US* a meeting for amateur singing. □ **sing along** sing in accompaniment to a song or piece of music. **sing out** call out loudly; shout. **sing the praises of** see PRAISE. **sing up** sing more loudly. □ **singable** *adj.* **singer** *n.* **singingly** *adv.* [Old English *singan*, from Germanic]

■ **Usage** The use of *sung* instead of *sang* for the past tense as in *She sung three songs* is non-standard.

sing. *abbr.* singular.
singalong /'sɪŋəlɒŋ/ *n.* **1** a tune etc. to which one can sing in accompaniment (also *attrib.*: *a singalong chorus*). **2** an occasion of community singing (also *attrib.*: *a singalong evening*).
singe /sɪn(d)ʒ/ *v.* & *n.* ●*v.* (**singeing**) **1** *tr.* & *intr.* burn superficially or lightly. **2** *tr.* burn the bristles or down off (the carcass of a pig or fowl) to prepare it for cooking. **3** *tr.* burn off the tips of (the hair) in hairdressing. ●*n.* a superficial burn. □ **singe one's wings** suffer harm esp. in a risky attempt. [Old English *sengan*, from West Germanic]
singer-songwriter *n.* a person who sings and writes songs, esp. professionally.
Singh /sɪŋ/ *n.* **1** a title adopted by the warrior castes of northern India. **2** a surname adopted by male Sikhs. [Punjabi *siṅgh* 'lion' from Sanskrit *siṃha* 'lion']
Singhalese var. of SINHALESE.
singing hinny *n.* a currant cake baked on a griddle.
singing saw *n.* = MUSICAL SAW.
single /'sɪŋg(ə)l/ *adj.*, *n.*, & *v.* ●*adj.* **1** one only, not double or multiple. **2** united or undivided. **3 a** designed or suitable for one person (*single room*). **b** used or done by one person etc. or one set or pair. **4** one by itself; not one of several (*a single tree*). **5** regarded separately (*every single thing*). **6** not married; not involved in a sexual relationship. **7** *Brit.* (of a ticket) valid for an outward journey only, not for the return. **8** (with *neg.* or *interrog.*) even one; not to speak of more (*did not see a single person*). **9** (of a flower) having only one circle of petals. **10** lonely, unaided. **11** *archaic* free from duplicity, sincere, consistent, guileless, ingenuous. ●*n.* **1** a single thing, or item in a series. **2** *Brit.* a single ticket. **3** a short record with one piece of music etc. on each side. **4 a** *Cricket* a hit for one run. **b** *Baseball* a one-base hit. **5** (usu. *in pl.*) a game with one player on each side. **6** an unmarried person (*young singles*). **7** *US colloq.* a one-dollar note. ●*v.tr.* (foll. by *out* and often by *for*, *as*) select from a group as worthy of special attention, praise, etc. (*singled out for praise; singled out as the finest*). □ **singleness** *n.* **singly** *adv.* [Middle

ɪ zoo ʃ *she* ʒ decision θ *th*in ð *th*is ŋ ri*ng* x loch tʃ *ch*ip dʒ jar (*see over for vowels*)

English via Old French from Latin *singulus*, related to *simplus* SIMPLE]

single acrostic *n.* an acrostic using the first letter only of each line.

single-acting *adj.* (of an engine etc.) having pressure applied only to one side of the piston.

single-breasted *adj.* (of a jacket etc.) having only one set of buttons and buttonholes, not overlapping.

single combat *n.* a duel.

single cream *n. Brit.* thin cream with a relatively low fat content.

single cut *adj.* (of a file) with grooves cut in one direction only, not crossing.

single-decker *n.* esp. *Brit.* a bus having only one deck.

single entry *n.* a system of bookkeeping in which each transaction is entered in one account only.

single file *n. & adv.* ● *n.* a line of people or things arranged one behind another. ● *adv.* one behind another.

single-handed *adv. & adj.* ● *adv.* **1** without help from another. **2** with one hand. ● *adj.* **1** done etc. single-handed. **2** for one hand. □ **single-handedly** *adv.*

single-lens reflex *adj.* denoting a reflex camera in which a single lens serves the film and the viewfinder.

single-line *attrib.adj.* with movement of traffic in only one direction at a time.

single market *n.* an association of countries trading without restrictions, esp. in the European Union.

single-minded *adj.* having or intent on only one purpose. □ **single-mindedly** *adv.* **single-mindedness** *n.*

single parent *n.* a person bringing up a child or children without a partner.

singles bar *n.* a bar for single people seeking company.

single-seater *n.* a vehicle with one seat.

single stick *n.* **1** a basket-hilted stick of about a sword's length. **2** one-handed fencing with this.

singlet /ˈsɪŋglɪt/ *n.* **1** esp. *Brit.* a garment worn under or instead of a shirt; a vest. **2** a single unresolvable line in a spectrum. [originally, a man's short jacket: SINGLE + -ET[1], on the pattern of *doublet*, the garment being unlined]

singleton /ˈsɪŋg(ə)lt(ə)n/ *n.* **1** one card only of a suit, esp. as dealt to a player. **2 a** a single person or thing. **b** an only child. **3** a single child or animal born, not a twin etc. [SINGLE, on the pattern of *simpleton*]

singletree /ˈsɪŋg(ə)ltriː/ *n. US* = SWINGLETREE.

sing-song *adj., n., & v.* ● *adj.* uttered with a monotonous rhythm or cadence. ● *n.* **1** a sing-song manner. **2** *Brit.* an informal gathering for singing. ● *v.intr. & tr.* (*past* and *past part.* **sing-songed**) speak or recite in a sing-song manner.

singular /ˈsɪŋgjʊlə/ *adj. & n.* ● *adj.* **1** unique; much beyond the average; extraordinary. **2** eccentric or strange. **3** *Gram.* (of a word or form) denoting or referring to a single person or thing. **4** *Math.* possessing unique properties. **5** single, individual. ● *n. Gram.* **1** a singular word or form. **2** the singular number. □ **singularly** *adv.* [Middle English via Old French *singuler* from Latin *singularis* (as SINGLE)]

singularity /sɪŋgjʊˈlarɪtɪ/ *n.* (*pl.* **-ies**) **1** the state or condition of being singular. **2** an odd trait or peculiarity. **3** *Physics & Math.* a point at which a function takes an infinite value, esp. in space-time when matter is infinitely dense as at the centre of a black hole. [Middle English via Old French *singularité* from Late Latin *singularitas* (as SINGULAR)]

singularize /ˈsɪŋgjʊlərʌɪz/ *v.tr.* (also **-ise**) **1** distinguish, individualize. **2** make singular. □ **singularization** /-ˈzeɪʃ(ə)n/ *n.*

sinh /ʃʌɪn, sɪnʃ, saɪˈneɪtʃ/ *abbr. Math.* hyperbolic sine. [*sine* + *h*yperbolic]

Sinhalese /sɪnhəˈliːz, sɪnə-/ *n. & adj.* (also **Singhalese** /sɪŋə-/) ● *n.* (*pl.* same) **1** a member of a people originally from N. India and now forming the majority of the population of Sri Lanka. **2** an Indic language spoken by this people. ● *adj.* of or relating to this people or language. [Sanskrit *siṁhalam* 'Sri Lanka' (Ceylon) + -ESE]

sinister /ˈsɪnɪstə/ *adj.* **1** suggestive of evil; looking malignant or villainous. **2** wicked or criminal (*a sinister motive*). **3** of evil omen. **4** *Heraldry* of or on the left-hand side of a shield etc. (i.e. to the observer's right). **5** *archaic* left-hand. □ **sinisterly** *adv.* **sinisterness** *n.* [Middle English from Old French *sinistre* or Latin *sinister* 'left']

sinistral /ˈsɪnɪstr(ə)l/ *adj.* **1** left-handed. **2** of or on the left. **3** (of a flatfish) with the left side uppermost. **4** (of a spiral shell) with whorls rising to the left and not (as usually) to the right. □ **sinistrality** /-ˈralɪtɪ/ *n.* **sinistrally** *adv.*

sinistrorse /ˈsɪnɪstrɔːs/ *adj.* rising towards the left (of the spiral stem of a plant. [Latin *sinistrorsus*, from *sinister* 'left' + *vorsus*, past part. of *vertere* 'turn']

sink /sɪŋk/ *v. & n.* ● *v.* (*past* **sank** /saŋk/ or **sunk** /sʌŋk/, *past part.* **sunk** or as *adj.* **sunken**) **1** *intr.* fall or come slowly downwards. **2** *intr.* disappear below the horizon (*the sun is sinking*). **3** *intr.* **a** go or penetrate below the surface esp. of a liquid. **b** (of a ship) go to the bottom of the sea etc. **4** *intr.* settle down comfortably (*sank into a chair*). **5** *intr.* **a** gradually lose strength or value or quality etc.; decline (*my heart sank*). **b** (of the voice) descend in pitch or volume. **c** (of a sick person) approach death. **6** *tr.* send (a ship) to the bottom of the sea etc. **7** *tr.* cause or allow to sink or penetrate (*sank its teeth into my leg*). **8** *tr.* cause the failure of (a plan etc.) or the discomfiture of (a person). **9** *tr.* dig (a well or bore (a shaft). **10** *tr.* engrave (a die) or inlay (a design). **11** *tr.* **a** invest (money) (*sunk a large sum into the business*). **b** lose (money) by investment. **12** *tr.* **a** cause (a ball) to enter a pocket in billiards, a hole at golf, etc. **b** achieve this by (a stroke). **13** *tr.* overlook or forget; keep in the background (*sank their differences*). **14** *intr.* (of a price etc.) become lower. **15** *intr.* (of a storm or river) subside. **16** *intr.* (of ground) slope down or reach a lower level by subsidence. **17** *intr.* (foll. by *on*, *upon*) (of darkness) descend (on a place). **18** *tr.* lower the level of. **19** *tr.* (usu. in *passive*; foll. by *in*) absorb; hold the attention of (*be sunk in thought*). ● *n.* **1** a fixed basin with a water supply and outflow pipe. **2** a place where foul liquid collects. **3** a place of vice or corruption. **4** a pool or marsh in which a river's water disappears by evaporation or percolation. **5** *Physics* a body or process used to absorb or dissipate heat. **6** (in full **sink-hole**) *Geol.* a cavity in limestone etc. into which a stream etc. disappears. □ **sink in 1** penetrate or make its way in. **2** become gradually comprehended (*paused to let the words sink in*). **sink or swim** even at the risk of complete failure (*determined to try, sink or swim*). □ **sinkable** *adj.* **sinkage** *n.* [Old English *sincan*, from Germanic]

■ **Usage** In the past tense either *sank* or *sunk* is acceptable in standard English, as in *It sank* or *sunk* its teeth into her hand.

sinker /ˈsɪŋkə/ *n.* **1** a weight used to sink a fishing line or sounding line. **2** *US* a doughnut. **3** *Baseball* a ball which drops markedly after being pitched or hit.

sinking feeling *n.* a bodily sensation, esp. in the abdomen, caused by hunger or apprehension.

sinking fund *n.* money set aside for the gradual repayment of a debt.

sinner /ˈsɪnə/ *n.* a person who sins, esp. habitually.

sinnet /ˈsɪnɪt/ *n.* (also **sennit**) *Naut.* braided cordage of flat or round or square form, made from 3 to 9 cords. [17th c.: origin unknown]

Sinn Fein /ʃɪn ˈfem/ *n.* a political movement and party seeking a united republican Ireland, now linked to the IRA. □ **Sinn Feiner** *n.* [Irish *sinn féin* 'we ourselves']

Sino- /ˈsʌɪnəʊ/ *comb. form* Chinese; Chinese and (*Sino-British*). [Greek *Sinai* 'the Chinese']

sinologue /ˈsʌɪnəlɒg, ˈsɪ-/ *n.* an expert in sinology. [French (as SINO- + Greek *-logos* 'speaking')]

sinology /sʌɪˈnɒlədʒɪ, sɪ-/ *n.* the study of Chinese language, history, customs, etc. □ **sinological** /-nəˈlɒdʒɪk(ə)l/ *adj.* **sinologist** *n.*

sinter /ˈsɪntə/ *n. & v.* ● *n.* **1** a siliceous or calcareous rock formed by deposition from springs. **2** a substance formed by sintering. ● *v.intr. & tr.* coalesce or cause to coalesce from powder into solid by heating. [German, = *Engl. sinder* CINDER]

sinuate /ˈsɪnjʊət/ *adj.* esp. *Bot.* wavy-edged; with distinct inward and outward bends along the edge. [Latin *sinuatus*, past part. of *sinuare* 'bend']

sinuosity /sɪnjʊˈɒsɪtɪ/ *n.* (*pl.* **-ies**) **1** the state of being sinuous. **2** a bend, esp. in a stream or road. [French *sinuosité* or medieval Latin *sinuositas* (as SINUOUS)]

sinuous /ˈsɪnjʊəs/ *adj.* with many curves; tortuous, undulating. □ **sinuously** *adv.* **sinuousness** *n.* [French *sinueux* or Latin *sinuosus* (as SINUS)]

sinus /ˈsʌɪnəs/ *n.* **1** a cavity of bone or tissue, esp. in the skull connecting with the nostrils. **2** *Med.* a fistula, esp. of a deep abscess. **3** *Bot.* the curve between the lobes of a leaf. [Latin, = bosom, recess]

sinusitis /sʌɪnəˈsʌɪtɪs/ *n.* inflammation of a nasal sinus.

sinusoid /ˈsʌɪnəsɔɪd/ *n.* **1** a curve having the form of a sine wave. **2** a small irregularly-shaped blood vessel, as found in the liver. □ **sinusoidal** /-ˈsɔɪd(ə)l/ *adj.* **sinusoidally** /-ˈsɔɪd(ə)lɪ/ *adv.* [French *sinusoïde* from Latin *sinus*: see SINUS]

Sion var. of ZION.

-sion /ʃ(ə)n, ʒ(ə)n/ *suffix* forming nouns (see -ION) from Latin participial stems in *-s-* (*mansion*; *mission*; *persuasion*).

Sioux /suː/ *n. & adj.* ● *n.* (*pl.* same) **1** a member of a group of N. American Indian peoples chiefly inhabiting the upper Mississippi and Missouri river basins. **2** the language of these peoples. ● *adj.* of or relating to these peoples or language. □ **Siouan** /ˈsuːən/ *adj. & n.* [N. American French from *Nadouessioux* from Ojibwa (Ottawa dialect) *nātowēssiwak*, with French pl. ending -x replacing Ojibwa pl. ending *-ak*]

sip /sɪp/ *v. & n.* ● *v.tr. & intr.* (**sipped**, **sipping**) drink in one or more small amounts or by spoonfuls. ● *n.* **1** a small mouthful of liquid (*a sip of brandy*). **2** the act of taking this. □ **sipper** *n.* [Middle English: perhaps a modification of SUP[1]]

sipe /sʌɪp/ *n.* a groove or channel in the tread of a tyre to improve its grip. [dialect *sipe* 'to ooze' from Old English *sīpian*, Middle Low German *sīpen*, of unknown origin]

siphon var. of SYPHON.

siphonophore /sʌɪˈfɒnəfɔː/ *n.* any usu. translucent marine hydrozoan of the order Siphonophora, e.g. the Portuguese man-of-war. [Greek *siphōno-* (as SYPHON, -PHORE)]

sippet /ˈsɪpɪt/ *n.* **1** a small piece of bread etc. soaked in liquid. **2** a piece of toast or fried bread as a garnish. **3** a fragment. [apparently diminutive of SOP]

sir /sɜː/ *n.* **1** a polite or respectful form of address or mode of reference to a man. **2** (**Sir**) a titular prefix to the forename of a knight or baronet. [Middle English, reduced form of SIRE]

sirdar /ˈsɜːdɑː/ *n.* (also **sardar** *pronunc.* same) **1** (esp. in the Indian subcontinent) a person of high political or military rank; a leader. **2** a Sikh. [Urdu *sardār*, from Persian *sar* 'head' + *dār* 'possessor']

sire /ˈsʌɪə/ *n. & v.* ● *n.* **1** the male parent of an animal, esp. a stallion kept for breeding. **2** *archaic* a respectful form of address, now esp. to a king. **3** *archaic poet.* a father or male ancestor. ● *v.tr.* (esp. of an animal) beget. [Middle English from Old French, ultimately from Latin *senior*: see SENIOR]

siren /ˈsʌɪər(ə)n/ *n.* **1 a** a device for making a loud prolonged signal or warning sound, esp. by revolving a perforated disc over a jet of compressed air or steam. **b** the sound made by this. **2** (in Greek mythology) each of a number of women or winged creatures whose singing lured unwary sailors on to rocks. **3** a sweet singer. **4 a**

EXHIBIT M

ESL/LEARNER'S EDITION

NEWER WORDS FASTER

RANDOM HOUSE WEBSTER'S DICTIONARY of American English

- Over 50,000 Words and Phrases
- Standard and International (IPA) Pronunciations
- Special New-Words Section

ABBREVIATIONS USED IN THIS DICTIONARY

adj.	adjective	N	north, northern
adv.	adverb	n.	noun
Brit.	British	nom.	nominative
cm	centimeter(s)	obj	object
conj.	conjunction	obj.	objective
def.	definition	part.	participle
defs.	definitions	pl.	plural
E	east, eastern	poss.	possessive
Eng.	English	pp.	past participle
esp.	especially	prep.	preposition
Fr.	French	pres.	present
ft.	foot, feet	pron.	pronoun
Ger.	German	pt.	preterit (past tense)
in.	inch(es)	S	south, southern
interj.	interjection	sing.	singular
It.	Italian	Sp.	Spanish
km	kilometer(s)	Syn.	Synonym (Study)
m	meter(s)	v.	verb
mi.	mile(s)	W	west, western
mm	millimeter(s)	yd.	yard(s)

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ticular form of a written letter, either capital (uppercase) or small (lowercase). —*v.* [~ + *obj*] **6.** to put or enclose in a case. **7.** *Slang.* to examine carefully (a house, etc.) esp. in planning a crime: *We cased the joint last night; we can get in, no problem.*

ca•sein (kā′sēn, -sē in) /ˈkeɪsiɪn, -siɪn/ *n.* [*noncount*] a protein from milk, forming the basis of cheese.

case•load or **case load** (kās′lōd′) /ˈkeɪsˌloʊd/ *n.* [*count; usually singular*] the number of cases handled by a court, agency, etc., over a period: *a caseload of ten clients a day.*

case•ment (kās′mənt) /ˈkeɪsmənt/ *n.* [*count*] Also called **case′ment win′dow.** a window that has hinges on the sides.

case•work (kās′wûrk′) /ˈkeɪsˌwɜrk/ *n.* [*noncount*] social work involving contact between the social worker and the client. —**case′work′er,** *n.* [*count*]

cash (kash) /kæʃ/ *n.* [*noncount*] **1.** money in the form of coins or banknotes: *$5,000 in cash and the rest in traveler's checks.* **2.** money or an equivalent, as a check, paid at the time of making a purchase. **3.** money: *We're completely out of cash.* See illustration at BANK. —*v.* **4.** [~ + *obj*] to give or obtain cash for (a check, etc.): *Can you cash this check here?* **5. cash in,** [~ + *in* + *obj*] to turn in and get cash for (one's chips), as in a gambling casino. **6. cash in on,** [~ + *in* + *on* + *obj*] to profit from; use to one's advantage: *He cashed in on the deal his partner made.* —**cash′less,** *adj.*

cash′ crop′, *n.* [*count*] a crop intended to be sold: *such cash crops as tobacco.*

cash•ew (kash′ōō, kə shōō′) /ˈkæʃuw, kəˈʃuw/ *n.* [*count*] **1.** a tropical American tree with yellowish pink flowers in open clusters. **2.** Also called **cash′ew nut′.** the small, edible nut of this tree.

cash•ier[1] (ka shēr′) /kæˈʃɪər/ *n.* [*count*] **1.** an employee who totals purchases and collects payment from customers, or who dispenses money in a bank. **2.** an executive who oversees the finances of a company.

cash•ier[2] (ka shēr′) /kæˈʃɪər/ *v.* [~ + *obj*] to dismiss from a position esp. with disgrace: *He was cashiered from the navy.*

cashier's′ check′, *n.* [*count*] a check drawn by a bank on its own funds and signed by its cashier.

cash′ machine′, *n.* AUTOMATED-TELLER MACHINE.

cash•mere or **kash•mir** (kazh′mēr, kash′-) /ˈkæʒmɪər, ˈkæʃ-/ *n.* [*noncount*] the fine, soft wool of the Kashmir goat, or yarn made from this wool.

cash′ reg′ister, *n.* [*count*] a machine in a business that indicates the amounts of individual sales and has a money drawer for making change. See illustration at SUPERMARKET.

cas•ing (kā′sing) /ˈkeɪsɪŋ/ *n.* [*count*] **1.** a case or covering; housing: *shell casings.* **2.** the framework around a door or window. **3.** the tube-shaped case for making the outside of sausage, etc.

ca•si•no (kə sē′nō) /kəˈsiynow/ *n.* [*count*], *pl.* **-nos.** a building used for professional gambling, for meetings, or for dancing.

cask (kask) /kæsk/ *n.* [*count*] **1.** a container like a barrel, for holding alcoholic drinks. **2.** the quantity such a container holds.

cas•ket (kas′kit) /ˈkæskɪt/ *n.* [*count*] **1.** a coffin. **2.** a small chest or box, such as for jewels.

cas•sa•va (kə sä′və) /kəˈsɑvə/ *n., pl.* **-vas. 1.** [*count*] a tropical American plant having thick roots. **2.** [*noncount*] flour or the starch from the roots of this plant, the source of tapioca.

cas•se•role (kas′ə rōl′) /ˈkæsəˌrowl/ *n.* [*count*] **1.** a usually large, covered baking dish, as of glass or pottery. **2.** any food baked in such a dish: *tuna casseroles.*

cas•sette (kə set′, ka-) /kəˈsɛt, kæ-/ *n.* [*count*] **1.** a plastic case in which audiotape or videotape runs between two reels for recording or playing back. **2.** a container for a roll of photographic film.

cas•sock (kas′ək) /ˈkæsək/ *n.* [*count*] a long, close-fitting garment like a robe, worn by members of the clergy.

cast (kast) /kæst/ *v.,* **cast, cast•ing,** *n.* —*v.* **1.** [~ + *obj*] to throw or hurl; fling: *to cast dice.* **2.** [~ + *obj*] to direct (the eye, etc.): *She kept casting glances at me across the room.* **3.** [~ + *obj*] to cause to fall; put or send forth: *This special lightbulb casts a soft light.* **4.** [~ + *obj*] to draw (lots), as in telling fortunes: *The soldiers cast lots to see who would draw guard duty.* **5.** [~ + *obj*] to throw out (a fishing line, etc.): *I was casting my line from the shore when it got tangled with hers.* **6.** [~ + *obj*] to shed or drop: *The snake cast its skin.* **7.** [~ + *obj*] to put or place, esp. by force: *The villain was cast into prison.* **8.** [~ + *obj*] to deposit or give (a ballot): *cast his ballot for president.* **9.** [~ + *obj*] to form or arrange; plan out: *He cast his speech in more military terms.* **10. a.** [~ + *obj*] to select actors for (a play, etc.): *The directors and producers were casting the part of Hamlet.* **b.** to assign a role to (an actor): [~ + *obj*]: *They cast him in the role of Caesar.* [~ + *obj* + *as* + *obj*]: *They cast him as Hamlet in their production.* **11.** [~ + *obj*] to form (an object) by pouring metal, etc., into a mold and letting it harden: *The statue was cast from bronze.* **12. cast about** or **around, a.** [~ + *about/around* + *obj*] to search; look: *I cast about the room to find a container.* **b.** [~ + *for* + *obj*] to seek; *always casting around for some way to make more money.* **c.** [*no obj*] to devise a plan; scheme: *She was casting about to get the boss's attention.* **13. cast away** or **aside,** to reject; discard: [~ + *away/aside* + *obj*]: *They cast aside our objections.* [~ + *obj* + *away/aside*]: *Don't cast it away.* **14. cast back,** [~ + *obj* + *back*] to refer to something past; go back to something past: *I cast my mind back to the days of my childhood.* **15. cast off, a.** [~ + *off* + *obj*] to discard; throw away; reject: *We cast off our doubts and signed the contract.* **b.** to let go or let loose, as a ship from a mooring: [~ + *off* + *obj*]: *The sailors cast off the ropes and set sail.* [~ + *obj* + *off*]: *They cast the ropes off and set sail.* **c.** [~ + *off* + *obj*] to complete a knitted fabric by looping over or removing (the final stitches): *began to cast off the last row of stitches.* **16. cast out,** [~ + *out* + *obj*] to force to leave; expel; banish: *They said he could cast out demons and heal the sick.* —*n.* [*count*] **17.** the act of throwing. **18.** a throw of dice: *After each cast, the player may bid or take a card.* **19.** the act of throwing a fishing line or net onto the water: *My first cast went out about fifteen feet.* **20.** [*usually singular*] the group of performers in a play, etc.; players: *The cast threw a party after the last performance.* **21.** something made by pouring liquid metal, etc., into a mold and letting it harden. **22.** a rigid, hard covering used to protect and hold in place a broken bone: *They put my arm in a cast.* **23.** sort; kind; style; quality: *minds of a philosophical cast.* **24.** a turning of the eye to the side.

cas•ta•net (kas′tə net′) /ˌkæstəˈnɛt/ *n.* [*count*] Usually, **castanets.** [*plural*] a small musical instrument made up of two shells of wood held in the palm of the hand and clicked together to accompany dancing.

cast•a•way (kast′ə wā′) /ˈkæstəˌweɪ/ *n.* [*count*] **1.** a person whose ship has been wrecked and who has landed on a deserted island. **2.** anything cast adrift or thrown away. **3.** an outcast.

caste (kast) /kæst/ *n.* **1.** [*count*] any of the social divisions of Hindu society. **2.** [*count*] a social division limited to people of the same rank, occupation, etc., by birth: *castes of rich and poor.* **3.** [*noncount*] the rigid system of dividing or distinguishing among people in social groups in these ways. **4.** [*noncount*] social position conferred upon one by a caste system: *to lose caste.*

cast•er (kas′tər) /ˈkæstər/ *n.* [*count*] **1.** a person or thing that casts. **2.** a small wheel on a swivel, set under a piece of furniture, etc., to make it easier to move.

cas•ti•gate (kas′ti gāt′) /ˈkæstɪˌgeɪt/ *v.* [~ + *obj*], **-gat•ed, -gat•ing.** to reprimand or criticize severely: *The principal castigated the pupils for vandalizing the school.* —**cas•ti•ga•tion** (kas′ti gā′shən) /ˌkæstɪˈgeɪʃən/ *n.* [*noncount*] —**cas′ti•ga′tor,** *n.* [*count*]

cast•ing (kas′ting) /ˈkæstɪŋ/ *n.* **1.** [*count*] something cast in a mold. **2.** [*noncount*] the process of choosing actors for a play, etc.

cast′ i′ron, *n.* [*noncount*] an alloy of iron, carbon, and other elements, cast as a soft and strong, or as a hard and brittle, iron.

cast′-i′ron, *adj.* [*before a noun*] **1.** made of cast iron. **2.** not subject to change or exception: *a cast-iron rule.* **3.** strong; hardy: *a cast-iron stomach.*

cas•tle (kas′əl) /ˈkæsəl/ *n., v.,* **-tled, -tling.** —*n.* [*count*] **1.** a fortified, protected building, usually with a wall around it, owned by a prince or noble esp. in former times. **2.** a large and stately residence, esp. one that imitates the forms of a medieval castle. **3.** any place providing security and privacy: *the old saying, a man's home is his castle.* **4.** *Chess.* the rook; one of the two corner pieces in the first row. —*v.* **5.** *Chess.* to move (the king) two squares to the side and bring the rook to the square the king has passed over: [~ + *obj*]: *He castled his king as a final defense.* [*no obj*]: *He tried castling to protect his king.*

cast-off (kast′ôf′, -of′) /ˈkæstˌɔf, -ˌɑf/ *adj.* [*before a noun*] **1.** thrown away; rejected; discarded: *He was wear-*

spending. —**reck′less·ly,** *adv.*: *drove recklessly.* —**reck′less·ness,** *n.* [*noncount*]

reck·on (rek′ən) /′rɛkən/ *v.* **1.** [~ + *obj*] to count, compute, or calculate: *to reckon profits.* **2.** to consider (someone or something) as; look upon (someone or something) as: [~ + *obj* (+ *as*) + *obj*]: *reckoned her (as) an outstanding expert.* [~ + *obj* + *among* + *obj*]: *She is reckoned among the most important experts of that field.* **3.** *Chiefly Midland and Southern U.S.* to think or suppose: [~ + (*that*) *clause*]: *I reckon (that) she'll be here soon.* [*no obj*]: *Will she come to the party? I reckon so.* **4.** to count, depend, or rely; expect: [~ + *on* + *obj*]: *The general didn't reckon on a surprise attack.* [~ + *to* + *verb*]: *The company reckons to sell over a million cars.* **5. reckon with,** [~ + *with* + *obj*] **a.** to consider or anticipate: *He hadn't reckoned with bad weather.* **b.** to deal with: *She has to reckon with this kind of complaint all day long.* **c.** to consider seriously: *a sales force to be reckoned with.*

reck·on·ing (rek′ə ning) /′rɛkənɪŋ/ *n.* [*noncount*] **1.** count; the way one figures something; computation; calculation: *By her reckoning we still owe money.* **2.** the settlement of accounts, as between two companies. **3.** judgment: *a day of reckoning.*

re·claim (ri klām′) /rɪ′kleym/ *v.* [~ + *obj*] **1.** to bring (uncultivated areas of land or wasteland) into a condition for farming, growing things, or for other use. **2.** to recover (substances) in a pure form or in a form that can be used, from waste material or from articles that have been thrown away: *to reclaim the copper from those wires.* See -CLAIM-.

rec·la·ma·tion (rek′lə mā′shən) /ˌrɛklə′meyʃən/ *n.* [*noncount*] **1.** the act of reclaiming or recovering substances from waste materials or articles that have been thrown away. **2.** the act of bringing back land into a condition for farming, growing things, or other uses. See -CLAIM-.

re·cline (ri klīn′) /rɪ′klayn/ *v.* **-clined, -clin·ing.** to (cause to) lean back or lie; to (cause to) be moved into a position that is flat or nearly flat: [*no obj*]: *reclined on the sofa.* [~ + *obj*]: *to recline a car seat.*

re·clin·er (ri klī′nər) /rɪ′klaynər/ *n.* [*count*] **1.** a person or thing that reclines. **2.** Also called **recliner chair′,** an easy chair with a back and footrest that adjust up or down.

rec·luse (*n.* rek′lōōs, ri klōōs′; *adj.* ri klōōs′, rek′lōōs) / *n.* 'rɛkluws, rɪ'kluws; *adj.* rɪ'kluws, 'rɛkluws/ *n.* [*count*] **1.** a person who deliberately lives apart from society. —*adj.* **re·cluse. 2.** shut off or apart from the world. —**re·clu·sive** (ri klōō′siv) /rɪ'kluwsɪv/ *adj.*

rec·og·ni·tion (rek′əg nish′ən) /ˌrɛkəg'nɪʃən/ *n.* [*noncount*] **1.** an act of recognizing or the state of being recognized. **2.** identification of a person or thing as having previously been seen, heard, known, etc.: *He looked at her with a growing sense of recognition.* **3.** perception or understanding of something as existing, true, or valid: *recognition that students need encouragement.* **4.** the acknowledgment of achievement, service, merit, ability, status, etc. **5.** an official act by which one state acknowledges the existence of another state or of a new government. See -GNOS-.

rec·og·nize (rek′əg nīz′) /'rɛkəg,nayz/ *v.* [~ + *obj*], **-nized, -niz·ing. 1.** to identify as something or someone previously seen, known, etc.: *I recognized my old car.* **2.** to identify from knowledge of appearance or characteristics: *to recognize a swindler.* **3.** to perceive or accept as existing, true, or valid: *She was able to recognize the problem.* **4.** to grant official permission to speak: *The chair recognizes the new delegate.* **5.** to accept formally as something entitled to treatment as a political unit: *The UN formally recognized the territory.* **6.** to show appreciation of: *Today we recognize your great achievements.* —**rec·og·niz·a·ble** (rek′əg nī′zə bəl) /ˌrɛkəg'nayzəbəl/ *adj.* See -GNOS-.

re·coil (*v.* ri koil′; *n.* rē′koil′, ri koil′) / *v.* rɪ'kɔyl; *n.* 'riy,kɔyl, rɪ'kɔyl/ *v.* [*no obj*] **1.** to jump or shrink back suddenly, as in alarm, horror, or disgust. **2.** to spring or fly back because of force of impact or because of a shooting of a bullet: *The rifle recoiled.* —*n.* **3.** the act or an instance of recoiling: [*noncount*]: *very little recoil with this gun.* [*count*]: *a small recoil.*

rec·ol·lect (rek′ə lekt′) /ˌrɛkə'lɛkt/ *v.* [*not: be* + ~*-ing*] to remember; recall: [~ + *obj*]: *Can you recollect the password?* [~ + *clause*]: *After that I don't recollect what happened.* [*no obj*]: *Sorry, I simply can't recollect.* See -LEC-.

rec·ol·lec·tion (rek′ə lek′shən) /ˌrɛkə'lɛkʃən/ *n.* **1.** [*noncount*] the act or power of recollecting or remembering or recalling to mind: *a sudden flash of recollection.* **2.** [*count*] something remembered; a memory: *He wrote down his recollections of the war.* See -LEC-.

rec·om·mend (rek′ə mend′) /ˌrɛkə'mend/ *v.* **1.** [~ + *obj*] to present (someone or something) as worthy of confidence, acceptance, or use, as by making a favorable judgment of; commend. **2.** to urge or suggest as proper, useful, or beneficial: [~ + *obj*]: *to recommend a special diet.* [~ + *verb-ing*]: *I recommend seeing a doctor immediately.* [~ + (*that*) *clause*]: *I recommend that you take her to the doctor at once.* **3.** [~ + *obj*] to make desirable or attractive: *The plan has little to recommend it.* —**rec′om·mend′a·ble,** *adj.* See -MAND-.

rec·om·men·da·tion (rek′ə men dā′shən) /ˌrɛkəmɛn'deyʃən/ *n.* **1.** [*noncount*] the act of recommending; advice. **2.** [*noncount*] the act of presenting someone or something as favorable, suitable, qualified, or the like, esp. for a job; *a letter of recommendation.* **3.** [*count*] a letter presenting someone as favorable, suitable, qualified, or the like, esp. for a job. See -MAND-.

rec·om·pense (rek′əm pens′) /'rɛkəm,pɛns/ *v.*, **-pensed, -pens·ing,** *n.* —*v.* [~ + *obj*] **1.** to give something to as payment for work done, injury suffered, or favors received. —*n.* [*noncount*] **2.** a repayment or reward, as for services, gifts, or favors. **3.** something offered to pay for an injury caused; reparation: *not enough money in recompense for the damages.* See -PEND-.

rec·on·cile (rek′ən sīl′) /'rɛkən,sayl/ *v.*, **-ciled, -cil·ing. 1.** [~ + *obj* + *to* + *obj*] to cause (a person) to accept or be resigned to something not desired: *He was reconciled to his fate.* **2.** to (cause to) become friendly or peaceable again, as by settling a quarrel: [~ + *obj*]: *to reconcile hostile persons.* [*no obj*]: *The husband and wife reconciled last week.* **3.** [~ + *obj*] to compose or settle (a quarrel, dispute, etc.): *They have reconciled their differences.* **4.** [~ + *obj*] to bring into agreement: *reconciled financial accounts.* —**rec′on·cil′a·ble,** *adj.*

rec·on·cil·i·a·tion (rek′ən sil′ē ā′shən) /ˌrɛkən,sɪliy'eyʃən/ *n.* **1.** the act of two or more people reconciling: [*noncount*]: *Reconciliation was still possible.* [*count*]: *a trial reconciliation.* **2.** [*noncount*] the act of bringing two different things into agreement: *reconciliation of accounts.*

rec·on·dite (rek′ən dīt′, ri kon′dīt) /'rɛkən,dayt, rɪ'kɒndayt/ *adj.* relating to or dealing with very deep, difficult, obscure, or abstract subject matter: *a recondite treatise.*

re·con·di·tion (rē′kən di′shən) /ˌriykən'dɪʃən/ *v.* [~ + *obj*] to restore or bring back to satisfactory condition: *reconditioned the car.*

re·con·nais·sance (ri kon′ə səns, -zəns) /rɪ'kɒnəsəns, -zəns/ *n.* the act of reconnoitering; a survey or examination of an area: [*noncount*]: *reconnaissance with telescopic cameras.* [*count*]: *ordered a reconnaissance.* See -GNOS-.

re·con·noi·ter (rē′kə noi′tər, rek′ə-) /ˌriykə'nɔytər, ˌrɛkə-/ *v.* to inspect, observe, or survey (an enemy position, strength, etc.) in order to gain information for military purposes: [~ + *obj*]: *reconnoitered the enemy positions.* [*no obj*]: *was ordered to reconnoiter.* See -GNOS-.

re·con·sid·er (rē′kən sid′ər) /ˌriykən'sɪdər/ *v.* to consider again, esp. with a view to a change of decision: [~ + *obj*]: *to reconsider a refusal.* [*no obj*]: *She said that she wouldn't reconsider.* —**re·con·sid·er·a·tion** (rē′kən sid′ə rā′shən) /ˌriykən,sɪdə'reyʃən/ *n.* [*noncount*]

re·con·sti·tute (rē kon′sti tōōt′, -tyōōt′) /riy'kɒnstɪ,tuwt, -,tyuwt/ *v.* [~ + *obj*], **-tut·ed, -tut·ing. 1.** to put together again: *to reconstitute the committee under a new name.* **2.** to return (food that has had the water removed or has been concentrated) to the liquid state by adding water. See -STIT-.

re·con·struct (rē′kən strukt′) /ˌriykən'strʌkt/ *v.* [~ + *obj*] **1.** to construct again; rebuild; make over: *to reconstruct the battle-torn country.* **2.** to re-create in the mind from available information: *to reconstruct the events of the murder.* —**re′con·struc′tion,** *n.* [*count*]: *a reconstruction of the events leading up to the accident.* [*noncount*]: *the money necessary for reconstruction of the country's infrastructure.* See -STRU-.

re·cord (*v.* ri kôrd′; *n.*, *adj.* rek′ərd) / *v.* rɪ'kɔrd; *n.*, *adj.* 'rɛkərd/ *v.* **1.** [~ + *obj*] to set down in writing or the like, such as for the purpose of preserving evidence: *recorded the dates of battles.* **2.** [~ + *obj*] to cause to be set down, stated, or indicated: *His no vote was recorded.* **3.** [~ + *obj*] to serve to tell of: *The instruments recorded the earthquake.* **4.** to use a special machine to preserve

ilt) /sɪlt/ *n.* [*noncount*] **1.** earth carried by moving and deposited as a sediment. —*v.* **2. silt up,** to : to) become filled or choked up with silt: [*no obj*]: *ake silted up.* [~ + *up* + *obj*]: *The mud silted up ke.* —**silt′y,** *adj.*

· (sil′vər) /ˈsɪlvər/ *n.* **1.** [*noncount*] a white metallic :nt, used for making mirrors, coins, photographic cals, and conductors. **2.** [*noncount; used with a ar verb*] coins made of this metal; money: *a hand- silver.* **3.** [*noncount*] this metal used or thought of standard for the value of currency. **4.** [*noncount; with a singular verb*] table articles, such as knives, and spoons, made of or plated with silver. **5.** [*non-*] a bright, grayish white or whitish gray color. **6.** !] a silver medal: *He brought home two silvers from lympics.* —*adj.* **7.** [*before a noun*] made of or with silver. **8.** of or relating to silver. **9.** producing lding silver: *a silver mine.* **10.** of the color silver; : *silver hair.* **11.** elegant and persuasive: *a silver e (= the ability to speak gracefully and convinc-* **12.** [*before a noun*] indicating the twenty-fifth of a series, such as a wedding anniversary.

·fish (sil′vər fish′) /ˈsɪlvərˌfɪʃ/ *n.* [*count*], *pl.* (*esp. thought of as a group*) **-fish,** (*esp. for kinds or spe-* **fish·es.** **1.** any of various silvery fishes, such as the ı. **2.** a wingless, silvery-gray insect that feeds on and damages books, wallpaper, etc.

· **lin′ing,** *n.* [*count*] a possibility or element of or comfort in an unfortunate or gloomy situation.

·smith (sil′vər smith′) /ˈsɪlvərˌsmɪθ/ *n.* [*count*] ho makes and repairs articles of silver.

·tongued′, *adj.* persuasive; able to speak well onvince others.

·ware (sil′vər wâr′) /ˈsɪlvərˌwɛər/ *n.* [*noncount; with a singular verb*] articles, esp. eating and serv- ensils, made of silver, silver-plated metals, stainless etc.

·y (sil′və rē) /ˈsɪlvəriy/ *adj.* **1.** resembling silver; of y grayish white color. **2.** having a clear, ringing : *the silvery peal of bells.* **3.** containing or covered lver.

ın (sim′ē ən) /ˈsɪmiyən/ *adj.* **1.** of or relating to an monkey. —*n.* [*count*] **2.** an ape or monkey.

. *root.* *-simil-* comes from Latin, where it has the ng "alike, similar." This meaning is found in such as: ASSIMILATE, ASSIMILATION, DISSIMILAR, DISSIMULATE, LE, SIMILAR, SIMILE, SIMULATE, SIMULCAST, SIMULTANE- ERISIMILITUDE.

ar (sim′ə lər) /ˈsɪmələr/ *adj.* having a likeness or blance; like or alike: *two similar houses.* [*be* + ~]: *The houses are similar to each other.* —**sim′i· y,** *n., pl.* **-ties.** [*noncount*]: *points of similarity be- the two paintings.* [*count*]: *There are many similar- etween the two paintings.* —**sim·i·lar·ly** (sim′ə-) /ˌsɪməˈlærɪtiy/ *adv.* See -SIMIL-.

e (sim′ə lē) /ˈsɪməliy/ *n.* **1.** [*noncount*] a figure of ı in which two distinct things are compared by us- ke" or "as," such as in "She is like a rose." **2.**] an example of this: *How many similes can you the first paragraph?* See -SIMIL-.

er (sim′ər) /ˈsɪmər/ *v.* **1.** to cook just below the point: [*no obj*]: *The sauce is simmering.* [~ + *immer the sauce.* **2.** [*no obj*] to be in a state in development, excitement, anger, etc., is present ld back: *He was simmering with anger.* **3. simmer** [*no obj*] to become calm or quiet: *"Simmer I warned him.* —*n.* [*count; usually singular*] **4.** the ır process of simmering: *Cook to a slow simmer en minutes.*

·ize (sim′mə nīz′) /ˈsɪməˌnayz/ *v.* [~ + *obj*], **-iz·ing.** to shine or polish to a strong brightness, th wax.

·ti·co (sim pä′ti kō′, -pat′i-) /sɪmˈpɑtɪˌkow, ' *adj.* agreeing in the mind or in the spirit; like- ; compatible. See -PAT-.

r (sim′pər) /ˈsɪmpər/ *v.* [*no obj*] **1.** to smile in a ılse, or self-conscious way: *She simpered at the s he made another corny joke.* —*n.* [*count*] **2.** a lse, self-conscious smile.

· (sim′pəl) /ˈsɪmpəl/ *adj.*, **-pler, -plest.** *n.* —*adj.* **1.** understand or deal with; not hard to do: *a simple n.* [*It* + *be* + ~ + *to* + *verb*]: *It was simple to ıer problems.* **2.** not elaborate or complicated; *a simple design.* **3.** not ornate or luxurious; una- : *a simple dress.* **4.** unassuming; modest; sincere: *simple man.* **5.** [*before a noun*] occurring or con- l alone; mere; bare: *the simple truth.* **6.** [*before a*

noun] common or ordinary: *a simple soldier.* **7.** not grand or sophisticated: *simple tastes.* **8.** humble or lowly: *simple folk.* **9.** lacking mental sharpness: *a simple, dull-witted peasant.* **10.** mentally deficient. **11.** *Chemistry.* made of only one substance or element: *a simple substance.* **12.** *Botany.* not divided into parts: *a simple leaf.* **13.** (of a sentence) having only one subject and verb (as opposed to compound): *The sentences* John likes Mary *and* John and Bill like Mary *are simple sentences.* —**sim′ple·ness,** *n.* [*noncount*] See -PLIC-.

sim·ple·mind·ed or **sim·ple-mind·ed** (sim′pəl mīn′did) /ˈsɪmˈpəl maydɪd/ *adj.* **1.** lacking in mental sharpness. **2.** lacking in complex thought: *a simple-minded solution to a complicated problem.* **3.** mentally weak; feeble-minded.

sim·ple·ton (sim′pəl tən) /ˈsɪmpəltən/ *n.* [*count*] an ignorant, foolish, or silly person.

sim·plic·i·ty (sim plis′i tē) /sɪmˈplɪsɪtiy/ *n., pl.* **-ties.** **1.** [*noncount*] the state or quality of being simple. **2.** [*count*] an instance or example of this. **3.** [*noncount*] the absence of luxury or ornament; plainness. See -PLIC-.

sim·pli·fy (sim′plə fī′) /ˈsɪmpləˌfay/ *v.* [~ + *obj*], **-fied, -fy·ing.** to make simple or simpler: *to simplify the problem.* —**sim·pli·fi·ca·tion** (sim′plə fi kā′shən) /ˌsɪmpləfɪˈkeyʃən/ *n.* [*noncount*]: *too much simplification in dealing with complex issues.* [*count*]: *Your essay is a simplification of a complex topic.*

sim·plis·tic (sim plis′tik) /sɪmˈplɪstɪk/ *adj.* being too simple, esp. in ignoring difficulties; oversimplified: *His proposals for reducing the deficit are simplistic.* See -PLIC-.

sim·ply (sim′plē) /ˈsɪmpliy/ *adv.* **1.** in a simple manner; clearly: *He spoke simply and directly.* **2.** plainly; unaffectedly: *In spite of her great wealth they live simply in a modest house.* **3.** merely; only: *It is simply a cold.* **4.** absolutely; really: *Her desserts are simply irresistible.* See -PLIC-.

sim·u·late (sim′yə lāt′) /ˈsɪmyəˌleyt/ *v.* [~ + *obj*], **-lat·ed, -lat·ing.** **1.** to create a model of: *During the drill we will simulate emergency conditions.* **2.** to pretend to do or have; feign: *to simulate illness.* **3.** to assume or have the appearance or characteristics of: *simulated leather.* See -SIMIL-.

sim·u·la·tion (sim′yə lā′shən) /ˌsɪmyəˈleyʃən/ *n.* **1.** [*noncount*] imitation: *simulation of real events.* **2.** [*count*] a model of a problem in an attempt to work out solutions, etc.: *computer simulations of planning a model city.* See -SIMIL-.

sim·u·la·tor (sim′yə lā′tər) /ˈsɪmyəˌleytər/ *n.* [*count*] a machine or device that models actual events and creates conditions similar to real conditions, used for training and practice: *A flight simulator re-created the conditions that pilots would encounter in such aircraft.* See -SIMIL-.

si·mul·cast (sī′məl kast′, sim′əl-) /ˈsaymə|kæst, ˈsɪmə|-/ *n., v.*, **-cast, -cast·ed, -cast·ing.** —*n.* [*count*] **1.** a program broadcast simultaneously on radio and television, or on more than one station, or in several languages, etc. —*v.* **2.** to broadcast in this manner: [~ + *obj*]: *to simulcast a concert.* [*no obj*]: *advancing technology in simulcasting.* See -SIMIL-.

si·mul·ta·ne·ous (sī′məl tā′nē əs, sim′əl-) /ˌsaymə|ˈteyniyəs, ˌsɪmə|-/ *adj.* existing, occurring, or operating at the same time: *simultaneous translation of all speeches at the United Nations.* —**si′mul·ta′ne·ous·ly,** *adv.*: *How can you have such contradictory opinions simultaneously?* See -SIMIL-.

sin (sin) /sɪn/ *n., v.*, **sinned, sin·ning.** —*n.* **1.** [*noncount*] disobedience of divine law: *a life full of sin.* **2.** [*count*] any act regarded as such disobedience, esp. a deliberate one: *He asked for forgiveness of his sins.* **3.** [*count*] any serious fault or offense: *He had committed sins against humanity.* —*v.* [*no obj*] **4.** to commit a sinful act: *He had sinned and so he begged God for forgiveness.* —***Idiom.*** **5. live in sin,** [*no obj*] to live together as husband and wife without being married. —**sin′ner,** *n.* [*count*] —**Syn.** See CRIME.

since (sins) /sɪns/ *adv.* **1.** from then till now (often preceded by *ever*): *Those elected in 1990 have been on the committee ever since.* **2.** between a particular past time and the present; subsequently: *She at first refused, but has since consented.* **3.** ago; before now: *She has long since left him; didn't you know?* —*prep.* **4.** starting continuously from or counting from: *It has been raining since noon.* **5.** between a past event and the present: *There have been many changes since the war.* —*conj.* **6.** in the period following the time when: *He has written once since he left.* **7.** continuously from or counting from the time when: *I've been busy since I arrived.* **8.** because; inasmuch as: *Since you've been here awhile, you might as well stay.* —**Usage.** The word SINCE very often appears with a verb in the present perfect tense, that is, with HAS or HAVE plus the *-ed/-en* form of the main verb.

sin·cere (sin sēr′) /sɪnˈsɪər/ *adj.*, **-cer·er, -cer·est.** **1.** not false or pretended: *a sincere apology.* **2.** genuine; real: *a sincere effort to improve.* —**sin·cere′ly,** *adv.* —**sin·cer·i·ty** (sin serˈi tē) /sɪnˈsɛrɪtiy/ *n.* [*noncount*]: *dealing with his students with sincerity.*

si·ne·cure (sī′ni kyŏŏr′, sin′i-) /ˈsaynɪˌkyʊr, ˈsɪnɪ-/ *n.* [*count*] a position requiring no work, esp. one that brings easy profit. See -CURA-.

si·ne qua non (sin′ā kwä nŏn′, non′, kwā) /ˈsɪnˈey kwɑ nɑn, ˈnɒn, kweyˈ *n.* [*count; usually singular*] something that cannot be left out; a necessity: *The actress's presence was the sine qua non of any party.*

sin·ew (sin′yōō) /ˈsɪnyuw/ *n.* **1.** [*count*] a tendon. **2.** [*noncount*] strength; power; resilience: *great moral sinew.*

sin·ew·y (sin′yōō ē) /ˈsɪnyuwiy/ *adj.* **1.** (of meat) tough; hard to chew. **2.** strong and hard from exercise or hard work: *sinewy hands.* **3.** strong and tough: *a sinewy rope.*

sin·ful (sin′fəl) /ˈsɪnfəl/ *adj.* **1.** showing, guilty of, or full of sin: *a sinful life.* **2.** very bad; seriously wrong; shameful: *a sinful waste of paper.* —**sin′ful·ly,** *adv.*

sing (sing) /sɪŋ/ *v.*, **sang** (sang) /sæŋ/ or, often, **sung** (sung) /sʌŋ/; **sung; sing·ing;** *n.* —*v.* **1.** [*no obj*] to make words or sounds one after the other, with musical changes in the pitch or tone of the voice: *All the members of my family can sing.* **2.** to perform (songs or music) with the voice: [*no obj*]: *Once she sang on national TV.* [~ + *obj*]: *They sang some old tunes around the campfire.* **3.** [~ + *obj*] to bring, send, etc., into a certain condition with or by such musical sound: *to sing a baby to sleep.* **4.** (of an animal) to produce a signal with the voice: [*no obj*]: *Some birds sing to attract a mate.* [~ + *obj*]: *Birds sing very specific songs.* **5.** [~ + *of* + *obj*] to tell about someone or something in verse or song, esp. with enthusiasm or admiration: *to sing of the times of King Arthur.* **6.** [~ + *obj*] to proclaim with enthusiasm: *to sing someone's praises (= to praise someone).* **7.** [*no obj*] to make a whistling or whizzing sound: *The bullet sang past his ear.* **8.** [*no obj*] *Slang.* to confess or act as an informer by telling the authorities about some crime or criminals. —*n.* [*count*] **9.** a meeting of people for singing: *a community sing.* —**sing′a·ble,** *adj.* —**sing′er,** *n.* [*count*]

sing., an abbreviation of: singular.

sing′-along′, *n.* SONGFEST.

Sin·ga·po·re·an (sing′gə pôr′ē ən, -pōr′-) /ˌsɪŋgəˈpɔriyən, -ˈpowr-/ *n.* [*count*] **1.** a person born or living in Singapore. —*adj.* **2.** of or relating to Singapore.

singe (sinj) /sɪndʒ/ *v.*, **singed, singe·ing,** *n.* —*v.* [~ + *obj*] **1.** to burn slightly; scorch: *The hot iron singed the shirt.* **2.** to burn the ends, edges, etc., of (hair, cloth, etc.): *The firefighter's hair was singed from her attempt to rescue the child.* —*n.* [*count*] **3.** a slight burn.

sin·gle (sing′gəl) /ˈsɪŋgəl/ *adj.*, *v.*, **-gled, -gling,** *n.* —*adj.* **1.** [*before a noun*] only one in number; one only; unique: *a single example.* **2.** [*before a noun*] of, relating to, or suitable for one person only: *a single room.* **3.** [*before a noun*] the only; lone: *He was the single survivor.* **4.** unmarried: *a single man.* **5.** [*before a noun*] of one against one: *single combat.* **6.** made of only one part: *a single lens.* **7.** [*before a noun*] separate, particular, or distinct: *I'll speak with every single one of you.* **8.** uniform; that applies to all: *a single safety code.* —*v.* **9. single out,** to choose (one) from others: [~ + *obj* + *out*]: *to single someone out for special mention.* [~ + *out* + *obj*]: *to single out a hardworking employee.* —*n.* [*count*] **10.** one person or thing; a single one. **11.** a room in a hotel, a bed, etc., for one person only. **12.** an unmarried person: *The bar is for singles only.* **13.** a one-dollar bill: *Give me change in singles, please.* **14.** (in baseball) a base hit that allows a batter to reach first base safely. **15. singles,** [*count*] *pl.* **singles.** a match or game with one player on each side, as a tennis match: *A tough singles has just ended.*

sin′gle-breast′ed, *adj.* (of a coat, jacket, etc.) having a front that closes in the center with a single button or row of buttons. Compare DOUBLE-BREASTED.

sin′gle file′, *n.* [*noncount*] **1.** a line of persons or things arranged one behind the other: *lined up in single file.* —*adv.* **2.** in such a line: *to walk single file.*

sin′gle-hand′ed, *adj.* **1.** done by one person alone; without aid from another. **2.** using only one hand: *a sin-*

EXHIBIT N

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Dayton T. Reardan et al. Examiner: Lena Najarian

Serial No.: 10/322,348 Group Art Unit: 3626

Filed: December 17, 2002 Docket: 101.031US1

For: SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

REPLY BRIEF UNDER 37 CFR § 41.41

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

The Examiner's Answer admits that the primary reference Moradi fails to disclose entering information into an exclusive computer database that is associated with an exclusive central pharmacy.[1] The Examiner's Answer contends however that Lilly et al. discloses entering information into an exclusive computer database that is associated with an exclusive central pharmacy.[2] The Appellant respectfully disagrees.

The Examiner's Answer contends that an exclusive computer database associated with an exclusive central pharmacy is disclosed in one or more of ¶¶ 11, 33, 54, 57, 58, 61, and 69 of Lilly et al. The Appellant respectfully disagrees, and respectfully submits that ¶ 11 relates to the cost of drug distribution, ¶ 33 relates to controlling information relating to controlled substances and pharmaceutical medications, ¶ 54 relates to government oversight agencies such as the DEA, the FBI, and the CDC, ¶ 57 relates to the ability of pharmacies to verify the drug usage of each purchaser, ¶ 58 relates to physicians' prescribing of prescription drugs, and ¶ 69 relates to the types of transactions that may occur with stored patient, doctor, and pharmaceutical data.

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[1] Examiner's Answer, p. 4.
[2] *Id.*, pp. 4-5.

Paragraph 61 relates to several types of entities that can use the system disclosed therein such as doctors, pharmacies, hospitals, pharmaceutical companies, insurance companies, government agencies, health care informatics companies, health researchers, managed care organizations, and other healthcare providers. It goes on to state that such users may typically maintain their own databases, and that such databases can be accessed by the other entities in the system as needed. The Appellant respectfully submits that such a distributed database system is not an exclusive database associated with an exclusive central pharmacy. Paragraph 61 goes on to state that pharmaceutical data can be stored in a data storage which is external to each entity's database. However, the storage of data in a data storage in addition to the data storage in each entity's database is not an exclusive database that is associated with an exclusive central pharmacy as is recited in the claims.

Consequently, the Appellant respectfully submits that, contrary to the assertions in the Examiner's Answer, Lilly et al. does not disclose entering information into an exclusive computer database that is associated with an exclusive central pharmacy, and for at least this reason, the rejection of the claims should be reversed.

The Examiner's Answer further states that the Examiner gave the claim language "exclusive computer database" the broadest reasonable interpretation.[3] The Appellant respectfully submits however that the broadest reasonable interpretation must be limited by the ordinary meaning of the word at issue. The term "exclusive" means "single" or "sole,"[4] and as pointed out above, Lilly et al. discloses that each entity typically maintains its own database. That is, there is not an exclusive, single, or sole database disclosed in Lilly et al.

The Examiner's Answer further points to paragraph [0022] of Moradi, even though the Examiner's Answer admits earlier that Moradi does not disclose an exclusive computer database. However, while paragraph [0022] discloses a Central Service Station (CSS) 102 that maintains databases, Moradi conspicuously does not state that any of these databases are exclusive.

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[3] *Id.*, pp. 15-16.
[4] www.merriamwebster.com

Regarding the Ukens reference, the Examiner's Answer contends that it too discloses an exclusive central pharmacy. The Examiner's Answer further takes issue with the Appellant's contention that the Ukens reference teaches away from the claimed subject matter.

The Ukens reference discusses the relationship among community pharmacies, specialty pharmacies, and specialty drugs. The Appellant respectfully submits that a specialty pharmacy is not an exclusive central pharmacy. A specialty pharmacy can be distributed throughout many locations, and an exclusive pharmacy may or may not deal with specialty drugs.[5] Moreover, there is simply no disclosure of an exclusive computer database in Ukens.

In response to the Appellant's pointing out that Ukens teaches away from a specialty pharmacy, the Examiner's Answer states that "the fact that the applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentabilty. . ." The Appellant respectfully submits that it did not recognize, identify, or discuss any advantage that would naturally flow from Ukens or any other cited reference. Rather, the Appellant specifically pointed to the section of Ukens that disparaged a specialty pharmacy, and hence taught away from the claimed subject matter.

The Examiner's Answer admits that Ukens "teaches disadvantages concerning the use of a central pharmacy." The Examiner goes on to state however that she has recognized an advantage, that is, limiting distribution of dangerous drugs. The Examiner further argues that the Appellant's statements are conclusory remarks that fail to provide any rationale or scientific or logical reasoning to support them. In reply, the Appellant respectfully submits that its statements are not at all conclusory. Rather, they are statements and teachings that appear in Ukens, that teach away from the claimed subject matter, and that need no further analysis. The Appellant further respectfully submits that the Examiner's citation of the advantage of limiting the distribution of dangerous drugs comes from the Appellant.[6] Ukens on the other hand relates to the distribution of

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[5] Specialty drugs, as defined in Ukens, relate to drugs that serve a limited population, such as drugs to treat ALS, and/or drugs that require special care in the distribution system, such as controlled atmospheric conditions. Ukens, p. 2.

[6] Appellant's specification, pp. 1-2.

specialty drugs, not dangerous drugs, and the concerns of distributing such specialty drugs. As noted in Ukens, specialty drugs refer to drugs for a limited patient population and/or that require special handling.[7]

For the foregoing reasons, and the reasons outlined in the Appellant's Brief, the Appellant respectfully submits that the rejection of the claims is in error, and that the rejection of the claims should be reversed.

Respectfully submitted,

DAYTON T. REARDAN et al.

By their Representatives,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402

Date December 3 2007 By _____
David D. Zuriilla
Reg. No. 36,776

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 3 day of December 2007.

John D. Crispin-Wrabetz _____
Name Signature

[7] Such specialty drugs can include pharmaceuticals to treat such diseases as amyotrophic lateral sclerosis, cancer, cystic fibrosis, growth hormone deficiency, hemophilia, HIV/AIDS, and multiple sclerosis.

EXHIBIT O

REMARKS

This responds to the Office Action mailed on June 29, 2005, and the references cited therewith.

Claims 1, 2, 4, 8 and 9 are amended. Claims 1-10 are now pending in this application.

Affirmation of Election

Restriction to one of the following claims was required:

As provisionally elected by Applicant's representative, Richard Schwartz on March 18, 2005, Applicant elects to prosecute the invention of Group I, claims 1-10.

The claims of the non-elected invention, claims 11-31, are hereby canceled. However, Applicant reserves the right to later file continuations or divisions having claims directed to the non-elected inventions.

Drawing Objection

The drawings were objected to as containing reference numbers not identified in the description. The description has been amended to include such reference numbers. Any text added to the description is fully supported by the drawings.

§112 Rejection of the Claims

Claims 1-10 were rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Amendments related solely to addressing antecedence have been made.

§101 Rejection of the Claims

Claims 1-10 were rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The claims have been amended to clarify that the database is a computer database. Thus, the recited process clearly involves the technological arts.

§103 Rejection of the Claims

Claims 1-2, 4-8 and 10 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Lilly et al. (US 2004/0176985 A1) and further in view of Califano et al. (US 2003/0033168 A1). Applicant reserves the right to swear behind each of the references at a later date. The rejection is respectfully traversed.

The Examiner has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). To do that the Examiner must show that some objective teaching in the prior art or some knowledge generally available to one of ordinary skill in the art would lead an individual to combine the relevant teaching of the references. *Id.*

The *Fine* court stated that:

> Obviousness is tested by "what the combined teaching of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 878 (CCPA 1981)). But it "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." *ACS Hosp. Sys.*, 732 F.2d at 1577, 221 USPQ at 933. And "teachings of references can be combined *only* if there is some suggestion or incentive to do so." *Id.* (emphasis in original).

The M.P.E.P. adopts this line of reasoning, stating that

> In order for the Examiner to establish a *prima facie* case of obviousness, three base criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *M.P.E.P.* § 2142 (citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed.Cir. 1991)).

An invention can be obvious even though the suggestion to combine prior art teachings is not found in a specific reference. *In re Oetiker*, 24 USPQ2d 1443 (Fed. Cir. 1992). At the same time, however, although it is not necessary that the cited references or prior art specifically suggest making the combination, **there must be some teaching somewhere which provides the suggestion or motivation to combine prior art teachings and applies that combination to solve the same or similar problem which the claimed invention addresses** *(emphasis added)*.

One of ordinary skill in the art will be presumed to know of any such teaching. (See, e.g., *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) and *In re Wood*, 599 F.2d 1032, 1037, 202 USPQ 171, 174 (CCPA 1979)).

The suggestion to combine the reference in the Office Action is not directed to solving the same or similar problem which the claimed invention addresses. Further, there is no teaching in the prior art of application of the combination to solve the same or similar problems which the claimed invention addresses. The Office Action indicates that the motivation for combining the features of Lilly within Moradi would be "to ensure that prescribers have an accurate view of their patients' use of prescription drugs and to help protect professionals from lawsuits and other potential liabilities (para. 58 of Lilly)." The purpose of the presently claimed invention is to track sensitive drugs and reduce the potential for abuse. These are very different problems, and there is no suggestion to apply the combination to solve the same or similar problem which the claimed invention addresses.

Moradi is directed to "securely providing prescription medication to patients." Abstract. Prescriptions are validated, a pharmacy is selected, and the prescribed medicine is delivered to the patient, as described in the Abstract. As the Office Action indicates, Moradi does not disclose that the drug is a sensitive drug, does not disclose the use of a central database for analysis of potential abuse situations, does not confirm that the patient has read educational material and does not generate periodic reports via a central database to evaluate potential abuse patterns. As is evident from these statements, Moradi lacks quite a few elements of the claimed invention, and the suggestion provided to combine Moradi with Lilly is improper, since the purpose stated is not related to the same or similar problem addressed by the claimed invention. It would seem that a suggestion to combine the references, drawing several different elements from each of the references, should be a very strong suggestion. As indicated above, the suggestion does not even apply the combination to solve the same or similar problem, and thus is a very weak suggestion at best.

Even if one were to combine multiple selected elements from each of Moradi and Lilly, an element of the claimed invention is still lacking. The Office Action indicates that the combination does not disclose "confirming with the patient that educational material has been read prior to shipping the drug." Califano is cited as providing this missing element, and that the

motivation for doing so "would have been to ensure that the patient knows about the risks and dangers associated with the drug (para. 43 of Califano)." Califano is directed to obtaining consent for a clinical trial. Abstract. The cited motivation is very different from the purpose of the presently claimed invention, making it very unlikely that one of skill in the art would be motivated to combine the references. As a proper prima facie case of obviousness has not been established, the rejection should be withdrawn.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143. The Examiner must avoid hindsight. *In re Bond*, 910 F.2d 831, 834, 15 USPQ2d 1566, 1568 (Fed. Cir. 1990). As indicated above, multiple elements from each of Moradi and Lilly were combined to make the rejection. Because multiple elements from each were used, there is no reasonable expectation of success in making the combination. Further, it points toward the improper use of hindsight, using the claims as a roadmap to make the combination.

A factor cutting against a finding of motivation to combine or modify the prior art is when the prior art teaches away from the claimed combination. A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path the applicant took. *In re Gurley*, 27 F.3d 551, 31 USPQ 2d 1130, 1131 (Fed. Cir. 1994); *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966); *In re Sponnoble*, 405 F.2d 578, 587, 160 USPQ 237, 244 (C.C.P.A. 1969); *In re Caldwell*, 319 F.2d 254, 256, 138 USPQ 243, 245 (C.C.P.A. 1963). Lilly describes the cooperative use of a database by multiple different pharmacies, prescribers and patients, to keep track of the prescription history for a patient. It would be an extremely daunting task to get the cooperation of all these parties. The presently claimed invention uses a central database for analysis of potential abuse situations for distribution of a sensitive drug, not to track all prescriptions for a patient. The ambitious path set forth in Lilly would discourage one of skill in the art from considering using it to solve the problems addressed in the presently claimed invention.

Claims 2, 4-8 and 10 depend from claim 1 and distinguish the references for at least the same reasons as claim 1. In addition, claim 2 recites a central pharmacy. The Office Action

states that Moradi discloses confirming receipt by a telephone call from the central pharmacy. Applicant has reviewed the cited sections of Moradi, and cannot find the concept of a central pharmacy. As the term is used in the present application, a central pharmacy is a pharmacy that exclusively controls the distribution of a sensitive drug. While it may have branches and affiliates, it uses the central database to keep track of all distribution of the sensitive drug. This enables a much improved ability to monitor abuse situations. Patients seeking prescriptions from different doctors will be detected, because the drug is tracked in the central database. Each pharmacy that distributes the sensitive drug also uses the central database. Practically, this is accomplished by obtaining FDA approval that requires the use of the central database. Since any entity that distributes the sensitive drug requires the FDA approval, all must use the same central database. The term central database is used to encompass any real or virtual manifestation of a central database that facilitates evaluation of potential abuse patterns for distribution of the sensitive drug.

Claim 3 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Lilly et al. (US 2004/0176985 A1) in view of Califano et al. (US 2003/0033168 A1) as applied to claim 1 above, and further in view of Andreasson et al. (US 2003/0160698 A1). Applicant further reserves the right to swear behind each of the references. This rejection is also respectfully traversed. Claim 3 depends from claim 1 and distinguishes from the references at least in the same manner as claim 1. Andreasson et al. describe monitoring distribution of medical products within a facility as indicated by the title. Claim 3 recites launching an investigation of lost shipments, which implies that the shipments have already left a facility. Monitoring within the facility would not address a lost shipment that has left the facility. As such, there is no showing of a reasonable likelihood of success in making the combination. As a proper prima facie case of obviousness has not been established, the rejection should be withdrawn.

Claim 9 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Lilly et al. (US 2004/0176985 A1) in view of Califano et al. (US 2003/0033168 A1) as applied to claim 1 above, and further in view of Mayaud (U.S. Patent

No. 5,845,255). Claim 9 depends from claim 1 and distinguishes from the references at least in the same manner as claim 1. The Office Action cites a motivation to combine the four references as "to reduce the reluctance of physicians to prescribe new drugs by providing them with the latest information about the drugs". This motivation has nothing to do with the problems addressed by the currently claimed invention as identified above. As a proper prima facie case of obviousness has not been established, the rejection should be withdrawn.

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 attorney at (612) 373-6972 to facilitate prosecution of this application.

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

Respectfully submitted,
DAYTON T. REARDAN ET AL.
By their Representatives,
SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6972

Date 9-29-2005 By _____
Bradley A. Forrest
Reg. No. 30,837

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 of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 29th day of September, 2005.

PATRICIA A. HULTMAN _____

Name Signature

EXHIBIT P

REMARKS

This responds to the Office Action mailed on December 29, 2005.

New claims 32 - 37 have been added. Claims 1-10 and 32-37 are now pending in this application.

New claims 32 - 37 distinguish the references for reasons similar to those provided below regarding claim 1. In addition, claim 32 recites the use of an exclusive central pharmacy and an exclusive central database to track distribution and potential diversion of the sensitive drug.

In paragraph E of the Response to Arguments section of the Final Office Action, it is stated that the then pending claims did not recite that a central pharmacy is a pharmacy that exclusively controls distribution of a sensitive drug. New claims 32 - 37 have been written based on claim 1 to include language that expressly addresses exclusivity of distribution. Such claims also address exclusivity of the central database. None of the references cited are believed to address such exclusivities. The original claims are also believed to describe aspects of centralization, as described in the previous response. The submission of new claims 32-37 is not an admission otherwise.

§103 Rejection of the Claims

Claims 1-2, 4-8 and 10 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Lilly et al. (US 2004/0176985 A1) and further in view of Califano et al. (US 2003/0033168 A1).

The suggestion to combine the reference in the Office Action is not directed to solving the same or similar problem which the claimed invention addresses. Further, there is no teaching in the prior art of application of the combination to solve the same or similar problems which the claimed invention addresses. The Office Action indicates that the motivation for combining the features of Lilly within Moradi would be "to ensure that prescribers have an accurate view of their patients' use of prescription drugs and to help protect professionals from lawsuits and other

potential liabilities (para. 58 of Lilly)." As stated in the response to arguments section A of the Final Office Action, Lilly also describes reducing misused and abused prescriptions and the need for better tracking and management of prescription in Paragraph 12. However, the purpose for such reductions is related to abuse by the patient, and not abuse of a sensitive drug as claimed. The purpose of the presently claimed invention is to track sensitive drugs and reduce the potential for abuse, such as diversion of the sensitive drug.

Moradi is directed to "securely providing prescription medication to patients." Abstract. In other words, it is directed to making sure that the patient receives the medication, not preventing abuse, such as further distribution by the patient. Prescriptions are validated, a pharmacy is selected, and the prescribed medicine is delivered to the patient, as described in the Abstract. As the Office Action indicates, Moradi does not disclose that the drug is a sensitive drug, does not disclose the use of a central database for analysis of potential abuse situations, does not confirm that the patient has read educational material and does not generate periodic reports via a central database to evaluate potential abuse patterns. As is evident from these statements, Moradi lacks quite a few elements of the claimed invention, and the suggestion provided to combine Moradi with Lilly is improper, since the purpose stated is not related to the same or similar problem addressed by the claimed invention. It would seem that a suggestion to combine the references, drawing several different elements from each of the references, should be a very strong suggestion.

Even if one were to combine multiple selected elements from each of Moradi and Lilly, an element of the claimed invention is still lacking. The Office Action indicates that the combination does not disclose "confirming with the patient that educational material has been read prior to shipping the drug." Califano is cited as providing this missing element, and that the motivation for doing so "would have been to ensure that the patient knows about the risks and dangers associated with the drug (para. 43 of Califano)." Califano is directed to obtaining consent for a clinical trial. Abstract. It is not directed toward preventing abuse. The cited motivation is very different from the purpose of the presently claimed invention of distributing a sensitive drug in a manner that helps prevent abuse, making it very unlikely that one of skill in the art would be motivated to combine the references. As a proper prima facie case of obviousness has not been established, the rejection should be withdrawn.

The Response to Arguments section B of the Final Office Action, the Examiner states that the test for obviousness is what the combined teachings of the references would have suggested to those of ordinary skill in the art. This, however, does not address the fact that there is no proper suggestion to combine the references in the first place, since they are not directed towards the same or similar problems. Thus, one does not even arrive at the question of what the combination suggests if the combination is not proper.

Further in section B of the response to arguments in the Final Office Action, the Examiner states: "In response to applicant's argument that the cited motivation is very different from the purpose of the presently claimed invention, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious." No such recognition is being stated by Applicant. Applicant is merely trying to say that the art addresses a different problem than that of the invention as claimed, and thus, the references are not properly combinable. The language quoted from the Final Office Action appears to state that Applicant simply recognized new advantages flowing from the combination of the references. This statement is respectfully traversed, as Applicant is merely stating that the combination is improper, since the references are directed to problems that are not similar to those addressed by the claimed invention.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143. The Examiner must avoid hindsight. *In re Bond*, 910 F.2d 831, 834, 15 USPQ2d 1566, 1568 (Fed. Cir. 1990). As indicated above, multiple elements from each of Moradi and Lilly were combined to make the rejection. Because multiple elements from each were used, there is no reasonable expectation of success in making the combination. Further, it points toward the improper use of hindsight, using the claims as a roadmap to make the combination.

The Final Office Action in section C, purports to address the above argument by reciting that reconstruction based on hindsight is proper so long as it takes into account only knowledge that was within the level of ordinary skill and does not include knowledge gleaned only from the applicant's disclosure. Section C does not state how only knowledge within the level of ordinary

skill was used, and further does not address the argument that a reasonable expectation of success in making the combination has not been shown.

A factor cutting against a finding of motivation to combine or modify the prior art is when the prior art teaches away from the claimed combination. A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path the applicant took. *In re Gurley*, 27 F.3d 551, 31 USPQ 2d 1130, 1131 (Fed. Cir. 1994); *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966); *In re Sponnoble*, 405 F.2d 578, 587, 160 USPQ 237, 244 (C.C.P.A. 1969); *In re Caldwell*, 319 F.2d 254, 256, 138 USPQ 243, 245 (C.C.P.A. 1963). Lilly describes the cooperative use of a database by multiple different pharmacies, prescribers and patients, to keep track of the prescription history for a patient. It would be an extremely daunting task to get the cooperation of all these parties. The presently claimed invention uses a central database for analysis of potential abuse situations for distribution of a sensitive drug, not to track all prescriptions for a patient. The ambitious path set forth in Lilly would discourage one of skill in the art from considering using it to solve the problems addressed in the presently claimed invention.

Claims 2, 4-8 and 10 depend from claim 1 and distinguish the references for at least the same reasons as claim 1. In addition, claim 2 recites a central pharmacy. The Office Action states that Moradi discloses confirming receipt by a telephone call from the central pharmacy. Applicant has reviewed the cited sections of Moradi, and cannot find the concept of a central pharmacy. As the term is used in the present application, a central pharmacy is a pharmacy that exclusively controls the distribution of a sensitive drug. While it may have branches and affiliates, it uses the central database to keep track of all distribution of the sensitive drug. This enables a much improved ability to monitor abuse situations. Patients seeking prescriptions from different doctors will be detected, because the drug is tracked in the central database. Each pharmacy that distributes the sensitive drug also uses the central database. Practically, this is accomplished by obtaining FDA approval that requires the use of the central database. Since any entity that distributes the sensitive drug requires the FDA approval, all must use the same central database. The term central database is used to encompass any real or virtual manifestation of a

central database that facilitates evaluation of potential abuse patterns for distribution of the sensitive drug.

Claim 3 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Lilly et al. (US 2004/0176985 A1) in view of Califano et al. (US 2003/0033168 A1) as applied to claim 1 above, and further in view of Andreasson et al. (US 2003/0160698 A1). Applicant further reserves the right to swear behind each of the references. This rejection is also respectfully traversed. Claim 3 depends from claim 1 and distinguishes from the references at least in the same manner as claim 1. Andreasson et al. describe monitoring distribution of medical products within a facility as indicated by the title. Claim 3 recites launching an investigation of lost shipments, which implies that the shipments have already left a facility. Monitoring within the facility would not address a lost shipment that has left the facility. As such, there is no showing of a reasonable likelihood of success in making the combination. As a proper prima facie case of obviousness has not been established, the rejection should be withdrawn.

In paragraph F of the Response to Arguments section of the Final Office Action, the Examiner indicates that para. 79 of Andreasson discloses tracking the delivery of medical products and immediately notifying healthcare workers of any missing medical product so they can investigate. Note that the start of para. 79 recites "..a closed-loop system for tracking and monitoring medical products within a healthcare facility,..." While Andreasson may describe launching an investigation, it lacks the concept of shipping drugs to a patient, and investigating lost shipments to the patient as claimed.

Claim 9 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Lilly et al. (US 2004/0176985 A1) in view of Califano et al. (US 2003/0033168 A1) as applied to claim 1 above, and further in view of Mayaud (U.S. Patent No. 5,845,255). Claim 9 depends from claim 1 and distinguishes from the references at least in the same manner as claim 1. The Office Action cites a motivation to combine the four references as "to reduce the reluctance of physicians to prescribe new drugs by providing them with the latest information about the drugs". This motivation has nothing to do with the problems

addressed by the currently claimed invention as identified above. As a proper prima facie case of obviousness has not been established, the rejection should be withdrawn.

In paragraph G of the Response to Arguments section of the Final Office Action, the Examiner again recites something about recognizing another advantage which would flow naturally from following the suggestion of the prior art, which as stated above, Applicant has not done. It is believed that such an argument incorrectly presupposes that the references are properly combinable, which Applicant believes they are not.

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 attorney (612) 373-6972 to facilitate prosecution of this application.

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

Respectfully submitted,

DAYTON T. REARDAN ET AL.

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6972

Date 3-29-2006

By _____
Bradley A. Forrest
Reg. No. 30,837

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 29 day of March, 2006.

JOHN D. GUSTAV-WRATHALL
Name

_____
Signature

EXHIBIT Q

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,

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Date July 25, 2013

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

EXHIBIT R

US 20140207480A1

(19) **United States**

(12) **Patent Application Publication**

Reardan et al.

(10) **Pub. No.: US 2014/0207480 A1**

(43) **Pub. Date: Jul. 24, 2014**

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

(71) Applicant: **Jazz Pharmaceuticals, Inc.**, Palo Alto, CA (US)

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

(21) Appl. No.: **14/219,904**

(22) Filed: **Mar. 19, 2014**

Related U.S. Application Data

(63) Continuation of application No. 14/196,603, filed on Mar. 4, 2014, which is a continuation of application No. 13/592,202, filed on Aug. 22, 2012, now Pat. No. 8,731,963, which is a continuation 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.

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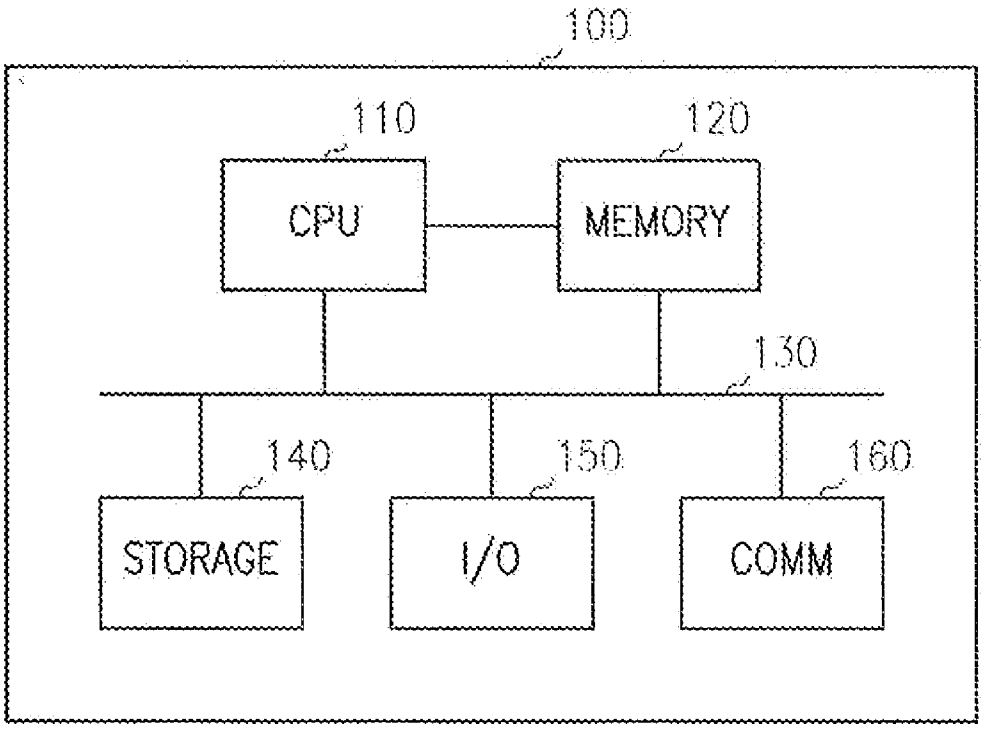
(52) **U.S. Cl.**
CPC ***G06F 19/3456*** (2013.01)
USPC **705/2**

(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.



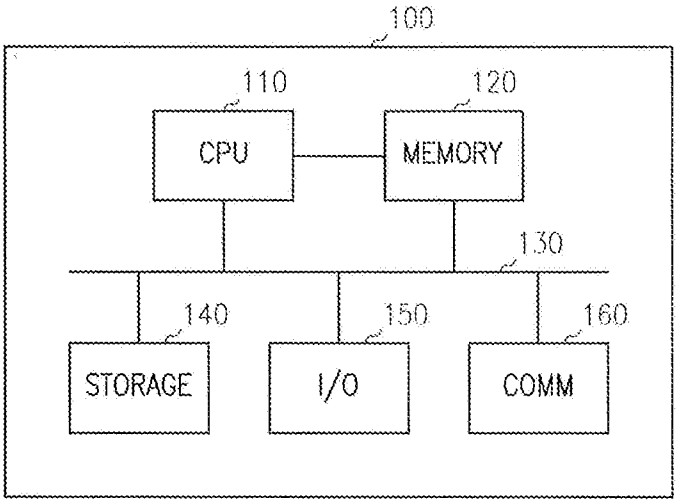


FIG. 1

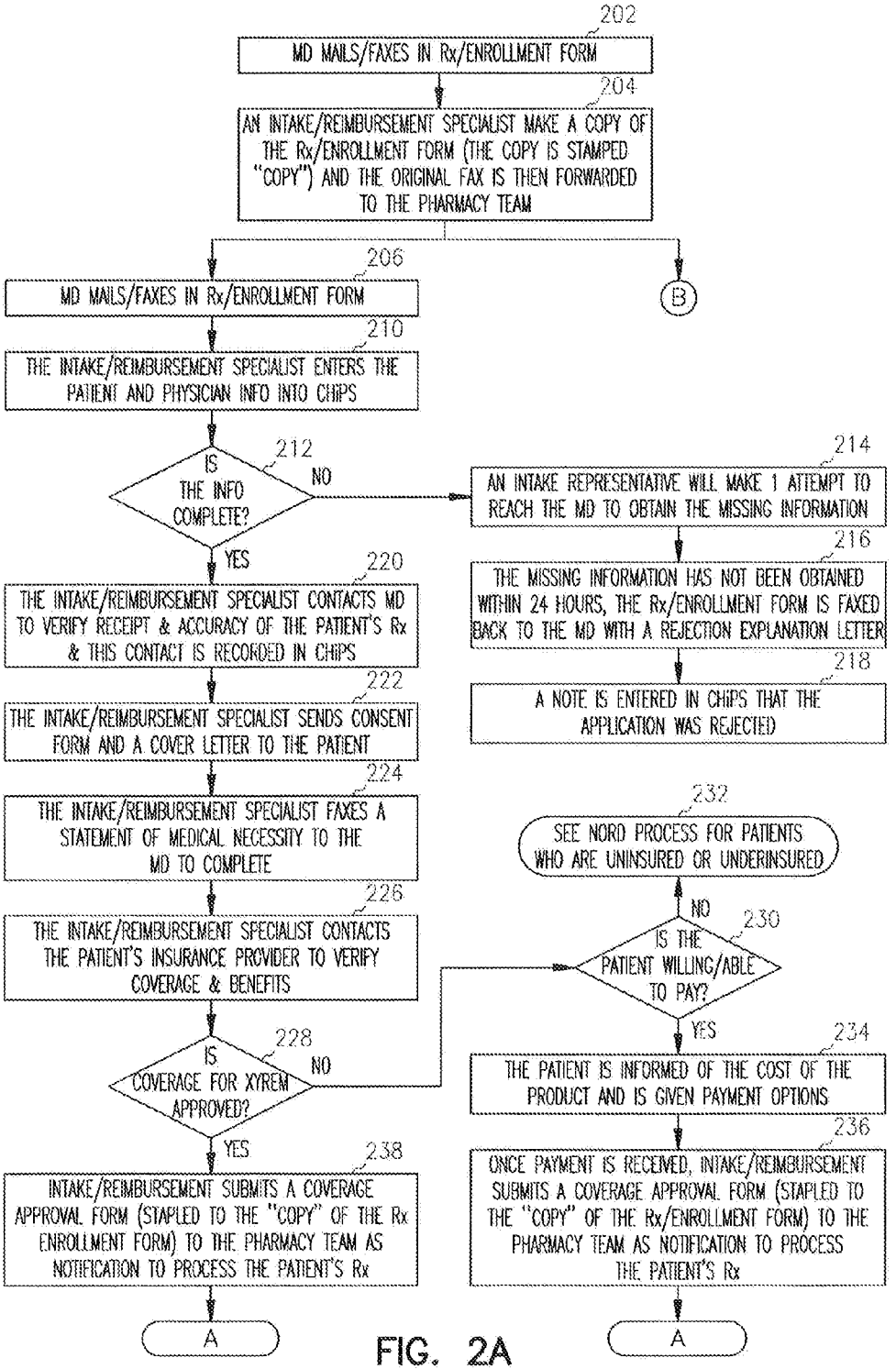

202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHIPS
212
IS THE INFO COMPLETE?
NO
YES
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
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
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
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

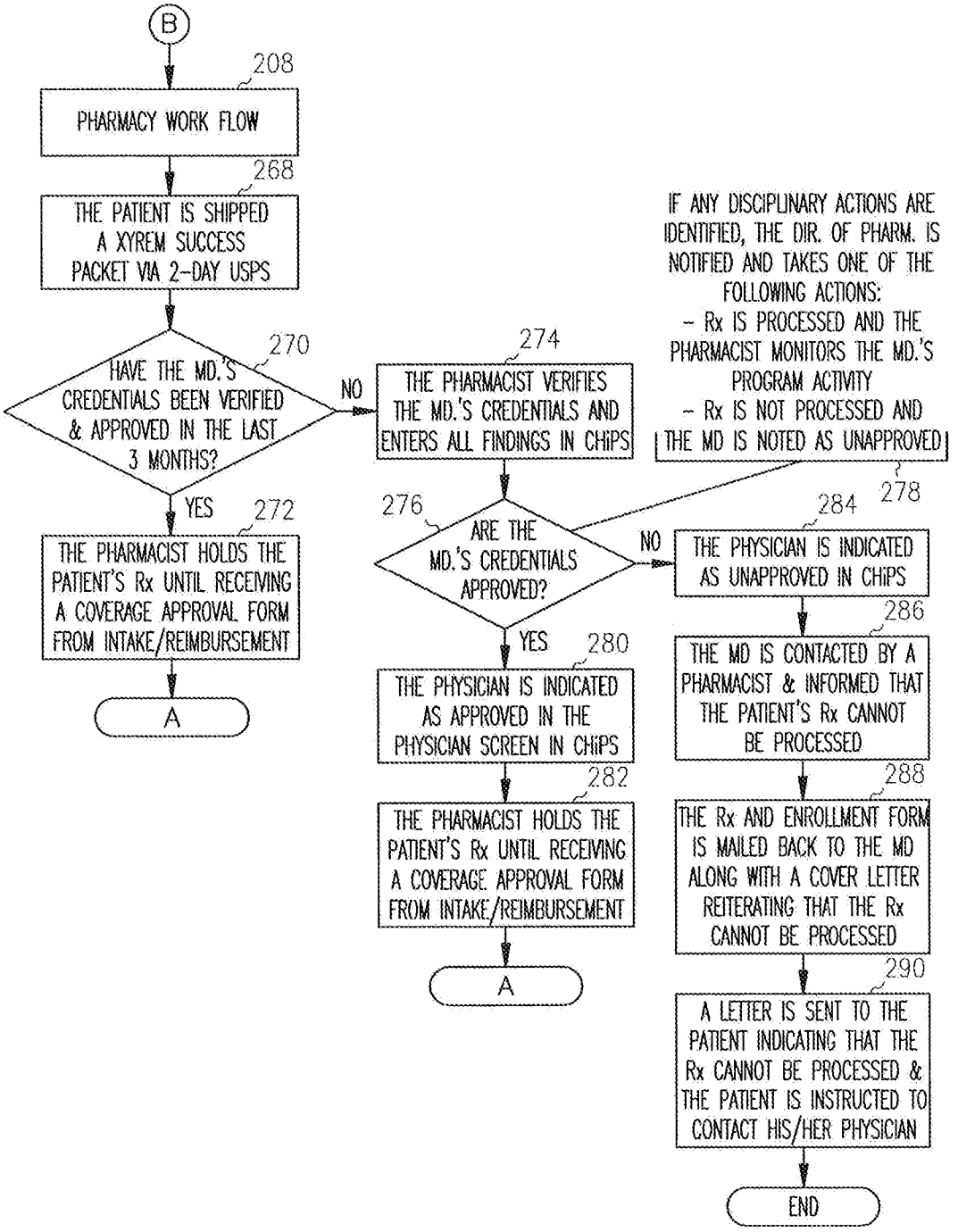

B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHIPS
276
ARE THE MD.'S CREDENTIALS APPROVED?
NO
YES
278
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
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
284
THE PHYSICIAN IS INDICATED AS UNAPPROVED IN CHIPS
286
THE MD IS CONTACTED BY A PHARMACIST & INFORMED THAT THE PATIENT'S Rx CANNOT BE PROCESSED
288
THE Rx AND ENROLLMENT FORM IS MAILED BACK TO THE MD ALONG WITH A COVER LETTER REITERATING THAT THE Rx CANNOT BE PROCESSED
290
A LETTER IS SENT TO THE PATIENT INDICATING THAT THE Rx CANNOT BE PROCESSED & THE PATIENT IS INSTRUCTED TO CONTACT HIS/HER PHYSICIAN
END

FIG. 2B

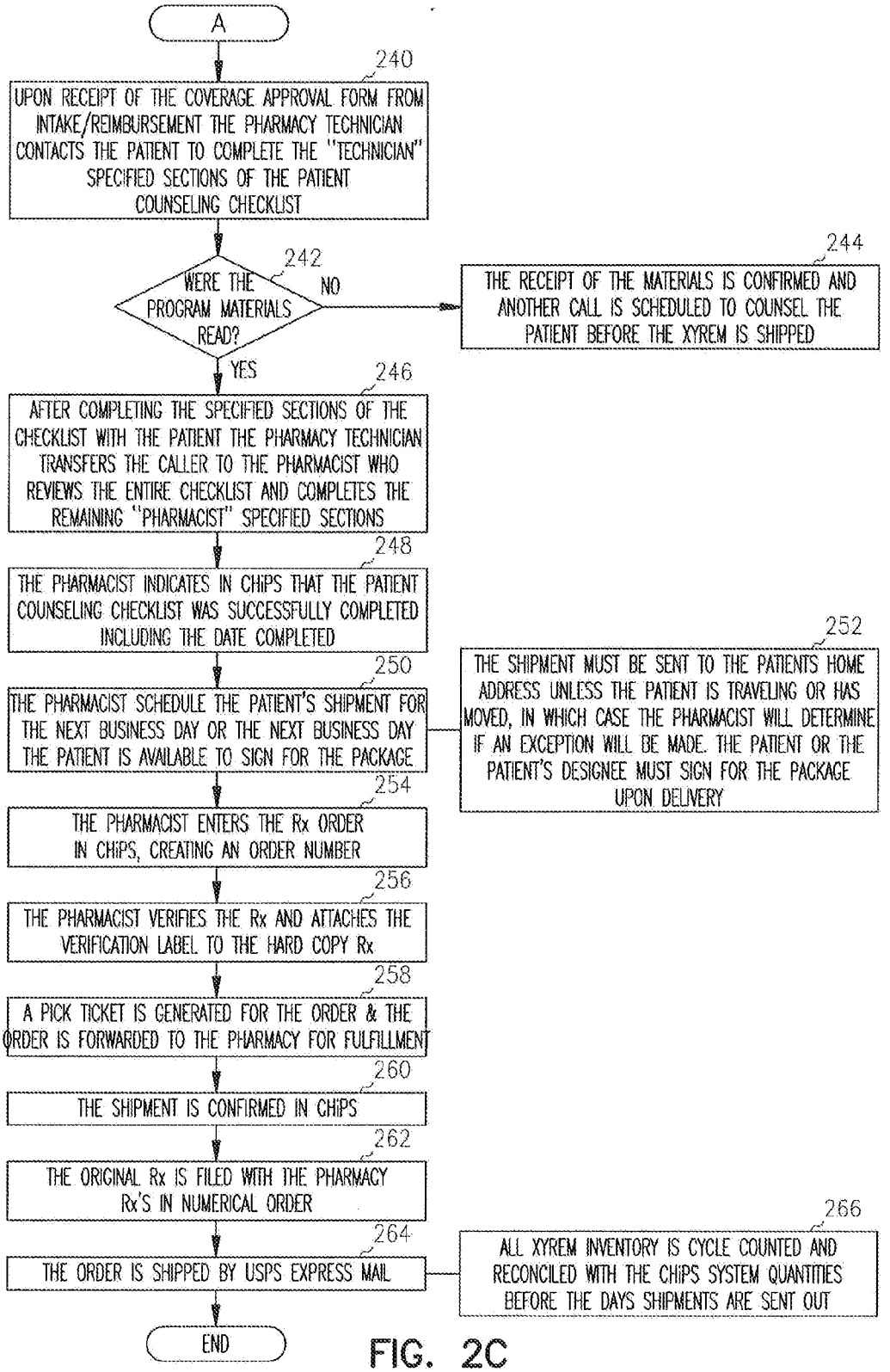

A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER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

FIG. 2C

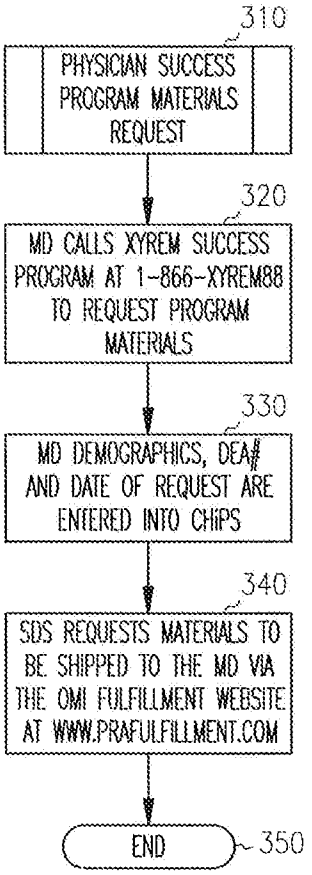

310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHIPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM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

FIG. 3

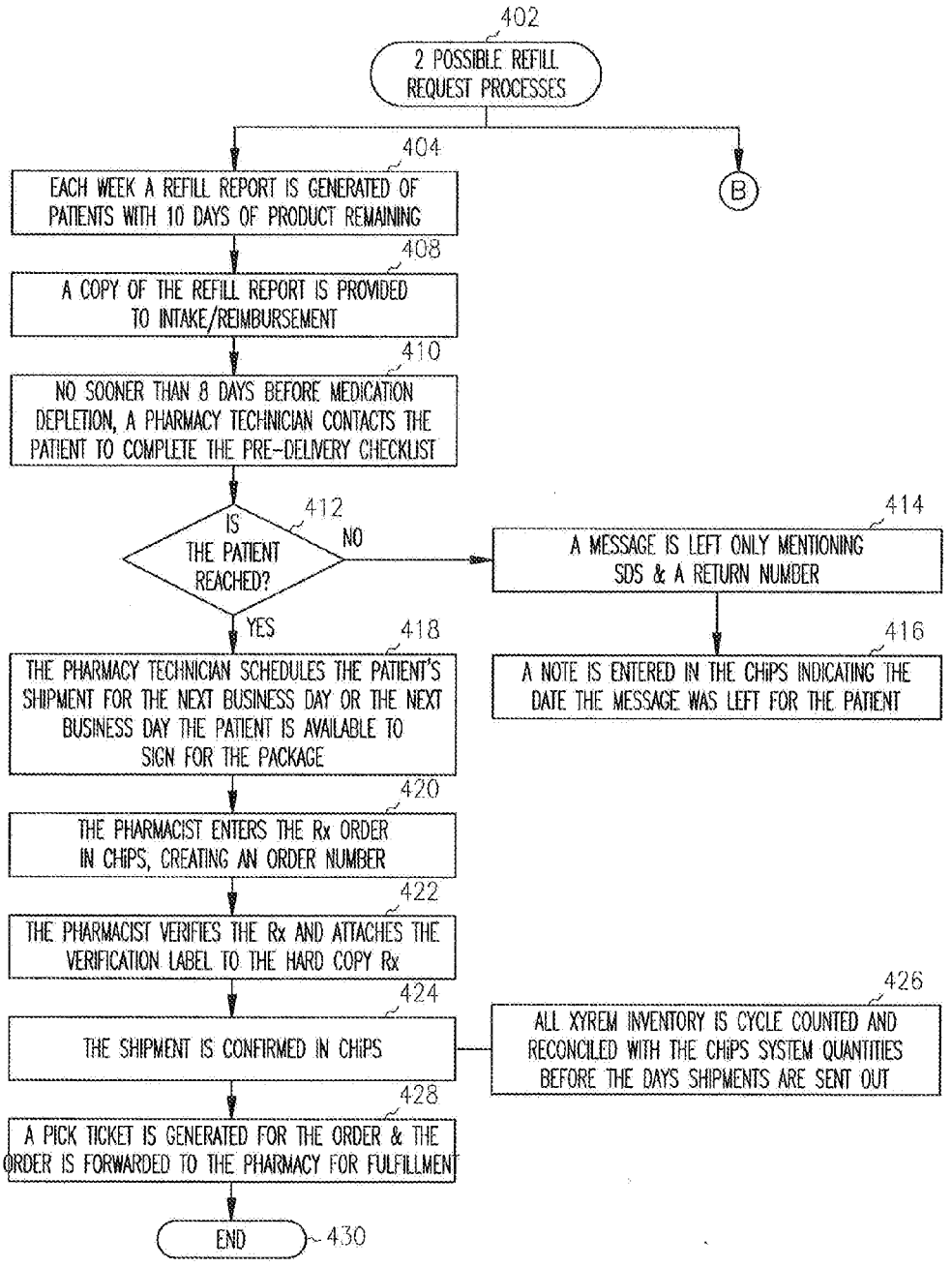

402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE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

FIG. 4A

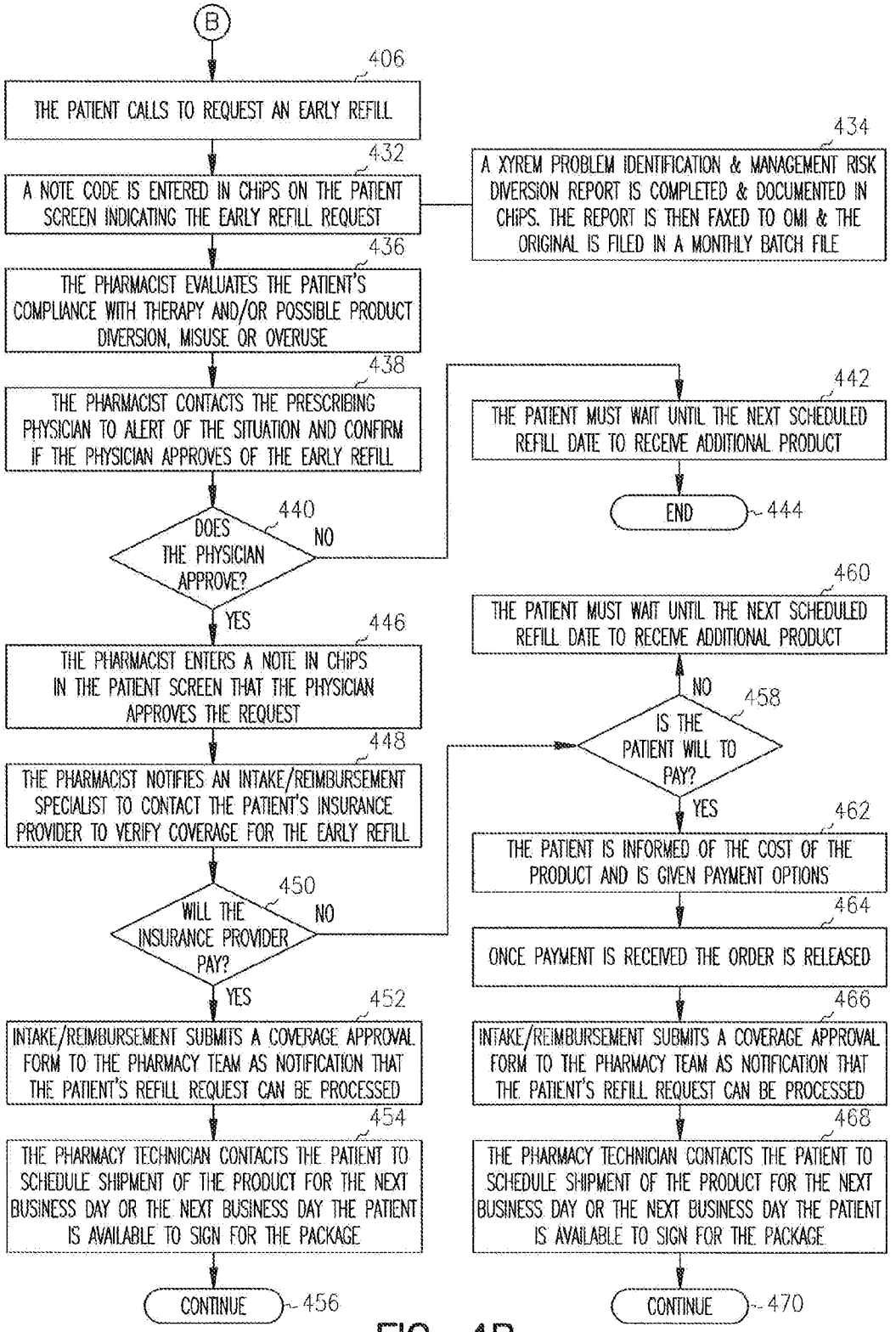

B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYREM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS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

FIG. 4B

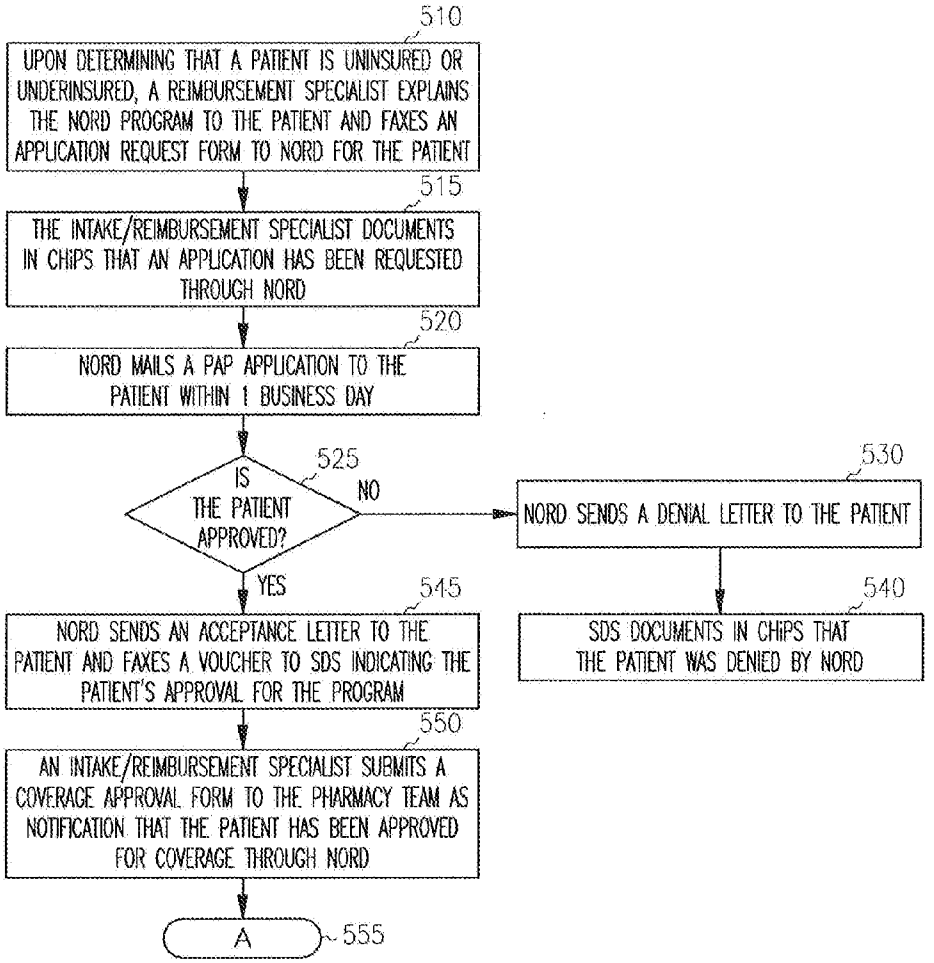

510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHIPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH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

FIG. 5

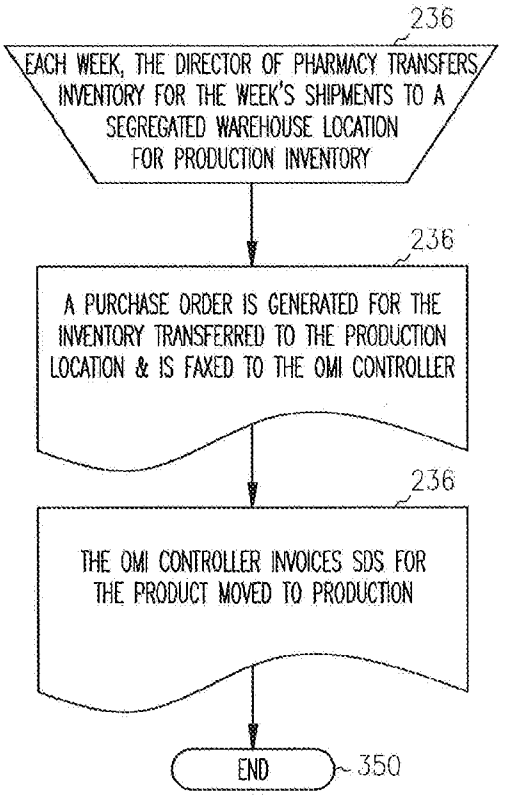


FIG. 6

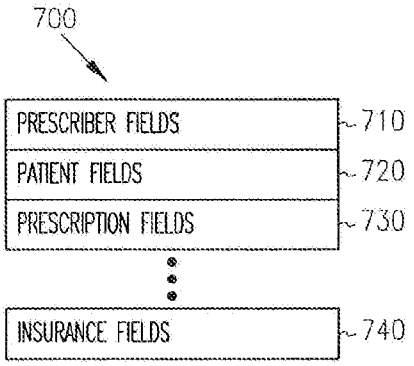


FIG. 7

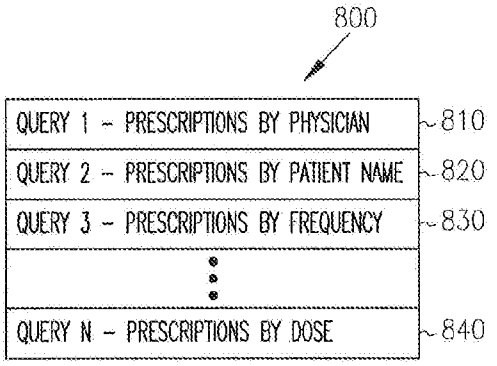


FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

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

PRESCRIPTION FORM

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

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

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

PATIENT INFORMATION

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

PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

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

FIG. 9


1000
PATIENT ASSISTANCE APPLICATION REQUEST FORM
DATE:
TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS
FAX #: 203-798-2291
PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:
PATIENT NAME
ADDRESS
TELEPHONE: ( )
PATIENT DOSAGE: (GRAMS) TWICE NIGHTLY FOR A TOTAL DOSAGE OF (GRAMS)
BOTTLES (THREE MONTHS SUPPLY)
BACKGROUND INFORMATION:

FIG. 10

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
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

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

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml btl	1

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

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

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

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

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

PHONE: <123-456-7890

CASE CODE: ********

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		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 APPLICATIONS

[0001] This application is a Continuation of and claims priority to U.S. application Ser. No. 14/196,603, filed on Mar. 4, 2014, which is a Continuation of and claims priority to U.S. application Ser. No. 13/592,202, filed on Aug. 22, 2012, which is a Continuation of and claims priority to U.S. application Ser. No. 13/013,680, filed on Jan. 25, 2011, which is a Continuation of and claims priority to 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 and claims priority to 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 herein incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs.

BACKGROUND OF THE INVENTION

[0003] 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.

[0004] 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.

[0005] 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

[0006] 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.

[0007] 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.

[0008] 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.

[0009] 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.

[0010] 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

[0011] FIG. **1** is a block diagram of a computer system for use in implementing the system and method of the present invention.

[0012] 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**.

[0013] 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**.

[0014] 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**.

[0015] 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**.

[0016] 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**.

[0017] FIG. **7** is a block diagram of database fields.

[0018] FIG. **8** is a block diagram showing a list of queries against the database fields.

[0019] FIG. **9** is a copy of one example prescription and enrollment form.

[0020] FIG. **10** is a copy of one example of a NORD application request form for patient financial assistance.

[0021] FIG. **11** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**.

[0022] FIG. **12** is a copy of certificate of medical need.

[0023] 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

[0024] 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.

[0025] 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.

[0026] 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.

[0027] 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.

[0028] 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.

[0029] 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.

[0030] 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.

[0031] 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.

[0032] 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.

[0033] 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.

[0034] 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.

[0035] 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**.

[0036] 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**.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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.

[0042] 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.

[0043] 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**.

[0044] 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.

[0045] 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**.

[0046] 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**.

[0047] 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 evalu-

ates 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**.

[0048] 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**.

[0049] 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**.

[0050] 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.

[0051] 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**.

[0052] 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**.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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.

1. (canceled)

2. 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;

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 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 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 time period are sent by using said database query to identify information in the prescription fields and patient fields.

3. The computer-implemented system of claim **2**, wherein the data processor arranges for delivery of the prescription drug to the patient in order to treat the patient with the prescription drug.

4. The computer-implemented system of claim **2**, wherein a pharmacy enters data into the single computer database.

5. The computer-implemented system of claim **2**, wherein the data processor selectively blocks shipment of the prescription drug to the patient.

6. The computer-implemented system of claim **2**, wherein an abuse pattern is associated with the patient, and shipment of the prescription drug is blocked based upon such association.

7. The computer-implemented system of claim **2**, wherein the prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

8. The computer-implemented system of claim **7**, wherein said GHB drug product treats cataplexy in the patient.

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

storing, using a computer processor, in a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields, the single computer database comprising one or more computer memories;

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 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;

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

reconciling inventory of the prescription drug before a shipment for a time period is sent by using said database query to identify information in the prescription fields and patient fields.

10. The method of claim **9**, comprising delivering the prescription drug to the patient in order to treat the patient with the prescription drug.

11. The method of claim **9**, wherein a pharmacy enters data into the single computer database.

12. The method of claim **9**, comprising selectively blocking shipment of the prescription drug to the patient.

13. The method of claim **9**, wherein an abuse pattern is associated with the patient, and shipment of the prescription drug is blocked based upon such association.

14. The method of claim **9**, wherein the prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

15. The method of claim **14**, wherein said GHB drug product treats cataplexy in said patient.

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

storing, using a computer processor, in a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields, the single computer database comprising one or more computer memories;

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, and wherein the company's prescription drug has been manufactured at a single manufacturing site;

said patient fields, contained within the database schema, storing information sufficient to identify the 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;

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

reconciling inventory of the prescription drug before the shipments for a time period are sent by using said database query to identify information in the prescription fields and patient fields.

17. The method of claim **16**, wherein a pharmacy enters data into the single computer database.

18. The method of claim **16**, comprising selectively blocking shipment of the prescription drug to the patient.

19. The method of claim **16**, wherein an abuse pattern is associated with the patient, and shipment of the prescription drug is blocked based upon such association.

20. A computer-implemented method for treatment of a patient with a single prescription drug that has a potential for misuse, abuse or diversion, comprising:

storing, using a computer processor, in a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields, the single computer database comprising one or more computer memories;

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

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

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

reconciling inventory of the single prescription drug before a shipment for a time period is sent by using said database query to identify information in the prescription fields and patient fields.

21. The method of claim **20**, comprising delivering the single prescription drug to the patient in order to treat the patient with the single prescription drug.

22. The method of claim **21**, comprising verifying two or more of the following using the computer processor prior to providing the single prescription drug to the 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.

23. The method of claim **20**, wherein a pharmacy enters data into the one or more computer memories.

24. The method of claim **20**, comprising selectively blocking shipment of the single prescription drug to the patient.

25. The method of claim **20**, wherein an abuse pattern is associated with the patient, and shipment of the single prescription drug is blocked based upon such association.

26. The method of claim **20**, wherein the single prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

27. The method of claim **26**, wherein said GHB drug product treats cataplexy in said patient.

28. The system of claim **2**, wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent.

* * * * *

EXHIBIT S

UNITED STATES PATENT AND TRADEMARK OFFICE

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EXAMINER	
NAJARIAN, LENA	

ART UNIT	PAPER NUMBER
3626	

NOTIFICATION DATE	DELIVERY MODE
03/02/2015	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. 14/219,904	Applicant(s) REARDAN ET AL.	
	Examiner LENA NAJARIAN	Art Unit 3626	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 MONTHS 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 *11/3/14*.

☐ 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) *2-28* 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) *2-28* 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.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *20140609; 20141107; 20141217*.

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.

DETAILED ACTION

Notice to Applicant

1. This communication is in response to the amendment filed 11/3/14. Claims 2, 9, 16, and 20 have been amended. Claim 1 has been cancelled. Claims 2-28 remain pending.

Terminal Disclaimer

2. The terminal disclaimer filed on 11/3/14 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on Application Number 14/219,941 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 101

3. 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.

4. Claims 2-28 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more. Claims 2-28 are directed to the abstract idea of reconciling inventory, which has been determined to be a method of organizing human activity. The claim does not include additional elements that are sufficient to amount to

significantly more than the judicial exception because the computer as recited is a generic computer component that performs functions (*i.e.*, storing information and processing a database query). These are generic computer functions (*i.e.*, storing information and processing a database query) that are well-understood, routine, and conventional activities previously known to the industry. The claims recite a computer memory and a data processor or a computer processor, which do not add meaningful limitations to the idea of reconciling inventory beyond generally linking the system to a particular technological environment, that is, implementation via computers. The claims do not amount to significantly more than the underlying abstract idea of reconciling inventory. Accordingly, claims 2-28 are ineligible.

Claim Rejections - 35 USC § 103

5. The following is a quotation of pre-AIA 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.

6. Claims 2-5 and 9-12 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), and further in view of Call (6,154,738).

(A) Referring to claim 9, Moradi discloses a computer-implemented method for treatment of a patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising (para. 45 of Moradi):

storing, via execution in a computer processor, in a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields, the single computer database comprising one or more computer memories (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. 27-31 and 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, 43-4, and 99 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);

processing, via execution in the computer processor, 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 expressly disclose reconciling inventory of the prescription drug with quantities of the prescription drug in the single computer database before a shipment for a time period is sent by using said database query to identify information in the prescription fields and patient fields.

Rosenblum discloses reconciling inventory of the prescription drug by using said database query to identify information in the prescription fields and patient fields (para. 100, 105 and 111 of Rosenblum).

Call discloses reconciling inventory with quantities in the single computer database before a shipment for a time period is sent (col. 29, lines 13-31 and col. 27, line 53 – col. 28, line 26 of Call).

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 Rosenblum and Call within Moradi. The motivation for doing so would have been to resolve all discrepancies (para. 111 of Rosenblum) and to insure consistency and synchronization (col. 29, lines 13-31 of Call).

(B) Referring to claim 10, Moradi discloses delivering the prescription drug to the patient in order to treat the patient with the prescription drug (para. 8 of Moradi).

(C) Referring to claim 11, Moradi discloses wherein a pharmacy enters data into the single computer database (para. 24 & 28 of Moradi).

(D) Referring to claim 12, Moradi discloses selectively blocking shipment of the prescription drug to the patient (para. 45 & 46 of Moradi).

(E) System claims 2-5 repeat the subject matter of claims 9-12 as a set of elements rather than a series of steps. As the underlying process has been shown to be fully disclosed by the teachings of Moradi, Rosenblum and Call in the above rejection of claims 9-12, it is readily apparent that the Moradi, Rosenblum and Call references include a system to perform the recited functions. As such, these limitations are rejected for the same reasons provided in the rejections of 9-12 and incorporated herein.

7. Claims 6 and 13 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), in view of Call (6,154,738), and further in view of Lilly et al. (US 2004/0176985 A1).

(A) Referring to claims 6 and 13, Moradi, Rosenblum and Call do not expressly disclose wherein an abuse pattern is associated with the patient, and shipment of the prescription drug or single 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. 57, 58, and 68-70 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, Rosenblum and Call. The motivation for doing so would have been to immediately detect and prevent problems related to abuse, fraud, and misuse of medications (para. 57 of Lilly).

8. Claims 7, 8, 14, 15, 20-24, 26 and 27 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), in view of Call (6,154,738), and further in view of Talk About Sleep ("An Interview with Orphan Medical about Xyrem").

(A) Referring to claims 7, 14, 26, 8, 15, and 27, Moradi, Rosenblum and Call do not disclose wherein the prescription drug comprises a gamma hydroxy butyrate (GHB) drug product and wherein said GHB drug product treats cataplexy in the 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 the 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 Moradi, Rosenblum and Call. The motivation for doing so would have been to help narcoleptic patients (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com).

(B) Referring to claim 20, Moradi discloses a computer-implemented method for treatment of a patient with a single prescription drug that has a potential for misuse, abuse or diversion, comprising (para. 45 of Moradi):

storing, via execution in a computer processor, in a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields, the single computer database comprising one or more computer memories (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 (para. 27-31 and 43-45 of Moradi), said patient fields, contained within the database schema, storing information sufficient to identify the patient for whom the company's single prescription drug is prescribed (para. 27, 43-45, and 99 of Moradi);

said prescriber fields, contained within the database schema, storing information sufficient to identify a physician or other prescriber of the company's single prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's single prescription drug (para. 27 and 43-45 of Moradi);

processing, via execution in the computer processor, a database query that operates over all data related to the prescription fields, prescriber fields, and patient fields for the single prescription drug (para. 31 and 37-38 of Moradi).

Moradi does not expressly disclose: reconciling inventory of the single prescription drug with quantities of the prescription drug in the single computer database before a shipment for a time period is sent by using said database query to identify information in the prescription fields and patient fields; and wherein the single prescription drug is sold or distributed by a company that obtained approval for

distribution of the single prescription drug, and wherein the distribution of the single prescription drug is 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.

Rosenblum discloses reconciling inventory of the single prescription drug by using said database query to identify information in the prescription fields and patient fields (para. 100, 105, and 111 of Rosenblum).

Call discloses reconciling inventory with quantities in the single computer database before a shipment for a time period is sent (col. 29, lines 13-31 and col. 27, line 53 – col. 28, line 26 of Call).

Talk About Sleep discloses wherein the single prescription drug is sold or distributed by a company that obtained approval for distribution of the single prescription drug, and wherein the distribution of the single prescription drug is 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 (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, Call and

Rosenblum within Moradi. The motivation for doing so would have been to better control access to the drug (see "An Interview with Orphan Medical about Xyrem," talkaboutsleep.com), so that all discrepancies may be resolved (para. 111 of Rosenblum) and to insure consistency and synchronization (col. 29, lines 13-31 of Call).

(C) Referring to claim 21, Moradi discloses delivering the single prescription drug to the patient in order to treat the patient with the single prescription drug (para. 8 of Moradi).

(D) Referring to claim 22, Moradi discloses verifying two or more of the following using the computer processor prior to providing the single prescription drug to the 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 (para. 24, 32, and 35 of Moradi).

(E) Referring to claim 23, Moradi discloses wherein a pharmacy enters data into the one or more computer memories (para. 24 & 28 of Moradi).

(F) Referring to claim 24, Moradi discloses selectively blocking shipment of the single prescription drug to the patient (para. 45 and 46 of Moradi).

9. Claims 16-18 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), in view of Call (6,154,738), and further in view of Levin (US 2002/0143320 A1).

(A) Referring to claim 16, Moradi discloses a computer-implemented method for treatment of a patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising (para.45 of Moradi):

storing, via execution in a computer processor, in a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields, the single computer database comprising one or more computer memories (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. 27-31 and 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, and 99 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 and 43-45 of Moradi);

processing, via execution in the computer processor, a database query that operates over all data related to the prescription fields, prescriber fields, and patient fields for the prescription drug (para. 31, 37, and 38 of Moradi).

Moradi does not expressly disclose:

reconciling inventory of the prescription drug with quantities of the prescription drug in the single computer database before the shipments for a time period are sent by using said database query to identify information in the prescription fields and patient fields;

and wherein the company's prescription drug has been manufactured at a single manufacturing site.

Rosenblum discloses reconciling inventory of the prescription drug by using said database query to identify information in the prescription fields and patient fields (para. 100, 105 and 111 of Rosenblum).

Call discloses reconciling inventory with quantities in the single computer database before a shipment for a time period is sent (col. 29, lines 13-31 and col. 27, line 53 – col. 28, line 26 of Call).

Levin discloses wherein the company's prescription drug has been manufactured at a single manufacturing site (para. 69 of Levin).

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 Levin, Rosenblum and Call within Moradi. The motivation for doing so would have been to easily track medical products (abstract of Levin), so that all discrepancies may be resolved (para. 111 of Rosenblum), and to insure consistency and synchronization (col. 29, lines 13-31 of Call).

(B) Claims 17-18 repeat the subject matter of claims 11 and 12, and are therefore rejected for the same reasons given above.

10. Claim 19 rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), in view of Call (6,154,738), in view of Levin (US 2002/0143320 A1), and further in view of Lilly et al. (US 2004/0176985 A1).

(A) Referring to claim 19, Moradi, Rosenblum, Call and Levin do not expressly disclose wherein an abuse pattern is associated with the patient, and shipment of the prescription drug or single 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. 57, 58, and 68-70 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, Rosenblum, Call and Levin. The motivation for doing so would have been to immediately detect and prevent problems related to abuse, fraud, and misuse of medications (para. 57 of Lilly).

11. Claim 28 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), in view of Call (6,154,738), and further in view of Brinkley et al. (5,963,919).

(A) Referring to claim 28, Moradi, Rosenblum and Call 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 Rosenblum, and Call. The motivation for doing so would have been to trigger replenishment (col. 4, line 62 - col. 5, line 8 of Brinkley).

12. Claim 25 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), in view of Call (6,154,738), 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 claim 25, Moradi, Rosenblum, Call and Talk About Sleep do not expressly disclose wherein an abuse pattern is associated with the patient, and shipment of the prescription drug or single 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. 57, 58, and 68-70 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, Rosenblum, Call and Talk About Sleep. The motivation for doing so would have been to

immediately detect and prevent problems related to abuse, fraud, and misuse of medications (para. 57 of Lilly).

Response to Arguments

13. Applicant's arguments with respect to claims 2, 9, 16 and 20 have been considered but are moot because the arguments do not apply to any of the references being used in the current rejection.

14. Applicant's additional arguments filed 11/3/14 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 11/3/14.

(1) Applicant argues that checks of physical inventories impart physical distinctions to the claims and therefore recite non- abstract, patentable subject matter.

(3) Applicant argues that the Xyrem Interview reference (from talkaboutsleep.com) does not disclose wherein the distribution of the single prescription drug is 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.

(A) As per the first argument, the Examiner respectfully submits that reconciling inventory can be performed mentally. Also, see 101 rejection above.

(B) Regarding Applicant's arguments for claim 20, Talk About Sleep discloses that a physician will write a prescription for Xyrem. As such, it is readily apparent that a prescription is only written if it is “medically necessary.” Talk About Sleep also discloses education materials. Insofar as the claim recites "two **or** more of," it is immaterial whether or not all of the elements are disclosed. The prior art only needs to show at least two of the recited features.

Conclusion

15. 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, Fonya Long can be reached on (571) 270-5096. 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 3626
2/11/15

EXHIBIT T

REMARKS

This communication responds to the Office Action dated March 2, 2015.

Claims 2, 9, 16, and 20 are currently amended; claim 1 is canceled; and no claims are added; as a result, claims 2-28 are now pending and subject to examination in this application.

The Rejection of Claims Under § 101

Claims 2-28 are rejected under 35 U.S.C. 101 because the claimed invention is allegedly directed to a judicial exception (*i.e.*, a law of nature, a natural phenomenon, or an abstract idea). Specifically, the Office Action contends that claims 2-28 are directed to an abstract idea of reconciling inventory, and further contends that the claims are an ineligible method of organizing human activity.

Applicant respectfully disagrees and respectfully traverses the rejection of the claims under section 101.

The Office Action contends that the claims "are directed to the abstract idea of reconciling inventory, which has been determined to be a method of organizing human activity." The Office Action further contends that the claims "do not amount to significantly more than the underlying abstract idea of reconciling inventory." As an initial matter, Applicant respectfully submits that the Office Action's contentions that reconciling inventory is an abstract idea and that it has been determined to be a method of organizing human activity are conclusory and not supported by evidence. Applicant therefore respectfully submits that for this reason alone, the rejection of the claims under section 101 is improper, and Applicant respectfully requests the withdrawal of the rejection of the claims.

The rejection of claims under section 101 must be based on evidence, and not unsupported opinions, conjecture, or conclusions, as was recently emphasized by the Patent Trial and Appeal Board (PTAB). In *Ex Parte Poisson,*[1] the PTAB stated that the determination of whether the claim at issue was directed to an abstract idea

> has not been made in this case based on evidence. Instead, the Examiner merely expresses an opinion that 'a

[1] Appeal No. 2012-011084 in U.S. Serial Application No. 12/427,040 (PTAB February 27, 2015), p. 5. A copy of the decision in *Ex Parte Poisson* is attached to this response for the convenience of the Examiner.

> set of rules qualifies as an abstract idea.' Yet, absent supporting evidence in the record—of which there is none, the Examiner's opinion is an inadequate finding of fact on which to base the *Alice* analysis

Applicant respectfully submits that this is exactly what has happened in the present case. The Office Action has stated that the claims are directed to an abstract idea of reconciling inventory. However, the Office Action has not come forth with any evidence to support its contention that reconciling inventory is an abstract idea. Additionally, the Office Action contends that reconciling inventory "has been determined to be a method of organizing human activity." However, once again, no evidence is provided to support this contention.

Applicant respectfully submits that the lack of evidence to support the contention that the claimed feature of "reconciling inventory" is an abstract idea is fatal to the rejection of the claims under section 101, that the rejection of the claims simply cannot stand, and that the rejection of the claims under section 101 must be withdrawn.

Irrespective of whether the claim feature of reconciling inventory is an abstract idea or not, Applicant respectfully submits that while the claims involve the concept of "reconciling inventory," the claims are not directed to the age-old concept of general inventory reconciliation because the claims recite significantly more than a simple reconciliation of inventory. A simple age-old reconciliation of inventory involves "well-known inventory control principles" of ***restocking*** an item when "actual inventory levels identify those stock items that are at or below their reorder points, [such that] orders for such items are generated . . . [and] a reconciliation process identifies whether there are any discrepancies between anticipated and actual amounts and locations of each item." (Rosenblum, ¶ [0111]; *cited* by the Office Action in rejecting the claims under 35 U.S.C. § 103). Similarly, in the Call reference, which is also cited by the Office Action in rejecting the claims under 35 U.S.C. § 103, a "conventional inventory control system" alters a "quantity on hand value" when a sale is made or when stock is replenished. (Call, column 27, line 54 - column 28, line 24).

In contrast, the claimed subject matter does not recite age-old inventory reconciliation between anticipated amounts and actual amounts when restocking a remote dispenser as in Rosenblum, or altering a quantity on hand value when a sale is made or stock is replenished as in

Call. Rather, the claimed subject matter recites "reconcil[ing] inventory of the prescription drug with quantities of the prescription drug in the single computer database before the shipments for a time period are sent by using said database query to identify information in the prescription fields, prescriber fields, and patient fields." Applicant's claimed subject matter is therefore significantly more than a simple reconciliation at a remote dispenser as in Rosenblum or a simple determination of quantity on hand such as in Call. Indeed, Applicant's claimed subject matter is an improvement to another field, the field of preventing prescription drug misuse, abuse or diversion through the use of a single computer database.

These additional elements that distinguish the claimed subject matter from a general reconciliation of inventory as in Rosenblum or Call are more specifically emphasized via the current amendments to the claims, which recite that the reconciliation of the inventory with quantities in the single computer database "identif[ies] misuse, abuse or diversion of the prescription drug." Applicant respectfully submits that this amendment more distinctly claims and particularly points out the difference between a general reconciliation of inventory to determine "quantity on hand" and Applicant's inventory reconciliation that, in conjunction with the single computer database, identifies misuse, abuse or diversion of the company's prescription drug.

In addition to contending that the claims do not recite significantly more than an abstract idea of reconciling inventory, the Office Action contends that the recited computer functions are conventional activities previously known in the industry. Applicant respectfully disagrees. As pointed out below in Applicant's response to the section 103 rejection of the claims, Applicant's claimed subject matter is both novel and non-obvious, and therefore was not previously known in the industry. Applicant respectfully submits that an invention that was not previously known in industry and that therefore passes muster under §§ 102 and 103 is likely to also pass muster under section 101. *See e.g., Ameritox, LTD. et al. v. Millennium Health, LLC,* Case No. 13-cv-832-wmc (W.D. Wisc. April 24, 2015) (" . . . there is enough in the combination of elements in the '680 patent to get over the patent eligibility threshold under current law, particularly in light of the jury upholding the patent on § 102 and § 103 grounds." *citing Alice Corp.,* 134 S. Ct. at 2354 (expressing a concern that its re-articulation of the § 101 claim not "swallow all of patent

law")).[2] Additionally, the fact that Applicant's claimed computer functions were not previously known in the industry is further illustrated by Applicant's previously issued patents relating to subject matter that is similar to Applicant's currently pending claims.[3]

The Office Action further contends that the alleged conventional activities of the claims simply amount to "storing information and processing a database query." Applicant respectfully responds that several U.S. District Court cases that have come down since the Supreme Court's *Alice* decision have turned away similar arguments. For example, in *Intellectual Ventures v. Capital One,*[4] in response to arguments that the claims were invalid under section 101, the court stated that the claims use "a structure that goes *beyond* relational databases and mere document sets." *Intellectual Ventures,* p. 20 (***emphasis in original***). Specifically, the court referred to the patent's specification that disclosed that the system's data structure is much more sophisticated than that of a relational database or set of XML documents. Finally, the *Intellectual Ventures* court stated that, unlike a relational database, the claimed subject matter uses complex data relationships, and users can easily define views of data that do not conform to constraints of a relational data model. *Id.* Similarly, Applicant's claims go beyond relational databases and document sets because the claims recite "storing a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields . . . and reconcil[ing] inventory of the prescription drug with quantities of the prescription drug in the single computer database before the shipments for a time period are sent by using said database query to identify information in the prescription fields, prescriber fields, and patient fields."

The *Intellectual Ventures* court further stated that while the claims do indeed recite words such as "organizing," "defining," and "identifying," those words cannot be read in isolation from the remainder of the claim. Similarly, Applicant respectfully submits that the recitation of "storing" and "processing" in its claims cannot be read in isolation from the detailed recitation of other features of the claims. (*See Intellectual Ventures,* page 30, the alleged infringer's

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[2] A copy of the court's decision in *Ameritox* is attached to this response for the convenience of the Examiner.

[3] *See e.g.,* U.S. Patent Nos. 7,668,730; 7,765,106; 7,797,171; 7,765,107; 7,895,059; 8,731,963; 8,589,182; 8,457,988.

[4] *Intellectual Ventures v. Capital One*, Case No. PWG-14-111 (D. Maryland; May 12, 2015) A copy of the *Intellectual Ventures* case is attached to this response for the convenience of the Examiner.

characterization of the claims ignores "the other verbiage in the claims."). The *Intellectual Ventures* court further concluded that the claims were not abstract because they did not embody an abstract idea such as intermediated settlement, hedging, algorithms, and the like (*Intellectual Ventures*, p. 31). Similarly, Applicant's claims do not recite an abstract idea such as intermediated settlement, hedging, algorithms, and the like. Rather, Applicant's claims are directed to a physical inventory of physical, tangible, and non-abstract prescription drugs, and the prevention of misuse, abuse, or diversion of these prescription drugs via a single computer database.

In *Mobile-Plan-It LLC v. Facebook Inc.*,[5] the court denied defendant's motion for judgment on the pleadings that the patent at issue disclosed only abstract ideas and therefore was invalid under section 101. The claims in *Mobile-Plan-It* were directed to a system that solved a technical problem of allowing meeting attendees to send messages to one another without divulging their primary electronic addresses. The patent accomplished this by using a proxy mailbox in computer storage. Applicant respectfully submits that its claims recite a similar technology. Applicant's claims permit the distribution of a sensitive drug that is susceptible to misuse, abuse, or diversion by using a single computer database. Applicant respectfully submits that the specialized proxy mailbox in computer storage in *Mobile-Plan-It* is analogous to the single computer database in Applicant's claims, and Applicant further respectfully submits that like the claims in *Mobile-Plan-It*, its claims pass section 101 muster.

In another recent case, *Messaging Gateway Solutions LLC v. Amdocs et al.*,[6] the court, in ruling that the claims were patent eligible, agreed with the patentee's contention that the defendants were over-generalizing the claims. Specifically, the court stated that if

> one looks at almost any patent from far enough away, it could arguably claim an abstract idea. For example, Alexander Graham Bell's patent could be said to claim the abstract idea of oral communication. But his invention was not the concept of oral communication itself; it was a

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[5] *Mobile-Plan-It LLC v. Facebook Inc.*, Case No. 14-CV-1709-RS (ND CA; April 20, 2015). A copy of the *Mobile-Plan-It* case is attached to this response for the convenience of the Examiner.
[6] *Messaging Gateway Solutions LLC v. Amdocs et al.*, Memorandum Opinion, Civil Action No. 14-732-RGZ (D Delaware, April 15, 2015). A copy of the *Messaging Gateway* case is attached to this response for the convenience of the Examiner.

> technological innovation that allowed a type of oral communication between people who could otherwise not communicate in that way.

Id. pp. 6, 10. The *Messaging Gateway* court further found persuasive that the claim at issue "contains sufficient limitations to prevent it from preempting an abstract idea." *Id.*, p. 11. Applicant respectfully submits that these points relating to the improper generalization of patent claims in a section 101 analysis are the same points that Applicant put forth in its responses in its U.S. Serial Application No. 14/196,603. Specifically, in its recent responses in the '603 application, Applicant stated that it is improper to extract the general purpose of a claim, label that general purpose as an abstract idea, and then conclude without proper support that the entire claim recites nothing more than that abstract idea.[7] Applicant therefore continues to respectfully submit that per *Messaging Gateway,* it is improper to label its pending claims as directed to an abstract idea of reconciling inventory, to ignore the other portions of the claim that recite sufficient limitations that prevent it from pre-empting a general inventory reconciliation,[8] and then to conclude that Applicant's claims are directed to non-statutory subject matter.

For the foregoing reasons, Applicant respectfully submits that the claims recite a novel, non-obvious, patent-eligible system that prevents the misuse, abuse, or diversion of prescription drugs through a single computer database and an associated inventory reconciliation system.

The Rejection of Claims Under § 103

Claims 2-5 and 9-12 are rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), and further in view of Call (6,154,738).

Claims 6 and 13 are rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), in view of Call (6,154,738), and further in view of Lilly et al. (US 2004/0176985 A1).

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[7] U.S. Serial Application No. 14/196,603, Applicant response dated November 6, 2014, p. 13 and Applicant response dated April 16, 2015, p. 16.
[8] *See Alice Corp. v. CLS Bank Inter.*, 134 S.Ct. 2347, 2354 (2014).

Claims 7, 8, 14, 15, 20-24, 26 and 27 are rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), in view of Call (6,154,738), and further in view of Talk About Sleep ("An Interview with Orphan Medical about Xyrem").

Claims 16-18 are rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), in view of Call (6,154,738), and further in view of Levin (US 2002/0143320 A1).

Claim 19 rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), in view of Call (6,154,738), in view of Levin (US 2002/0143320 A1), and further in view of Lilly et al. (US 2004/0176985 A1).

Claim 28 is rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), in view of Call (6,154,738), and further in view of Brinkley et al. (5,963,919).

Claim 25 is rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over Moradi et al. (US 2004/0019794 A1) in view of Rosenblum (US 2003/0050731 A1), in view of Call (6,154,738), 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).

Claim 2 recites "a data processor to . . . reconcile inventory of the prescription drug with quantities of the prescription drug in the single computer database before the shipments for a time period are sent by using said database query to identify information in the prescription fields, prescriber fields, and patient fields." Applicant's specification includes examples of inventory reconciliation, including at page 9, lines 13-15, wherein it discloses that "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 or prescription drug kiosk, and instead involves whether the aggregate amount of a drug in the physical inventory agrees with the aggregate amount in the database. If there is not an agreement between the amount in the physical inventory and the amount in the database, then a mismatch/discrepancy has been detected between the physical inventory and the database inventory amounts.

The Office Action of May 6, 2014, on pages 6 and 7, contended that Rosenblum discloses, for independent claims 2 and 9, this claim feature of "reconciling inventory of the prescription drug before a shipment for a time period is sent by using said database query to identify information in the prescription fields and patient fields." On pages 11-12 of its response of November 3, 2014, Applicant respectfully pointed out that Rosenblum only relates to determining whether an inventory at a particular remote dispenser was at a level that was to be expected at that particular remote dispenser, and further pointed out that in Rosenblum there is no disclosure that there is any reconciliation of inventory prior to sending shipments of the prescription drug. The current Office Action tacitly concedes these points, since the current Office Action now contends that Rosenblum only generally discloses "reconciling inventory of the prescription drug by using said database query to identify information in the prescription fields and patient fields." (*i.e.*, the current Office Action does not contend that Rosenblum discloses "before shipments of the prescription drug for a time period are sent."). The current Office Action on page 5 contends however that the Call reference discloses "reconciling inventory with quantities in the single computer database before a shipment for a time period is sent."

Notwithstanding the above, in order to advance the prosecution of this application, Applicant has amended the reconciling feature of claim 2 to recite "reconcile inventory of the prescription drug with quantities of the prescription drug in the single computer database before the shipments for a time period are sent by using said database query to identify information in the prescription fields, prescriber fields, and patient fields, thereby identifying misuse, abuse or diversion of the prescription drug.

Applicant respectfully submits that the Call reference's inventory checking is not a disclosure of this amended claim feature---that is, identifying misuse, abuse or diversion of a prescription drug via reconciling inventory. Rather, Call's point of sale terminal **421** in a retailer's brick and mortar store, or a retailer's web register **420,** relates only to a particular retailer's inventory (*see, e.g.,* column 27, lines 36-38; "web register **420** . . . effectively connect[s] the retailer's existing inventory control system **422** to the World Wide Web . . . "). The retailer's inventory control system can then determine whether a sale is made by a "point of sale register **421** in the physical retail store or by the web register **422** [*sic*, **420**], [can determine] the quantity on hand . . . [via] a database for each retailer [that] indicates the products available for sale and the quantity on hand . . . [and the system can therefore] accurately inform the customer when shipments can be expected for goods on hand and when goods which must be replenished will be shipped with a delay." (Call, column 27, line 60 – column 28, line 14). That is, the Call system is a typical inventory control system that determines the amount of goods on hand and when the goods must be replenished. In contrast, the claims more particularly recite that the inventory reconciliation uses the single database to identify misuse, abuse or diversion. Applicant respectfully submits that there is a patentable distinction between an inventory system that determines simple quantity on hand and an inventory system that uses a single computer database to identify abuse, misuse or diversion of a prescription drug.

Applicant respectfully submits that the subject matter of claim 2 would not have been obvious in view of the references of record, either alone or in combination, and Applicant respectfully requests the withdrawal of the rejection of claim 2. Furthermore, since independent claims 9, 16, and 20 recite the same or substantially the same subject matter as claim 2, Applicant respectfully submits that claims 9, 16, and 20 also would not have been obvious in view of the references of record, and respectfully requests the withdrawal of the rejection of claims 9, 16, and 20.

Additionally, independent claim 16 recites that "the company's prescription drug has been manufactured at a single manufacturing site." The Office Action contends that this feature is disclosed in paragraph [0069] of the Levin reference. Applicant respectfully disagrees.

Paragraph [0069] of Levin states that "a source facility **412** such as a drug manufacturer or blood bank may transport the medical product to a distribution facility **414** . . ." Applicant respectfully submits that this general disclosure of a source facility is not the specific recitation of a ***single*** manufacturing site as in claim 16. In patent drafting, the use of the indefinite article "a" means one or more.[9] Therefore, the disclosure of a source facility in Levin does not teach specifically limiting the manufacture of a prescription drug to one manufacturing site, and is therefore not a disclosure of a single manufacturing site. For this additional reason, Applicant respectfully submits that claim 16 would not have been obvious in view of the references of record, and Applicant respectfully requests the withdrawal of the rejection of claim 16.

Claim 28, which depends on claim 2, recites that 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 contends that this feature is disclosed in the Brinkley reference. Applicant respectfully disagrees.

The Brinkley reference admittedly mentions cycle counting. However, the cycle counting of Brinkley is only for determining if the "inventory level for an item falls below a reorder point, [and if it does] an order is placed." (Brinkley, column 4, lines 65-67). There is no disclosure of reconciling this cycle count with database quantities before a shipment for a day or other time period is sent so as to identify misuse, abuse, or diversion of the prescription drug, as is recited in the claims. That is, the use of cycle counting in Brinkley is for typical inventory control, like in the Rosenblum or Call references. For this additional reason, Applicant respectfully submits that claim 28 was rejected in error, and Applicant respectfully requests the withdrawal of the rejection of claim 28.

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[9] *01 Communique Laboratory, Inc. v. Logmein, Inc.*, 687 F.3d 1292, 1297 (Fed. Cir. 2012) ("As a general rule, the words 'a' or 'an' in a patent claim carry the meaning of 'one or more,'" *citing TiVo, Inc. v. EchoStar Communications Corp.*, 516 F.3d 1290, 1303 (Fed. Cir. 2008)).

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 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,

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Date Jul 8, 2015

By / David D'Zurilla /
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EXHIBIT U

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC. and JAZZ PHARMACEUTICALS IRELAND LIMITED, **Plaintiffs,** **v.** **WATSON LABORATORIES, INC.,** **Defendant.**	**Civil Action No. 14-7757 (ES)(JAD)** **(Filed Electronically)**

JAZZ'S MEMORANDUM OF LAW IN OPPOSITION TO WATSON'S MOTION TO DISMISS PURSUANT TO RULE 12(b)(6)

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Plaintiffs Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals Ireland Limited (collectively, "Jazz") respectfully submit this Memorandum of Law in Opposition to Watson Laboratories, Inc.'s ("Watson's") Motion to Dismiss Pursuant to Rule 12(b)(6) ("Motion") (D.I. 13).

INTRODUCTION

Watson's motion to dismiss relies entirely on a mischaracterization of Jazz's asserted patents.[1] Specifically, Watson argues that the asserted patents are directed to an abstract idea. The patents, however, actually claim specific methods and systems for distributing sensitive drugs using a specialized central computer database to store prescription information and to detect and identify potential abuse, misuse, or diversion of the drug. These methods offer a particular advantageous solution to the longstanding problem of prescription drug abuse, misuse, and diversion. The claims of the asserted patents recite different central computer databases, with different implementations, for achieving this goal.

The Supreme Court's decision in *Alice Corp. Pty. Ltd. v. CLS Bank Int'l* expressed the framework for determining patent eligibility under 35 U.S.C. § 101 in two alternative ways: (1) a claim satisfies Section 101 if it does not preempt any abstract idea; or (2) a claim satisfies Section 101 if it contains an "inventive

[1] Only a subset of the patents asserted in this case are at issue in Watson's motion to dismiss. *See infra* p. 4. In the context of Jazz's opposition, "asserted patents" refers only to those patents on which Watson has moved.

concept" such that its practice amounts to significantly more than a patent on just the abstract idea. Here, the asserted patents satisfy both inquiries.

First, the claims of the asserted patents recite specific, new methods, and do not preempt any abstract idea. Watson's brief does not discuss preemption, much less identify an abstract idea that is plausibly preempted by the claims of the asserted patents. Although Watson characterizes the asserted patents as directed to the abstract ideas of either "risk mitigation" or "drug distribution," a cursory reading of the claims makes clear that they do not preempt those concepts – nor does Watson even suggest otherwise. If the specific limitations of a claim are ignored, as Watson does here, any invention can be characterized as an abstract idea (*e.g.*, a claim to a method of treatment with a drug can be the abstract idea of "treating illness"). Thus, to argue that the claims are directed to an abstract idea, Watson necessarily ignores essential claim limitations tying the invention to a novel combination of numerous specific activities and requiring the use of a specific, novel machine – the central computer database. Watson ignores the claim limitations in an attempt to draw parallels to patents in other cases that merely claimed generic computer implementations of well-known business practices. Watson's approach runs contrary to established and recent Supreme Court and Federal Circuit precedent, and should be rejected.

Second, the claims of the asserted patents include inventive concepts beyond

any abstract idea to which they may relate. Specifically, each claim of the asserted patents recites numerous required activities as well as a central computer database that is configured specially to detect and identify potential abuse, misuse or diversion of a drug product. The patent office itself repeatedly recognized that the combination of the required claim limitations including a central computer database to perform these functions was novel and unconventional, and issued seven patents claiming various forms of the method. Watson's argument to the contrary ignores clear Supreme Court precedent requiring the inventiveness of the claims to be considered *as a whole*. Instead, Watson improperly dissects the claims into individual oversimplified limitations and then dismisses those limitations as "routine" or "conventional." Properly analyzed, the claims as a whole include inventive concepts.

Moreover, Watson's arguments raise questions as to underlying facts, such as what practices were considered routine or conventional in the pharmaceutical field, or present new issues of claim construction, such as the precise scope of the claims with respect to the central computer database limitation. These issues cannot appropriately be resolved on a motion to dismiss, and constitute an independent reason to deny Watson's motion at this time.

STATEMENT OF FACTS

Jazz is a biopharmaceutical company that developed and manufactures Xyrem®, the only pharmaceutical product FDA approved for use in the treatment of both cataplexy and excessive daytime sleepiness, which are devastating symptoms associated with the sleep disorder narcolepsy.[2] *See* Ex. 1,[3] Xyrem® Risk Evaluation and Mitigation Strategy (REMS), at 3.[4] Jazz owns several patent families that cover the: (1) chemical composition of Xyrem®; (2) methods of use and administration of Xyrem®; and (3) unique drug distribution system controlling the distribution of Xyrem® through a single pharmacy and central database to mitigate the risk of abuse, misuse, and diversion. Jazz has asserted all three families of patents against Watson in this action. Watson's motion to dismiss relates only to the drug distribution system patents.

A. Xyrem® Is Subject To Restricted Distribution

Xyrem®'s active ingredient is sodium oxybate, which is a form of gamma-

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[2] Jazz and its predecessor with respect to Xyrem®, Orphan Medical Inc., are referred herein collectively as "Jazz."

[3] " Ex. __" refers to the exhibits to the Declaration of William C. Baton submitted herewith.

[4] The Court may take judicial notice of the Xyrem® REMS, which is publicly available on the FDA's website: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM436562.pdf (last visited April 20, 2015). *See In re Lipitor Antitrust Litig.*, No. 3:12-cv-2389 (PGS), 2013 WL 4780496, at *1 (D.N.J. Sept. 5, 2013) ("On motions to dismiss … [a] court may also properly look at public records, including judicial proceedings, the relevant patents and the patents' prosecution histories.").

hydroxybutyrate (GHB). GHB has been recognized by Congress and numerous federal agencies as a dangerous substance, frequently misused as a "date rape drug" in cases of drug-facilitated sexual assault. *See, e.g.*, Exs. 2-5; Ex. 6 at 4 (describing problems associated with GHB). Because of its high potential for abuse and misuse, GHB has been classified as a Schedule I controlled substance under the Controlled Substances Act. *See* 21 U.S.C. § 812(b)(1); 21 C.F.R. § 1308.11(e)(1). However, the FDA and Congress recognized the need for GHB as the only method for treating symptoms of narcolepsy. Thus, Xyrem® was classified as a Schedule III controlled substance, acknowledging its legitimate medical purposes. *See* 21 U.S.C. § 812(b)(3); 21 C.F.R. § 1308.13(c)(6); Ex. 7 at 1. In doing so, however, both Congress and the FDA noted that availability of Xyrem® must be strictly controlled to ensure that it could not be illicitly obtained for use as a "date rape drug." *See* Ex 8 at H58; Ex. 9 at 1.

Given the unique status of GHB as a drug that had been congressionally designated a "date rape drug," the U.S. Food and Drug Administration (FDA) conditioned approval of Xyrem® on Jazz's development and implementation of a restricted distribution program. *See* Ex. 9. This restricted distribution program was first approved in 2002 and again in 2005, and subsequently deemed a REMS under the applicable provisions of the Federal Food, Drug and Cosmetic Act in 2008, with final approval received in February 2015. The Xyrem® REMS includes

elements to ensure safe use, such as special certifications for prescribing physicians, registration of all patients, prescriptions, and prescribing physicians in a single central computer database, and the use of a single central pharmacy to distribute and dispense Xyrem®. *See* Ex. 1 at 2-9.

B. Xyrem®'s Restricted Distribution Program Targets Risks to the Public as Well as Risks to Patients

Because the active ingredient of Xyrem® has a unique history and has potential for use against third parties, the Xyrem® REMS is categorically different from restricted distribution programs for other drugs. Restricted distribution programs frequently aim to prevent unintentional misuse of a drug (such as use of drugs known to cause birth defects if used during pregnancy) or to mitigate known adverse side effects of a drug. This is typically accomplished by educating physicians and patients about potential risks. *See, e.g.*, Ex. 10 (Thalomid REMS) (listing goals as "prevent[ing] the risk of embryo-fetal exposure" and "inform[ing] prescribers, patients, and pharmacists on the serious risks"); Ex. 11 (Chantix REMS) ("The goal of this REMS is to inform patients about the potential serious risk of neuropsychiatric adverse events associated with the use of CHANTIX."). A handful of programs also seek to reduce risks associated with substance abuse and addiction. *See, e.g.*, Ex. 12 (ER/LA Opioid REMS) ("The goal of this REMS is to reduce serious adverse outcomes.... Adverse outcomes of concern include addiction, unintentional overdose, and death."). By contrast, the Xyrem® REMS

must address the unique problem of *intentional misuse against others* – specifically, diversion of Xyrem® for use as a "date rape drug." Thus, the Xyrem® REMS states as a goal, "Ensuring that pharmacy controls exist prior to filling prescriptions for XYREM® that: … Monitor for inappropriate prescribing, misuse, abuse, and diversion of XYREM."

Although Watson contends that "risk mitigation" and "drug distribution" were known generally prior to the filing of the applications for the asserted patents (*see* Motion at 4), programs aimed to minimize intentional misuse of prescription drugs *against others*, such as the Xyrem® REMS, were practically nonexistent at the time. As Watson's own motion and supporting evidence demonstrate, "risk mitigation" programs in the pharmaceutical industry have historically focused on informed consent and patient education to prevent undesirable adverse effects associated with certain drugs.[5] *See, e.g.*, Motion at 4-6; Def's Ex. E at 1 (discussing "[w]ho has the responsibility for conveying to patients the risks associated with prescription drugs"); Def's Ex. I at 8 (listing categories of risks from medical products as "known side effects," "medication or device errors," "product defects," and other "uncertainties"). These programs provided no means for detecting and preventing *intentional* abuse, misuse, and diversion of

[5] To the extent Watson contends otherwise, this dispute creates a factual issue and precludes dismissal on the pleadings. *See infra* Argument Section II.

prescription drugs. Moreover, the fact that some risk mitigation systems existed does not mean that there can be no invention of new or improved methods of preventing or at least reducing the risks of drug misuse and abuse. Older methods of deterring abuse of other drugs were far from successful, as opposed to the remarkable record of success achieved by the invention claimed in the patents at issue to prevent abuse of Xyrem®.

The Xyrem® REMS addresses the problem of intentional abuse, misuse, and diversion by requiring numerous specific controls and tracking all prescriptions and associated information in a single central computer database that identifies and flags behavior that may indicate abuse, misuse, or diversion. Specifically, as the inventions claimed in the patents at issue require, the Implementation System required under the REMS calls for dispensing Xyrem® only through the "REMS Program Certified Pharmacy," and for "a secure and validated XYREM® REMS Program Central Database" that tracks "patient and prescriber enrollment status, all completed data forms, prescription and shipment data, as well as information related to dosing, concomitant medications, and behavior that raises suspicion of abuse, misuse, or diversion." Ex. 1 at 8. The certified pharmacy and central computer database are part of a proprietary drug distribution system developed by Jazz specifically in response to the unique risks of abuse, misuse, and diversion associated with Xyrem®.

C. The Asserted Patents Cover the Xyrem® REMS

The methods claimed in the asserted patents address the unique problem the Xyrem® REMS was invented to solve – the potential for intentional misuse of the drug against others. At a high level, each patent discloses drug distribution systems and methods using a central computer database to track prescriptions for sensitive drugs and identify potential abuse, misuse and diversion. *See, e.g.*, '730 Patent at Abstract.[6] The central computer database described in the asserted patents is a specific machine, implemented as a relational database that stores multiple fields of information relating to prescribing physicians, patients, and prescriptions, as well as relationships between those fields. *Id.* at 7:38-52. The central computer database also tracks and flags indications of abuse, misuse, or diversion, such as disciplinary actions against a prescribing physician or early refill requests by a patient. *See, e.g.*, *id.* at 5:15-26, 6:33-46.

The claims of the asserted patents recite methods that use Jazz's proprietary central computer database associated with an exclusive central pharmacy as part of a drug distribution system. Each claim recites a central computer database that stores prescription information and identifies behaviors that may indicate abuse, misuse, or diversion. *See, e.g.*, '730 Patent, claim 1 ("requiring entering of the

[6] The asserted drug distribution patents share a common specification, and citations to the '730 Patent are exemplary.

information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations"); '182 patent, claim 1 ("receiving, using a computer processor, into a single computer database … all prescriptions for the company's prescription drug with the potential for abuse, misuse or diversion; … checking for abuse, using the computer processor and the single computer database"). The combination of the numerous control steps, including a specialized central computer database differentiates the invention from other drug distribution methods used in the pharmaceutical arena. *See, e.g.*, Ex. 13 ('730 Patent Notice of Allowability). Different claims recite different configurations or uses of the database, as well as different combinations of controls and processes. *See, e.g.*, '106 patent, claim 1 (reciting numerous controls used by the central database to identify potential abuse, misuse, or diversion).

Watson's characterization of the asserted patents is deliberately misleading. Watson suggests that the claims of the patents merely "involve receiving and acting on a prescription request" (Motion at 14), but simply ignores the numerous controls and processes that each and every claim requires and ignores the use of a central computer database operating in conjunction with those controls and processes to detect and flag potential abuse, misuse and diversion of the drug.

These limitations – which are the essence of the invention[7] – are mentioned only once in Watson's entire motion and simply labeled as "subsequent steps" in the claims, without further analysis. *See* Motion at 14. Despite contending generally that the elements of the claims "can be done by humans" (Motion at 15), Watson does not once argue specifically that a centralized system for identifying and preventing abuse of a prescription drug like Xyrem® ever has been, much less could be, feasibly implemented without the claimed special purpose computer that is a central database exclusively controlled by a central pharmacy. Furthermore, the Supreme Court in *Bilski v. Kappos,* 561 U.S. 593 (2010), held that a patentable process was not limited to one that required a machine or transformation of matter. That a novel and non-obvious activity can be performed "by humans" does not disqualify it as patentable subject matter.

For these exact reasons, the use of a central computer database is far from a "superficial" recitation of a computer, as Watson contends (Motion at 12). The central computer database is specially configured to limit distribution and analyze prescription information for indicators of misuse and flag potential abuse, misuse, and diversion – a process that was not and could not effectively be performed by

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[7] The specifications of the asserted patents confirm that the problem that the patents aim to solve is the "need for a distribution system and method that directly addresses these abuses [of controlled prescription drugs]." *E.g.*, '730 patent at 1:30-31.

drug manufacturers or pharmacies. Nor is the central computer database merely a general purpose computer that applies (and effectively preempts) an abstract idea. For example, claim 1 of the '963 patent claims a specific machine that implements the misuse detection and prevention technologies underlying the inventions of the asserted patents:

> 1. A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising:
>
> one or more computer memories for storing a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;
>
> said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug;
>
> said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;
>
> said prescriber fields, contained within the database schema, storing information sufficient to identify a physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug;
>
> a data processor 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.

'963 Patent, claim 1. The other claims of the asserted patents recite different configurations of the central computer database, with different specific programming and controls for identifying potential abuse, misuse, and diversion.

D. Watson's Use of a Single Representative Claim Is Improper

The Federal Circuit has never held that a single representative claim may always be used in the context of a Section 101 analysis of multiple patents and multiple claims; rather, the Court approved the use of representative claims only when "the claims are substantially similar and linked to the same abstract idea." *Content Extraction and Transmission LLC v. Wells Fargo Bank, Nat'l Ass'n*, 776 F.3d 1343, 1348 (Fed. Cir. 2014) (internal quotation marks omitted). Accordingly, the Court in *Content Extraction* rejected the argument that it was required as a matter of law to engage in a detailed analysis of each of the 242 asserted claims when the plaintiff did not differentiate any claim from those presented as representative and did not otherwise point to any inventive concepts in other claims. *Id.*

Watson's reliance on claim 1 of the '730 patent as a representative claim for all claims of all asserted patents is improper under this standard. As an initial matter, the claims of the asserted patents are not directed to an abstract idea, much less the *same* abstract idea. *See* Facts Section C, *supra*. Regardless, the claims of each patent are not substantially similar: they recite distinct and different implementations of the central computer database used in the various claimed drug distribution systems and methods. For example, the '963 patent claims recite various possible hardware implementations of the central computer database, and the '106 patent claims include a detailed set of controls used by the central computer database to detect potential abuse, misuse, or diversion. *See, e.g.*, '963 patent claims 1, 24; '106 patent claim 1; *see also* Facts Section C, *supra*. Accordingly, Watson's discussion of claim 1 of the '730 patent cannot, by itself, carry its burden to justify the dismissal of all claims of all seven asserted patents.

LEGAL STANDARD

A motion to dismiss for failure to state a claim should be denied if the complaint "contains sufficient factual matter to 'state a claim to relief that is plausible on its face.'" *Data Distribution Techs., LLC v. BRER Affiliates, Inc.*, No. 12-4878, 2014 WL 4162765, at *5 (D.N.J. Aug. 19, 2014) (quoting *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009). Although patent eligibility under Section 101 presents a question of law, the "legal conclusion may contain underlying factual

issues."[8] *Accenture Global Servs., GmbH v. Guidewire Software, Inc.*, 728 F.3d 1336, 1340-41 (Fed. Cir. 2013). A party seeking to establish that patent claims are invalid under Section 101 must present clear and convincing evidence of invalidity, including a showing that "the only plausible construction" of the claims renders them patent ineligible. *Data Distribution*, 2014 WL 4162765, at *5 (quoting *Clear with Computers, LLC v. Dick's Sporting Goods, Inc.*, Civ. 12-674, 2014 WL 923280, at *3 (E.D. Tex. Jan. 21, 2014)).[9]

ARGUMENT

I. THE CLAIMS OF THE ASSERTED PATENTS SATISFY THE PATENT-ELIGIBILITY REQUIREMENTS UNDER *ALICE*

The Supreme Court's decision in *Alice Corp. Pty. Ltd. v. CLS Bank Int'l* provided two ways to show patent eligibility under 35 U.S.C. § 101. 134 S. Ct. 2347 (2014). First, a claim satisfies Section 101 if it does not preempt any abstract

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[8] The question of whether a patent is obvious under 35 U.S.C. § 103, an issue frequently tried by a jury, is subject to the same standard. *See, e.g.*, *Insite Vision Inc. v. Sandoz, Inc.*, No. 2014-1065, 2015 WL 1566882, at * (Fed. Cir. Apr. 9, 2015) ("Obviousness is a question of law, based on underlying factual determinations….").

[9] Watson's Section 101 arguments may also raise new issues of claim construction that preclude dismissal on the pleadings. *See, e.g.*, *Bancorp Servs., L.L.C. v. Sun Life Assur. Co. of Canada (U.S.)*, 687 F.3d 1266, 1273-74 (Fed. Cir. 2012) ("[I]t will ordinarily be desirable—and often necessary—to resolve claim construction disputes prior to a § 101 analysis, for the determination of patent eligibility requires a full understanding of the basic character of the claimed subject matter."); *Data Distribution*, 2014 WL 4162765, at *6 (denying motion to dismiss based on claim construction disputes).

idea. *Id.* at 2355. Second, even if the claim appears to be directed to an abstract idea, the claim satisfies Section 101 if it contains an "inventive concept"— "i.e., an element or combination of elements that is 'sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.'" *Id.* (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1294 (2012)). Either inquiry is independently sufficient to satisfy the *Alice* analysis and survive a Section 101 challenge.

Here, the claims of the asserted patents satisfy both *Alice* inquiries. The patents do not claim an abstract idea; the claims are directed to controls and procedures linked to a central computer database specially configured as part of a drug distribution system invented to address a specific problem of mitigating risks associated with a dangerous prescription drug by storing prescription information and detecting behavior indicating potential abuse, misuse, or diversion – and not to the abstract idea of drug distribution generally. The novel combination is an "inventive concept" that amounts to more than just the concepts of "drug distribution" or "risk mitigation" generally.

A. The Claims of the Asserted Patents Are Directed to Methods of Preventing Abuse, Misuse, and Diversion Through Specific, Special Purpose Machines

1. Section 101 Protects Against Preemption

Section 101 permits patenting of "any new and useful process, machine,

manufacture, or composition of matter, or any new and useful improvement thereof." In selecting such broad language, "Congress plainly contemplated that the patent laws would be given wide scope." *Bilski v. Kappos*, 561 U.S. 593, 601 (2010) (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)). Nevertheless, the courts have adopted certain narrow exceptions prohibiting patenting of "[l]aws of nature, natural phenomena, and abstract ideas" because they "are basic tools of scientific and technological work." *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2116 (2013) (quoting *Mayo*, 132 S. Ct. at 1293). The Supreme Court has cautioned, however, that "too broad an interpretation of this exclusionary principle could eviscerate patent law. For all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas. " *Id.* (quoting *Mayo*, 132 S. Ct. at 1293).

The exceptions to Section 101 "distinguish patents that claim the 'buildin[g] block[s]' of human ingenuity, which are ineligible for patent protection, from those that integrate the building blocks into something more, thereby 'transform[ing]' them into a patent-eligible invention . . ." *Alice*, 134 S. Ct. at 2354 (quoting *Mayo*, 132 S. Ct. at 1294, 1303) (internal citations omitted). Because all inventions are necessarily based on these "building blocks," the mere use of an abstract idea does not render an invention patent ineligible, as long as it is an "application … to a new and useful end." *Id.* (quoting *Gottschalk v. Benson*, 409 U.S. 63, 37 (1972)).

The same rule applies for patents that claim a computer-implemented method: the mere use of a computer does not automatically render the claims patent ineligible. *Diamond v. Diehr*, 450 U.S. 175, 187 (1980) ("[A] claim drawn to subject matter otherwise statutory does not become nonstatutory simply because it uses a mathematical formula, computer program, or digital computer."); *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1257 (Fed. Cir. 2014) (holding claims patent eligible when they "do not merely recite the performance of some business practice known from the pre-Internet world along with the requirement to perform it on the Internet"). Here, the asserted claims are directed to a specially programmed central computer database that implements specific controls for detecting and identifying potential abuse, misuse, or diversion of prescription drugs. This specific application is patent eligible.

2. The Asserted Patents Do Not Preempt Any Abstract Ideas

The claims of the asserted patents are plainly directed to specific methods and systems for preventing abuse, misuse, and diversion of dangerous drugs using a specially programmed central computer database to detect and identify behaviors indicating abuse, misuse, or diversion. They do not preempt an abstract idea. Each claim expressly requires a list of numerous controls and procedures as well as a central computer database that stores prescription information and analyzes that information to detect and identify specific indicators of abuse, misuse, or

diversion. The different claims specify different choices of controls and different central computer databases that are designed and configured to perform this task. *See* Facts Section C, *supra*.

Although the claims relate to a specific problem in the field of drug distribution – abuse, misuse, and diversion of a dangerous drug – none of the claims purport to claim the concept of "drug distribution" or "risk mitigation" generally. Nor do the claims preempt all methods of preventing abuse, misuse, or diversion in the context of drug distribution. Rather, the claims cover only the specific solution developed by Jazz. Indeed, Watson's citation to several different risk management systems employed for other drugs – none of which fall within the claims of the asserted patents – conclusively demonstrates that the asserted patents do not claim the abstract idea of risk management of drugs. Tellingly, other pharmaceutical companies have also marketed drugs that have a potential for abuse, and have been able to implement REMS that do not incorporate Jazz's proprietary central computer database. *See, e.g.*, Ex. 16 (Suboxone REMS); 21 C.F.R. § 1308.13(e)(2) (listing buprenorphine, the active ingredient in Suboxone, as a Schedule III controlled substance); Ex. 12 (ER/LA Opioid REMS) (Addressing problems of "inappropriate prescribing, misuse, and abuse" through

educational programs for prescribing physicians).[10]

Supreme Court and Federal Circuit precedent confirms that the types of claims recited in the asserted patents are not foreclosed by Section 101. For example, in *Diamond v. Diehr*,[11] the Supreme Court found that claims directed to using a computer to automate the process of curing rubber were patent eligible. 450 U.S. 175 (1980). Although the underlying formula was well known and the remaining steps of the claims – such as installing rubber in a press, closing the mold, determining the temperature of the mold, and opening the press – were not themselves novel, the Court found that the combination of these elements constituted a specific process for molding rubber, and not an attempt to patent an abstract idea. *Id.* at 187. The Court recognized that "one does not need a 'computer' to cure natural or synthetic rubber, but if the computer use incorporated in the process patent significantly lessens the possibility of 'overcuring' or 'undercuring,' the process as a whole does not thereby become unpatentable

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[10] Restricted distribution methods implemented in other REMS are covered by their own patents. *See, e.g.*, Thalomid REMS™, Revlimid REMS™, and E.A.S.E. ENTEREG REMS. (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm; http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021880&Product_No=001&table1=OB_Rx; http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021775&Product_No=001&table1=OB_Rx) (last visited April 20, 2015).

[11] The Supreme Court recently reexamined *Diehr* in *Alice* and reaffirmed its prior holding. 134 S. Ct. at 2358.

subject matter." *Id.* at 187. Precisely the same can be said of the claims of the asserted patents: like the claims in *Diehr*, the asserted claims are directed to specific processes that use a specially designed central computer database to improve detection and prevention of drug abuse, misuse, or diversion. Although other methods of drug misuse detection and prevention may be possible without the use of a central computer database, that fact alone does not render the claims patent ineligible.

In *In re Alappat*, the Federal Circuit held that claims directed to an anti-aliasing algorithm for generating smooth waveforms on an oscilloscope display were patent eligible. 33 F.3d 1526 (Fed. Cir. 1994), *abrogated on other grounds*, *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008). The court recognized that the claims recited only mathematical operations and structures "known in the electronic arts before Alappat made his invention." *Id.* at 1539. Nevertheless, the Court held that the claimed invention "is not a disembodied mathematical concept which may be characterized as an 'abstract idea,' but rather a specific machine to produce a useful, concrete, and tangible result." *Id.* at 1544. The Court rejected the argument that the claims were patent ineligible because they could be implemented on a general-purpose computer, holding that "a general purpose computer in effect becomes a special purpose computer once it is programmed to perform particular functions pursuant to instructions from program software." *Id.* at 1545. Like the

claims in *Alappat*, the claims of the asserted patents are directed to a specially configured computer – the central computer database – that performs specific methods for detecting and identifying indicators of abuse, misuse, or diversion associated with prescriptions.

Most recently, in *DDR*, the Federal Circuit rejected a Section 101 challenge to claims directed to systems and methods of generating composite web pages for electronic commerce websites. 773 F.3d 1245. The Court recognized that "the claims address a business challenge," but nevertheless concluded that they did not "recite a fundamental economic or longstanding commercial practice" and were patent eligible. *Id.* at 1257. Specifically, the Court noted that "the claims at issue do not attempt to preempt every application of the idea.... Rather, they recite a specific way to … solve a problem [in the art]." *Id.* at 1258. The Court acknowledged that the claims at issue were "similar" to the claims at issue in cases such as *Ultramercial* (cited extensively in Watson's motion and discussed in more detail below), but distinguished the asserted claims "because they do not merely recite the performance of some business practice known from the pre-Internet world along with the requirement to perform it on the internet." *Id.* at 1257. The same holds true for the claims of the asserted patents. The configuration of a system around a central database to store *all* prescription information, control distribution, and detect and identify potential abuse, misuse, or diversion of a

dangerous prescription drug is not a fundamental or longstanding economic or commercial practice. Risk mitigation programs in the pharmaceutical field have historically focused on *inadvertent* misuse of a drug or known side effects associated with proper use, not intentional abuse, misuse, or diversion – and certainly not intentional misuse *against others*. *See* Facts Section B, *supra*. Thus, the claims of the asserted patents, like the claims in *DDR*, are more than just the generic implementation of an age old business practice on a computer.

Watson does not contend that any abstract idea is preempted by any claim of any asserted patent. Indeed, Watson has difficulty identifying what the abstract idea even is. Watson's motion alternates between characterizing the alleged abstract idea that the asserted patents claim as "risk mitigation" (*e.g.*, Motion at 2) or "drug distribution" (*e.g.*, *id.* at 1), but the claims on their face do not preempt these concepts or their computerized implementation. *See DDR*, 773 F.3d at 1257 ("Indeed, identifying the precise nature of the abstract idea is not as straightforward as in *Alice*…. NLG's own varying formulations of the underlying abstract idea illustrate this difficulty."). Nor does Watson suggest that they do: the word "preempt" does not even appear in Watson's motion.

In order to equate the claims of the asserted patents with the abstract idea of "drug distribution" or "risk mitigation," Watson attempts to read out the fundamental aspect of every claim: the central computer database. For example,

Watson describes claim 1 of the '730 patent as "a method of organizing a basic human activity" by reducing it to the steps of "(1) receiving a request for a drug; (2) checking if the drug should be provided; and (3) providing the drug to the intended recipient." Motion at 21. Watson also purports to analyze "excerpts" of the claim. Motion at 23-24. But, as shown below, a review of claim 1 in its entirety reveals just how much Watson has omitted to construct its argument:

> 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

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

'730 Patent claim 1 (Watson's omissions highlighted). Likewise, Watson glosses over claims with substantial implementation details by arguing that they only "recite the use of particular well-known 'controls'" (Motion at 15). But, again, the claims themselves belie Watson's argument. For example, claim 1 of the '106 patent includes the following limitation regarding the implementation of misuse detection on the central 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;

'106 Patent col. 8:54-9:32.

The claims on their face are not as broad or simplistic as Watson's characterization suggests and certainly fall far short of preempting an abstract idea. Rather, each claim recites one of several implementations of a central computer database that stores and analyzes prescription information to detect and identify potential abuse, misuse, and diversion. The central computer database does not "organize" any "basic human activity," but rather provides an improved method, available only through a centralized computer and not reproducible with pen and paper, of analyzing prescription data and controlling distribution to minimize misuse. Although other methods of misuse detection and prevention may be possible without the use of software and computers, "if the computer use incorporated in the process patent significantly lessens the possibility" of abuse, misuse, or diversion, "the process as a whole does not thereby become unpatentable subject matter." *Diehr*, 450 U.S. at 187.

Watson has provided no basis for concluding that the asserted claims

preempt any abstract ideas or "building blocks" of technology. Accordingly, the claims cannot be found patent ineligible under the broad standard of patent eligibility articulated in Section 101 and Watson's motion should be denied.

3. Watson's Cited Cases Are Inapposite

Watson argues that courts have rejected claims "very similar" to those in the asserted patents. However, Watson can identify only superficial similarities between the claims, such as similarities between individual words or hand-picked claim elements, and concludes without further analysis that rejection must be appropriate. This approach cannot sustain Watson's burden.

Ultramercial, Inc. v. Hulu LLC, Watson's chief case, is distinguishable on several grounds. 772 F.3d 709 (Fed. Cir. 2014). First, the claims in *Ultramercial* on their face recited an abstract method with "no particular concrete or tangible form." *Id.* at 712, 714. By contrast, the claims of the asserted patents are directed to a concrete and tangible implementation: the drug distribution system premised on a specially configured central computer database. Second, the claims in *Ultramercial* were "not tied to any particular novel machine or apparatus"; they simply implemented the abstract idea of using advertising as currency over the Internet. *Id.* at 716. The Court held that use of the Internet could not render the claims patent eligible because the Internet "is a ubiquitous information-transmitting medium, not a novel machine. And adding a computer to otherwise

conventional steps does not make an invention patent-eligible." *Id.* at 716-17.[12] The claims of the asserted patents, by contrast are not merely abstract concepts and *are* tied to a novel machine: the central computer database, which analyzes prescription information and detects indicators of abuse. Finally, the claims in *Ultramercial* recited only "conventional steps, specified at a high level of generality," rather than any inventive concept. *Id.* at 716. The Federal Circuit in *DDR* similarly distinguished *Ultramercial* along the same lines in holding that the specific computer implementation at issue in that case was patent eligible because it specified not only use of the internet but "how interactions with the Internet are manipulated to yield a desired result." *DDR*, 773 F.3d at 1258-59.

There is nothing "conventional" about the central computer database in the asserted patents and the numerous controls required by the claims: Traditional risk mitigation programs did not even consider practices for detecting and preventing intentional misuse of prescription drugs against others. *See* Facts Section B, *supra*. Watson does not even attempt to characterize the central computer database of the asserted patents to be routine or conventional in the art.

Watson's reliance on *Money Suite Co. v. 21st Century Ins. & Fin. Servs., Inc.* is similarly misplaced. Nos. 13-984, -985, -986, -1747, -1748 , 2015 WL 436160

[12] Notably, the claims at issue in *Ultramercial* also required a "facilitator," but the specification made clear that the facilitator could "be a person and not a machine"; thus, the claim was not tied to any specific novel apparatus. *Id.* at 717.

(D. Del. Jan. 27, 2015). There, the Court determined that the claims at issue were directed generally to a fundamental economic or conventional business practice: the concept of price quoting. *Id.* at *3-*4. The claims of the asserted patents are not directed to any such "fundamental" or "conventional" practice. Although Watson attempts to characterize the patents as claiming "the concept of drug distribution" generally (Motion at 25), the claims on their face belie this characterization: each claim is clearly directed to the central computer database, which tracks prescriptions and monitors them for indicators of abuse. In addition, the *Money Suite* court held the patents at issue invalid only after conducting a preemption analysis, and concluding that the patents essentially monopolized computerized implementations of the concept of price quoting. *Money Suite*, 2015 WL 436160, at * 5. Watson has not even argued that the claims of the asserted patents would preempt any concept, much less offered any support for such an argument. Indeed, Xyrem® is the *only* drug out of thousands of drugs being distributed today that currently uses the patented methods. This demonstrates that the patented methods cannot preempt the host of other restricted distribution programs that do not include this technology. *See, e.g.*, Ex. 10 (Thalomid REMS); Ex. 12 (ER/LA Opioid REMS).

Enpat, Inc. v. Tenrox Inc. is similarly inapposite. No. 6:13-cv-948, 2015 WL 541673 (M.D. Fla. Feb. 10, 2015). The court in that case held that claims

expressly directed toward the known concept of project management carried out on a computer were not patent eligible. *Id.* at *2. Further, the claims in *Enpat* are not comparable to those in the asserted patents. For example, representative claim 32 at issue in *Enpat* recited:

> 32. A method that is automatic in nature and for coordinating the management of a project, said method comprising:
>
> receiving an electronic message;
>
> allocating at least one resource between each plurality of project tasks represented in a common database, based on said received electronic message; and
>
> leveling allocation of said at least one resource between said plurality of project tasks with built-in triggers in response to said electronic message.

Id. at *2. The only similarity between claim 32 and the claims of the asserted patents is that they use a computer. The *Enpat* patents simply automated the concept of project management. They did not use a specially configured computer to solve a problem in the art, like the central computer database of the asserted patents is used to solve the problem of drug abuse, misuse, and diversion for prescription drugs. *See id.* at *5 ("The claimed invention … simply takes an abstract idea and computerizes it.")

Watson's reliance on other cases involving mere implementation of a known business practice on a computer, without more, is similarly unavailing. For example, in *Alice*, the Court held the asserted claims unpatentable because they recited nothing more than a known business practice ("intermediated settlement"),

implemented on any generic computer performing generic computer functions. *Alice*, 134 S. Ct. at 2359. *See also, e.g.*, *Planet Bingo, LLC v. VKGS LLC*, 576 F. App'x 1005, 1009 (Fed. Cir. 2014) ("[T]he claims recite a program that is used for the generic functions of storing, retrieving, and verifying a chosen set of bingo numbers against a winning set of bingo numbers."); *MyMedicalRecords, Inc. v. Walgreen Co.*, No. 2:13-cv-631, 2014 WL 7339201, at *2 (C.D. Cal. Dec. 23, 2014) ("Unlike the claims in *DDR* the '466 Patent claims are directed to nothing more than the performance of a long-known abstract idea 'from the pre-Internet world'"). The same is simply untrue for the claims of the asserted patents: the central computer database is not a generic computer that simply automates a preexisting practice, but is a specially configured machine that solves a problem in the field of pharmaceutical drugs. In sum, none of the cases cited by Watson hold that claims such as those in the asserted patents are not patent eligible.

B. The Claims of the Asserted Patents Include Inventive Concepts

Because the claims of the asserted patents are not directed to an abstract idea, the Court may end the Section 101 inquiry here and find the claims patent eligible. *See Alice*, 134 S. Ct. at 2355. The claims are also independently patent eligible for including an inventive concept.

1. The Asserted Patents Recite a Specially Designed Machine To Solve a Problem in the Art

Each claim of each asserted patent recites a central computer database that is

specially programmed to analyze prescription information for indicators of misuse and flag potential abuse, misuse, and diversion. Different claims of different patents recite specific implementations of the central computer database. The central computer database is not merely a general-purpose computer that implements a business practice or other abstract idea in a generic way. First, the claims specifically call for a specific computer implementation – that is, on a *single, central* computer. Second, the central computer is specially configured to implement the specific misuse detection and prevention technologies underlying the inventions of the asserted patents. *See* Facts Section C, *supra*.

Watson's characterization of the claims as using "a general purpose computer … for unremarkable, routine steps" (Motion at 28) is incorrect. As an initial matter, that an invention may be implemented on a general-purpose computer does not, in itself, render it patent ineligible. *See, e.g.*, *Alice*, 134 S. Ct. at 2359 (holding claims unpatentable because "each step does no more than require a generic computer ***to perform generic computer functions***" (emphasis added)); *DDR*, 773 F.3d at 1258-59 (holding claims implemented on general-purpose computers patentable because they do not use a "routine and conventional sequence of events"); *Alappat*, 33 F.3d at 1545 ("[A] general purpose computer in effect becomes a special purpose computer once it is programmed to perform particular functions pursuant to instructions from program software."). Here, the

claims of the asserted patents do not perform routine or conventional steps: rather, they use a particular computer implementation configured in a specialized way to perform the novel functions of the patent (*i.e.*, using a central database to detect and prevent prescription drug abuse, misuse, and diversion).

Watson resorts to oversimplified, stripped down versions of the claims to argue that they implement only "routine" steps. Watson narrowly focuses on fragments of limitations, characterizes them as "routine" or "conventional steps," and then dismisses the claims in their entirety as generic. For example, Watson characterizes claim 1 of the '730 patent as follows:

> They consist of receiving and maintaining data in a computer database. '730 patent at 8:40-53. Checks are performed to determine if distribution of a drug product to a particular patient is authorized. *Id* at 8:54-61. If so, then the drug is delivered. *Id.* at 8:62-67. Records of the transactions are maintained in the computer database so that reports can occasionally be generated. *Id.* at 9:1-3.

Motion at 29; *see also* pp. 24-25, *supra.* But this characterization ignores the inventive concepts in the claims.

First, as the patent office recognized, the use of a single central computer database to store and analyze *all* prescription information for potential abuse, misuse or diversion was itself novel and *un*conventional:

> [T]he 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.

Ex. 13 ('730 Patent Notice of Allowability) (emphasis in original); *see also* Ex. 14 ('106 Patent Notice of Allowability); Ex. 15 ('107 Patent Notice of Allowability). Watson does not address this aspect of the claims because it fails to address the claims as a whole. It is precisely the use of this central database that permits the claimed systems to control distribution and discover diversionary schemes, such as obtaining multiple prescriptions from different physicians. *See* '730 Patent at 1:24-26. To the extent Watson disputes the file history's analysis of the claims, this raises a factual issue and requires denial of Watson's motion to dismiss.

Second, whereas the claims rejected in *Alice* and similar cases simply used generic computer functions necessary for *any* computerized transaction, without any special implementation relating to the claimed invention, the claims of the asserted patents recite a specially configured *un*conventional central database for detecting and preventing potential abuse, misuse, or diversion. Thus, various claims of the patents (many of which Watson do not directly address) recite different analytic methods used to detect indicators of abuse. *See, e.g.*, '106 patent, claim 1; '963 patent, claim 1; *see also* pp. 25-26, *supra*. Watson glosses over these limitations by characterizing them as a series of operations that receive, check, and store information. But Watson cannot simply look at the first word of a limitation and end the inquiry there.

Third, Watson does not consider the inventiveness of the claims as a whole. As Watson acknowledges, the Section 101 analysis must "consider the elements of each claim both individually and as an ordered combination to determine whether the additional elements transform the nature of the claim into a patent-eligible application." Motion at 19 (quoting *Alice*, 134 S. Ct. at 2355). Noticeably absent from Watson's motion is any analysis of *any* claim taken "as an ordered combination." Instead, Watson dissects the claims into individual oversimplified limitations, dismisses those limitations as "routine" or "conventional" and concludes that no inventive concept could be found. This is precisely the approach that was rejected by the Supreme Court in *Diehr*:

> In order for the dissent to reach its conclusion it is necessary for it to read out of respondents' patent application all the steps in the claimed process which it determined were not novel or "inventive." That is not the purpose of the § 101 inquiry and conflicts with the proposition recited above that a claimed invention may be entitled to patent protection even though some or all of its elements are not "novel."

450 U.S. at 193 n.15.

When considered "as a whole," the claims of the patents-in-suit are patent eligible on their face. The claims recite more than just a generic computer implementation of a drug distribution method: they recite a specific, novel solution to the problem of abuse, misuse, and diversion of a dangerous prescription drug by using the specified controls and procedures in conjunction with a single central computer database to track *all* prescription information and detect behaviors

indicating abuse, misuse, or diversion. It is this inventive concept in the claims that allows them to address the problem of distributing a dangerous prescription drug while mitigating its risk, and not the mere fact that a computer may be faster or more efficient than a human, as Watson argues.

2. The Asserted Patents Do Not Claim "Mental Processes"

Watson alternatively contends that the asserted claims are unpatentable "mental processes," or mere computerized implementations of mental processes. The "mental process" exception, however, is narrowly limited to claims that can ***entirely*** be performed in the human mind, or using pen and paper. *See CyberSource Corp. v. Retail Decisions, Inc.*, 654 F.3d 1366, 1372 (Fed. Cir. 2010) (finding claims unpatentable because "***All*** of claim 3's method steps can be performed in the human mind, or by a human using a pen and paper" (emphasis added)). *See also Ultramercial, LLC v. Hulu, LLC*, 657 F.3d 1323, 1329-30 (Fed. Cir. 2011), *vacated on other grounds*, 132 S. Ct. 2431 (2012) ("The eligibility exclusion for ***purely*** mental steps is particularly narrow."). Claims where "the use of a computer is required to perform the claimed method" cannot, "as a practical matter, be performed entirely in the human mind." *Cybersource*, 654 F.3d at 1376.

In general, the types of claims that courts have rejected as "mental processes" are methods that not only can be, but frequently are, performed entirely by humans mentally or using pen and paper. For example, in *In re Comiskey*, 554

F.3d 967, 980 (Fed. Cir. 2009), the Federal Circuit rejected claims directed to "[a] method for mandatory arbitration resolution" that the patentee conceded did not require a machine. 554 F.3d at 981. In *Cybersource*, the Court rejected claims reciting "a method and system for detecting fraud in a credit card transaction" that did not expressly require a computer and could feasibly be performed by a human manually reviewing transaction information. 654 F.3d at 1372-73. In *In re Schrader*, the Court rejected claims directed to "[a] method of competitively bidding on a plurality of items" that required no "physical effect or result" except for recording the bids – which could be done by writing the bids on a piece of paper. 22 F.3d 290, 292-93 (Fed. Cir. 1994). The common theme among these cases is that the claims were directed to processes that humans performed for years without machines.

As at least one court has recognized, the "mental process" analysis is largely unhelpful in the context of computer-implemented inventions:

> Many inventions could be theorized with pencil and paper, but pencil and paper can rarely produce the actual effect of the invention. Likewise, with regard to software, a human could spend months or years writing on paper the 1s and 0s comprising a computer program and applying the same algorithms as the program. At the end of the effort, he would be left with a lot of paper that obviously would not produce the same result as the software.

Cal. Inst. Of Tech. v. Hughes Commc'ns Inc., No. 2:13-cv-7245, 2014 WL 5661290, at *16 (C.D. Cal. Nov. 3, 2014). As that court recognized, the "mental

process" test "is a stand-in for another concern: that humans engaged in the same activity long before the invention of computers." *Id.* Thus, the court did "not ask whether a human can [perform the claim] using pencil and paper. Instead, the Court must ask whether [the claim] constitutes an inventive concept that sufficiently limits the claim's preemptive effect." *Id.*

As an initial matter, the claims of the asserted patents on their face cannot be performed by a human or using pencil and paper, as they expressly recite a machine – the central computer database – that operates on stored data by analyzing it for indicators of abuse, misuse, or diversion. In addition, they recite many activities and controls that require physical activity in the real world and cannot be performed solely by thinking. Thus, each claim recites explicit hardware implementation on a specially configured machine.

Moreover, unlike the typical "mental process" claims, the claims of the asserted patents are not directed to a process that conventionally has been performed by humans mentally or using pen and paper. Historic literature on risk mitigation programs for prescription drugs offers no discussion of the problem of drug abuse, misuse, and diversion, much less any solutions. *See* Facts Section B, *supra*. Pen and paper are insufficient to accomplish distribution of a dangerous prescription drug to patients who need it while mitigating the risks associated with abuse, misuse, and diversion of that drug – and Watson certainly has not

established otherwise (nor could it on a motion to dismiss). The claims of the asserted patents, by contrast, offer novel, specific solutions to unsolved problems in the art. The claims do not preempt any abstract idea – they provide a specific implementation that solves the problem. *See* Argument Section I.A.2, *supra*.

II. AT BEST, THE PATENTABILITY OF THE CLAIMS RAISES ISSUES OF FACT OR NEW CLAIM CONSTRUCTION DISPUTES

Watson has failed to establish that the "only plausible reading of the patent is that there is clear and convincing evidence of ineligibility." Accordingly, its motion should be denied. *Card Verification Solutions, LLC v. Citigroup Inc.*, No. 13-6339, 2014 WL 4922524, at *2 (N.D. Ill. Sept. 29, 2014). Even if Watson's arguments cast any doubt as to the patentability of the claims of the asserted patents, these arguments necessarily raise questions relating to underlying factual issues or present new claim construction disputes that must be resolved. In particular, Watson's characterization of the claims as "routine" or "conventional" begs the question of how safe distribution of a drug like Xyrem, which the legislature and DEA have characterized as a "date rape drug," could be accomplished prior to the invention of the asserted patents. Watson does not purport to answer this question, and the exhibits attached to Watson's motion indicate that the opposite is true: historic literature regarding drug distribution or risk mitigation focused on minimizing inadvertent misuse or adverse side effects, not preventing intentional misuse against others. Watson's motion similarly calls

for a factual investigation of the scope of any preemption of abstract ideas by the asserted claims – an issue Watson does not address in its motion. These factual issues cannot and should not be resolved at the pleadings stage.

To the extent that Watson contends the claims' recitation of a central computer database requires no more than a general purpose computer performing generic functions, this argument raises new claim construction issues that must be decided before the patentability of the claims may be conclusively determined. Faced with similar issues, this court recently denied a motion to dismiss on Section 101 grounds and held that claim construction was necessary in those circumstances. Specifically, in *Data Distribution*, the parties disputed whether the claims required a "specific computerized method" or "generic computer jargon." *Data Distribution*, 2014 WL 4162765, at *13. The Court concluded that "[w]ithout claim construction, agreement between the parties, proposals from Plaintiff, or an evidentiary record, the Court cannot assume the meaning of the '908 Patent's claim terms" and denied the motion to dismiss.

Applying the same principles, Watson's motion should be denied here.

III. CONCLUSION

For the foregoing reason, Watson's motion should be denied.

Respectfully submitted,

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